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Advances in polypeptide synthesis

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Synthetic polypeptides are a class of important biomaterials due to their protein-like properties, unique secondary structures, capability to form a variety of complex self-assemblies, and excellent biocompatibility. These polypeptides are typically synthesized through the ring-opening polymerization (ROP) of amino acid *N*-carboxyanhydrides (NCAs), a widely used method that enables the production of polypeptides on a larger scale and with higher molecular weights (MWs) than other chemical and biological techniques. Conventional controlled NCA ROP methods often require expensive catalysts, rigorously anhydrous conditions, and complex apparatus, which restricts the broader application of polypeptides. In the past 20 years, our research group, along with many synthetic polypeptide chemists around the world, has made significant strides in simplifying controlled polypeptide synthesis. Our efforts began with the discovery of simplified NCA ROPs mediated by *N*-trimethylsilyl (*N*-TMS) amine initiator under anhydrous conditions, which minimizes the rate disparity between initiation and propagation and thus achieves excellent control. Building on this, we further uncovered the unprecedented α-helix-induced auto-acceleration in solvents with low dielectric constants and developed the cooperative covalent polymerization (CCP), which eventually brought the controlled synthesis to the open-air benchtop. This ultra-fast polymerization surpasses water-induced NCA hydrolysis, enabling the reaction to proceed in the presence of water. To further diminish the impurity-induced chain termination in CCP, we employed a bio-inspired water/oil emulsion system to achieve *in situ* segregation of impurities from NCA monomers. The new strategy, termed as Segregation-Induced Monomer-Purification and initiator-Localization promoted rate-Enhancement (SIMPLE) polymerization, facilitates the rapid, streamlined synthesis of well-defined polypeptides from amino acids. By eliminating the need for expensive catalysts, stringently anhydrous conditions, and tedious monomer purification, SIMPLE polymerization significantly simplifies the polymerization process and broadens the application of NCA ROP in developing high-performance polypeptides for advanced biomaterials.

polypeptide, *N*-carboxyanhydride, ring-opening polymerization, controlled polymerization, α-helix

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1 Introduction

Polypeptides are a class of synthetic polymers composed of amino acid units linked by amide bonds. Sharing the same backbone structure as natural proteins, polypeptides offer multifunctionality, biocompatibility and biodegradability, making them ideal for constructing advanced structures in diverse biomedical applications [1–5]. To meet the stringent criteria for high-performance biomaterials, synthetic methods that provide precise control over molecular weights (MWs), molecular weight distributions (MWDs), and polymer architectures have been actively pursued.

In 1906, Leuchs [6,7] first reported the synthesis of α-amino acid *N*-carboxyanhydrides (NCAs). By 1921, NCAs were being used as monomers in ring-opening polymeriza-

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tion (ROP) to produce polypeptides, marking the beginning of a new era in polypeptide-based biomaterials and significantly expanding synthetic strategies [8]. Over the subsequent decades, extensive efforts were made to understand the mechanisms of NCA ROP and to develop new technologies for preparing well-defined polypeptides [9,10]. However, well-controlled polymerization strategies remained scarce for many years until 1997, when Deming's group [11] reported the first organonickel complex-initiated ROP of NCAs, which effectively suppressed side reactions to yield well-defined homopolypeptides and copolypeptides. This breakthrough heralded a period of rapid development in NCA chemistry, characterized by intensive research aimed at controlling polymerization kinetics and minimizing side reactions. These efforts can be grouped into three major categories: (1) the development of novel initiators with specific structures, including metal-based complexes [12–14], ammonium salts [15–17], silanes [18–20], thiols [21–24], triphenylphosphines [25], and amino alcohols [26]; (2) the optimization of polymerization conditions, such as low reaction temperatures [27], protecting atmospheres [28], and high vacuum [29]; and (3) the creation of highly efficient catalysts, including rare earth complexes [30], thioureas [31,32], tetramethylguanidine [33,34], cationic catalysts [35], fluorinated alcohols [26], and organic acids [36–40]. The recent advancements have been comprehensively reviewed in several excellent papers [41–43].

Over the past two decades, our team has contributed to the efforts mentioned above by developing several novel polymerization strategies for the simplified, controlled NCA ROP. These strategies include the discovery of trimethylsilyl-carbamate (TMS-CBM)-mediated controlled chain propagation mechanism and the intrinsic auto-catalysis of NCA ROP induced by the polypeptide's α-helical structure, leading to unprecedented rate acceleration and streamlined polymerization setups. Our findings have progressively simplified the chemistry of polypeptide synthesis, evolving from the use of inexpensive organosiliane initiators in an anhydrous system to an open-air, oil-water biphasic system that controls polypeptide chain propagation through autocatalytic processes. In this feature article, we chronologically review our research progress to illustrate how our understanding of NCA ROP has evolved. We also provide a comprehensive outlook on the future of NCA chemistry.

2 Controlled synthesis of polypeptides in anhydrous systems

The conventional NCA ROP initiated by amines typically alternates between the "normal amine" mechanism (NAM) and the "activated monomer" mechanism (AMM), where initiation is generally much slower than chain propagation [41]. As a result, only a small fraction of active chains participate in the polymerization, leading to elevated MWs and broad MWDs. In this section, we systemically review our representative works on employing a unique TMS-CBM-mediated chain propagation to achieve precise control over NCA ROP.

2.1 HMDS-initiated NCA ROP

Our synthesis began with the development of amine initiators capable of controlling NCA ROP under stringently anhydrous conditions. Cheng [44], the corresponding author of this feature article, was inspired by the rapid advancements in organocatalysts, particularly the work of Waymouth and Hedrick [45,46] on lactide polymerization using amines to activate the lactide monomer and control chain propagation. It prompted Cheng and his student to search for "superamines" with similar controlling capabilities. Lu *et al*. [18] screened numerous amines that potentially function as both initiators and catalysts for the ROP of γ-benzyl-L-glutamate *N*-carboxyanhydride (BLG-NCA). While most amines failed to show any control over polymerization, one stood out: hexamethyldisilazane (HMDS), which exhibited excellent control over the ROP of BLG-NCA. The resulting polypeptide, poly(γ-benzyl-L-glutamate) (PBLG), displayed the anticipated MW and narrow MWD ($Đ \sim 1.2$) (Figure 1a). Additionally, the living polymerization behavior enabled the preparation of well-defined block copolypeptide poly(γ-benzyl-L-glutamate)-block-poly(ε-Cbz-L-lysine) (PBLG-*b*-PZLL). Further mechanism study revealed an unusual chain propagation process driven by intermediate TMS-CBM through a synergistic catalysis mechanism (Figure 1b). Initially, one TMS group from HMDS transfers to CO-2 position of the NCA, forming intermediate **2** in a coordinated manner. The *in situ* generated TMS-amine then nucleophilically adds to the CO-5 position of intermediate **2**, producing TMS-CBM **4**. This TMS group subsequently transfers to another monomer, forming a new TMS-CBM propagating center **5**. This repetitive process drives the controlled polymerization and avoids the drawbacks associated with conventional ROPs driven by NAM or AAM.

We then expanded the application of HMDS-initiated NCA ROP to a broader range of NCA monomers. Our attention was particularly drawn to the polymerization of NCA monomers containing conjugation-amenable functional groups, such as γ-(4-vinylbenzyl)-L-glutamate *N*-carboxyanhydride (VBLG-NCA), due to its potential for post-functionalization of the vinyl side groups. However, these vinyl groups also led to interchain cross-linking, resulting in significantly elevated MW with fairly broad MWD ($Đ > 2.0$). To address this issue, we introduced a radical scavenger, nitrobenzene (NB), into the polymerization system to suppress the unwanted cross-linking [47]. The simple mod-

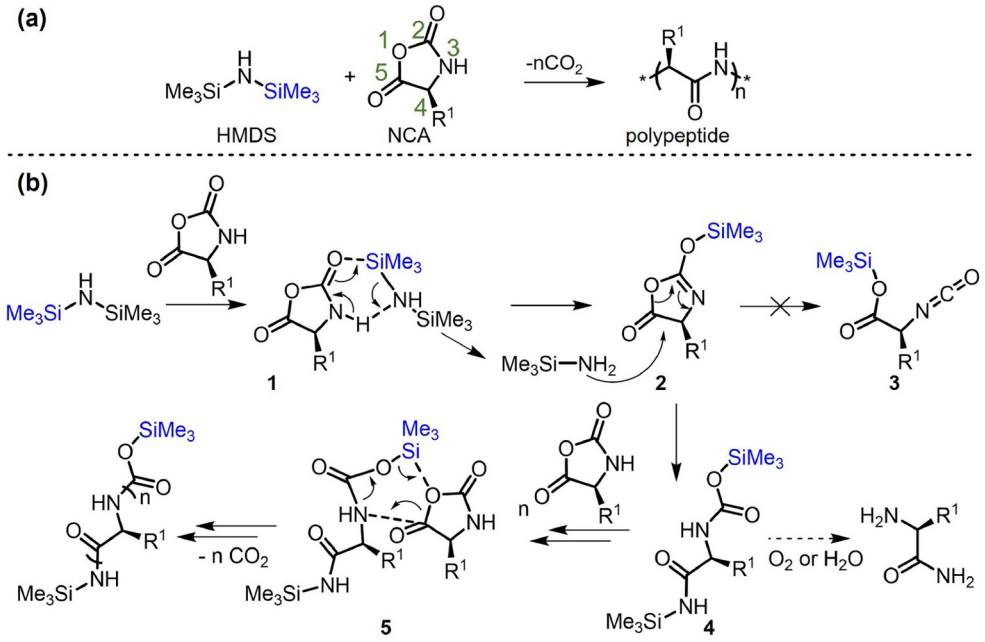

Figure 1 (Color online) TMS-CBM mediated NCA ROP. (a) HMDS-initiated NCA ROP. (b) The speculated mechanism of TMS-CBM mediated chain propagation.

ification yielded well-defined polypeptide PVBLG ($Đ$ =1.08). Despite the much-improved controllability, the low polymerization rate remained a challenge in the preparation of PVBLG. We, therefore, screened various catalysts and identified 1,5,7-triazabicyclo-[4.4.0]dec-5-ene (TBD) as an efficient accelerator. With a catalytic amount of TBD, the monomer was quantitatively consumed within 20 h, and the resulting PVBLG maintained a well-defined structure ($Đ$ = 1.08) (Figure 2a). Subsequent post-functionalization on PVBLG, as illustrated in Figure 2, confirmed that the vinyl group could be efficiently converted into a diverse array of functional groups through appropriate treatments.

In the subsequent research, the well-defined PVBLG was employed to develop a series of water-soluble polypeptides featuring ionic side-chains and ultra-stable α-helical confirmations by distally locating the charge-bearing moieties with longer spacers (Figure 2b) [48–52]. These polypeptides demonstrated exceptional tolerance to harsh pH conditions, elevated temperatures, and even the presence of denaturing agents, positioning them as strong candidates for high-performance biomaterials [53–56].

2.2 *N*-TMS amine-initiated linear NCA ROP

While studying the mechanism of HMDS-mediated polymerization, we recognized that only one TMS group of HMDS participates in mediating the polymerization at the N-end of the polypeptide, while the other TMS group remains intact at the C-end. It led us to consider whether the C-end TMS could be replaced by other groups to directly achieve C-end functionalization of the resulting polypeptides. Polypeptides with chain-end functionalities are of significant interest in biomedical applications, including gene and drug delivery [13], tissue engineering [57], biosensors [58], and catalysis [59]. Consequently, we designed *N*-TMS amines, an analogue of HMDS with one TMS substituted by other functional groups, to serve as the initiators for controlled NCA ROP.

N-TMS allylamine was the first example tested in the polymerization of BLG-NCA, which successfully produced allyl-functionalized PBLG with anticipated MW and narrow MWD [19]. In contrast, the polymerization initiated by allylamine without *N*-TMS group resulted in a poorly defined product ($Đ$ =1.52). The superior control achieved was also attributed to the TMS-CBM-mediated living chain propagation, as confirmed by mechanism studies. Subsequently, various *N*-TMS-containing amines, such as benzylamine, morpholine, propargylamine, *N*-(aminoethylene)-5-norbornene-endo-2,3-dicarboximide, and PEG-amine, were also shown to initiate and mediate well controlled NCA ROP, providing numerous opportunities to develop hybrid biomaterials with unique structures and properties (Figure 3a). As an example, we reported the synthesis of a hybrid block copolymer, polypeptide-poly(oxa)norbornene-polypeptide (Figure 3b) [60]. The poly(oxa)norbornene block, functionalized with *N*-TMS amine groups at both ends, was first synthesized via ring-opening metathesis polymerization (ROMP). The ROP of NCAs was then initiated by the bifunctional macroinitiator, resulting in well-defined hybrid copolymers.

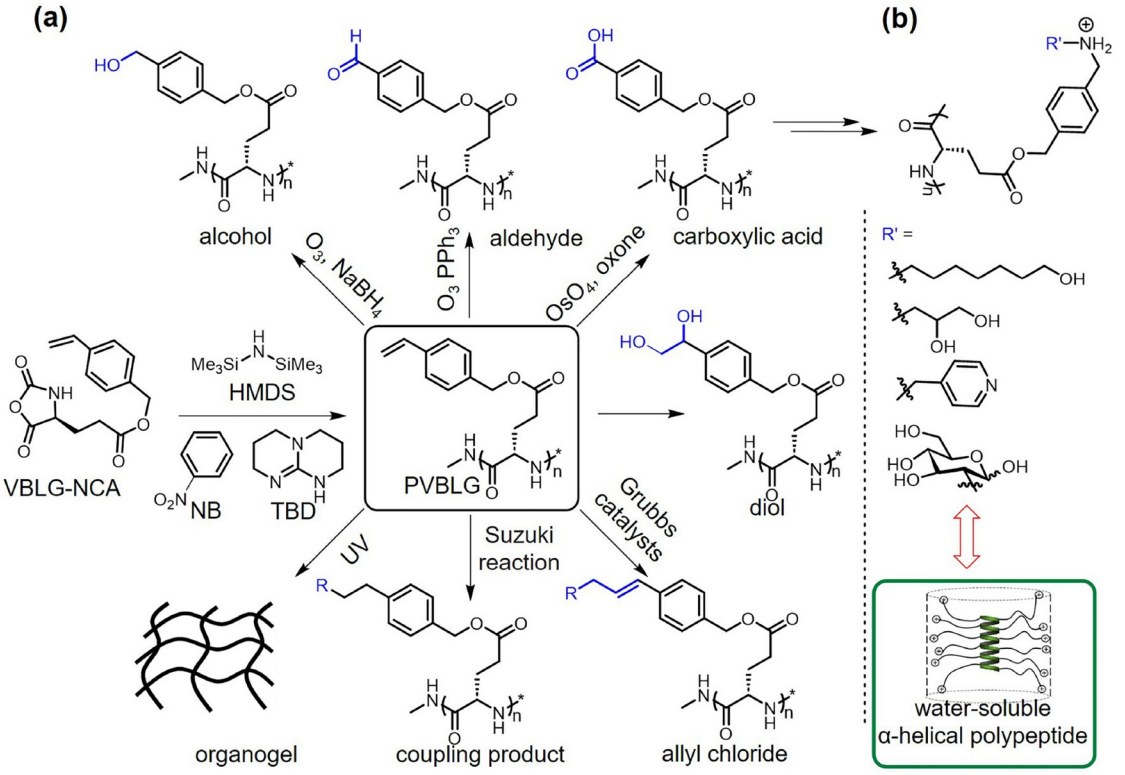

Figure 2 (Color online) (a) Preparation and functionalization of PVBLG; (b) synthesis of water-soluble polypeptides with robust α-helical structure.

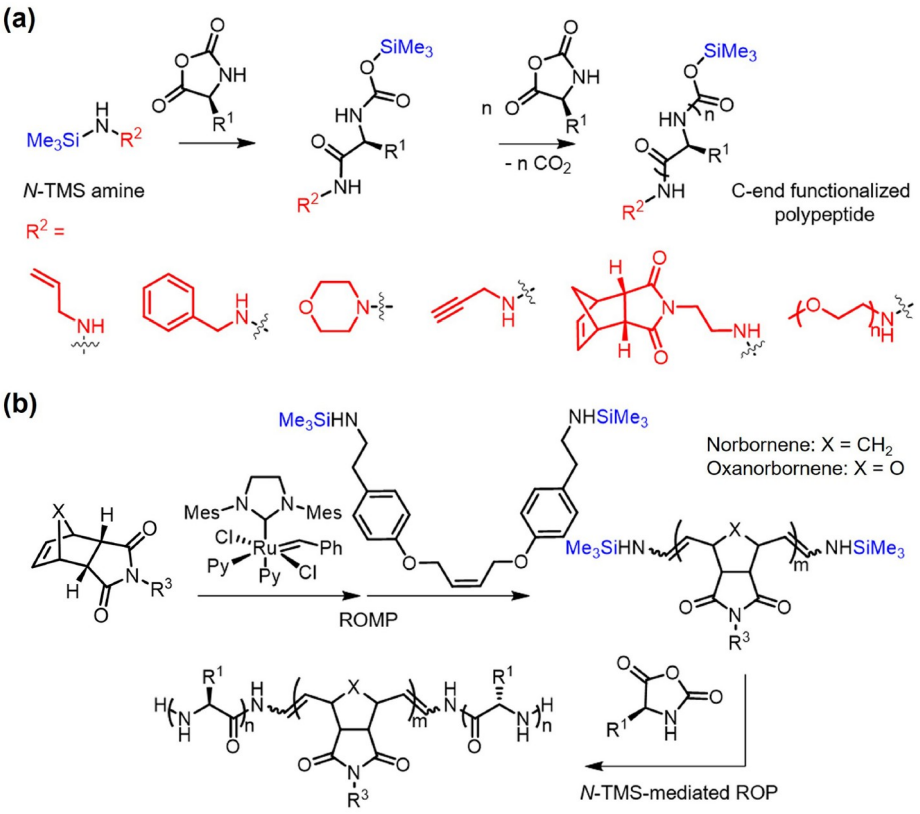

Figure 3 (Color online) (a) *N*-TMS amine-initiated NCA ROP; (b) synthesis of linear hybrid block copolymers *via* ROMP and *N*-TMS amine-initiated NCA ROP.

2.3 *N*-TMS amine-initiated brush-like NCA ROP

Brush-like polymers bearing polypeptide side chains are believed to exhibit unprecedented properties due to their unique topologies and intrinsic secondary structures. However, conventional synthetic strategies using polymers bearing amine side groups as macroinitiators often suffer from poor controllability [61–63]. Given the *N*-TMS amine-initiated polymerization can preserve the C-end structures and functions, we incorporated *N*-TMS amine groups into the side chains of macroinitiators to achieve controlled graft polymerization (Figure 4a) [64]. The macroinitiator polynorbornene (PNB) was synthesized by the random ROMP of NB bearing either an *N*-TMS amine group or an *N*-benzyl group, with the latter used to regulate the density of *N*-TMS amine moieties. Graft polymerization of hydrophobic NCAs including BLG-NCA, ZLL-NCA, and Leu-NCA was then initiated by the pendant *N*-TMS amine groups in a controlled manner [18,19]. The resulting brush-like hybrid polymers exhibited well-defined structures, with the polypeptide side chains self-assembling into α-helices [65]. Next, we synthesized a more complex dual-brush block copolymer featuring hydrophilic polyethylene glycol (PEG) and hydrophobic polypeptide side chains. The amphiphilic hybrid copolymer demonstrated a well-defined structure ($Đ$ < 1.1, Figure 4b) [66].

In conclusion, this novel TMS-CBM-mediated polymerization strategy offers an accessible route to well-defined polymeric materials with complex architectures, fulfilling the needs of diversified applications.

3 Transition of the controlled synthesis of polypeptides from an anhydrous system to an open-air system

Despite significantly improved controllability, *N*-TMS amine-initiated NCA ROP in *N*,*N*-dimethylformamide (DMF) usually takes days to complete. Consequently, side reactions, particularly water-induced hydrolysis of NCA monomers, become a considerable concern. This is why maintaining a stringently anhydrous environment is crucial. A promising approach to overcoming the limitations of anhydrous conditions is to accelerate the polymerization to outpace the side reactions. While exploring methods to enhance the polymerization rate, an unexpected observation by Baumgartner *et al.* [67] during his efforts to further expand Lu's early work on brush polypeptide [64], led to the discovery of a new field for rapid and controlled NCA ROP. In this section, we review the discovery of α-helix-induced auto-acceleration and the developmentof CCP, illustrating how the novel and robust methodology was gradually established.

3.1 α-Helix-induced auto-acceleration in NCA ROP in brush-like system

Conventional NCA ROP typically employed solvents with high dielectric constant and strong hydrogen bonding, such

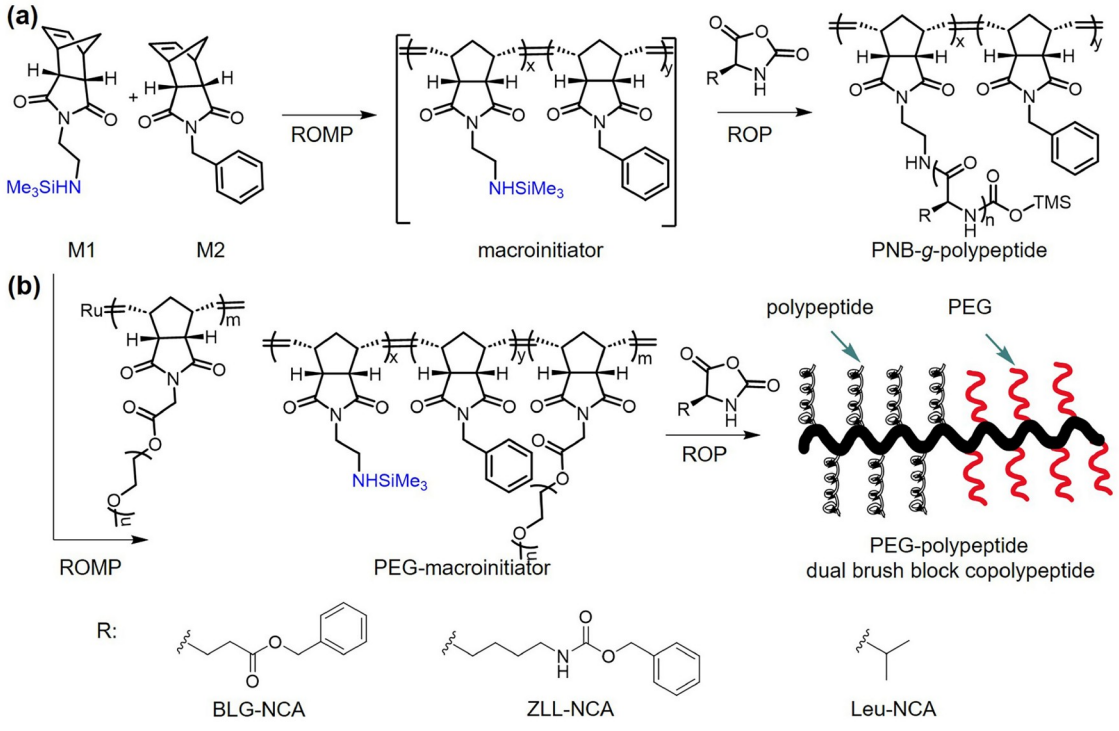

Figure 4 (Color online) (a, b) Synthesis of brush-like polymers via integrated ROMP and *N*-TMS amine-initiated NCA ROP.

as DMF, to effectively dissolve the generated polypeptides to minimize the influence of electrostatic effects [42]. However, while screening polymerization conditions for the synthesis of hybrid brush-like copolymers containing polypeptide side chains, we unexpectedly found that solvents with low dielectric constants and weak hydrogen bonding, such as dichloromethane (DCM) and chloroform, dramatically accelerate the polymerization process (Figure 5a, b)

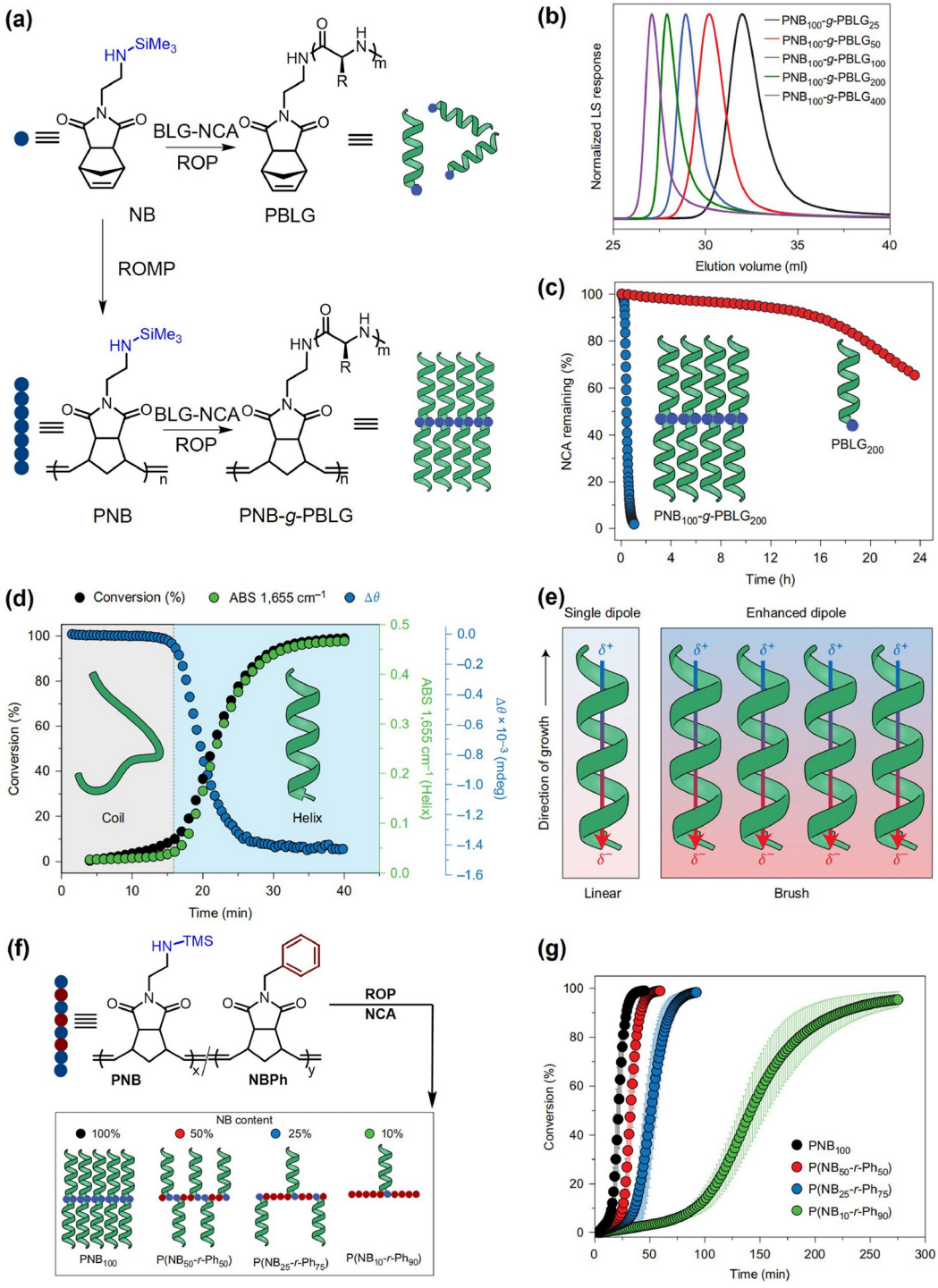

Figure 5 (Color online) Cooperative covalent polymerization in brush-like system. (a) Polymerization of BLG-NCA initiated by bush-like macroinitiator and small molecular initiator. (b) GPC traces of brush-like polymers. (c) The consumption of BLG-NCA against time in linear (red) and brush-like (blue) systems. (d) The two-stage polymerization kinetics is demonstrated by the conversion of monomers (black), the formation of α-helix (green), and the change in ellipticity (blue). (e) Illustration of the cooperative macrodipole of α-helices growing in proximity. (f) The brush-like copolymers are initiated by homopolymer macroinitiators and random copolymer macroinitiators. (g) Monomer consumption against time in the polymerization initiated by homopolymer macroinitiator and random copolymers macroinitiators. Reproduced with permission from Ref. [67], Copyright©2019, Nature Publishing Group.

[67]. The significant acceleration was observed only in the brush-like system; in contrast, polymerization initiated by small molecular units containing single *N*-TMS amine moieties proceeded much more slowly (Figure 5c). The surprising anomaly sparked our interest in uncovering the underlying mechanism.

Through kinetic studies, we found that NCA polymerization in DCM occurs in two distinct stages, a primary nucleation stage and a second elongation stage. During the first stage, the consumption of NCA monomers is rather slow. Once the MWs of the resulting polypeptides reach a critical point that allows them to fold into stable α-helices (DP = 8–12) [68,69], the polymerization suddenly switches into the second stage, where monomer consumption is markedly accelerated (Figure 5d). The observation suggested that the formation of α-helices somehow induces ultra-fast NCA polymerization while providing excellent control over the polypeptide chain length. For linear polymerization initiated by small-molecular initiators, the ratio of the rate constants between the second and primary stages (k_2/k_1) is less than 10, whereas in the brush-like system, the value exceeds 1000. We speculated the enormous difference arises from the proximity and orientation of the polypeptide side chains. In the primary stage, the polypeptides grow slowly as random coils until they reach the critical length to fold into α-helices. The conformation transition induces the formation of a macrodipole moment, which creates a more favorable electrostatic environment for chain propagation at the active center, resulting in modest acceleration in the linear polymerization system. In the brush-like system, the macrodipole is greatly amplified by the cooperation interaction of closely packed α-helices growing outward from the dense initiating groups along the macroinitiator, leading to the markedly enhanced k_2 (Figure 5e). The mechanism is somewhat analogous to the Juliá-Colonna epoxidation of chalcone [70,71]. To validate the decisive role of the macrodipole, we utilized racemic BDLG-NCA monomers to disrupt the formation of α-helices. As expected, the two-stage propagation pattern disappeared, and the polymerization remained slow. To further confirm the importance of the proximity of polypeptide helices, we adjusted the density of initiating sites by varying the fraction of *N*-TMS amine-containing monomer in random copolymer initiators (Figure 5f). The reduction in *N*-TMS amine fraction directly caused a decrease in the polymerization rate (Figure 5g). The observations indicated that the polymerization follows a unique mechanism of α-helix-induced auto-acceleration. We named the new polymerization method as cooperative covalent polymerization (CCP).

Based on the mechanism of CCP, the initiation system can be further simplified. First, the accelerated polymerization process greatly enhances the controllability, reducing the reliance on *N*-TMS amine moieties. Second, the architecture of initiators can be simplified to maintain only the essential cooperative macrodipole effect. To confirm this point, we selected a diamine, C_6-diNH_2, as a minimalist initiator (Figure 6a). Remarkably, the rate constant of the polymerization initiated by C_6-diNH_2 was over 600 times higher than that of the analogous monoamine C_6-NH_2 (Figure 6b) [72]. Increasing the length of the alkyl spacer (n) between the two amine initiation groups led to a decrease in the apparent propagation rate, with the α-helix-induced auto-acceleration diminishing rapidly when $n > 10$ (Figure 6c). The study not

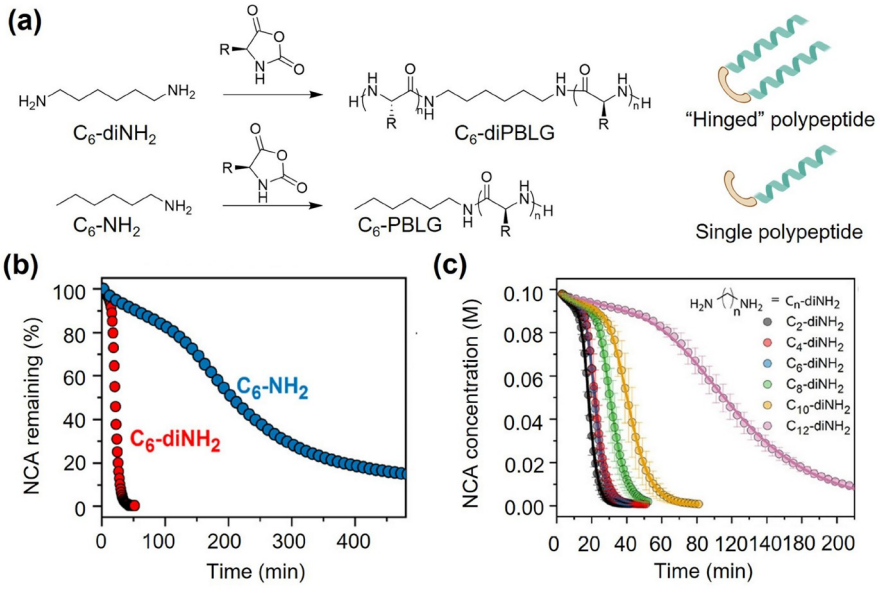

Figure 6 (Color online) (a) Polymerization of BLG-NCA initiated by C_6-diNH_2 and C_6-NH_2. (b) The consumption of NCA against polymerization time. (c) Kinetic studies of BLG-NCA using C_n-diNH_2 (n = 2, 4, 6, 8, 10, 12) as initiators. Reproduced with permission from Ref. [72]. Copyright©2019, American Chemical Society.

only deepened our understanding of the unique polymerization mechanism, but also broadened the application scope of CCP.

3.2 PAMAM-initiated NCA ROP

Unimolecular polypeptide micelles are emerging as promising vehicles in drug and gene delivery. Compared to the widely used self-assembled micelles, unimolecular micelles offer higher stability under extreme conditions and eliminate interference from free polymers. We hypothesized that dendritic molecules with dense peripheral amino groups, such as polyamidoamine (PAMAM), could serve as effective initiators for synthesizing well-defined unimolecular polypeptide micelles through CCP (Figure 7a) [73]. To test this concept, we used PAMAM of different generations (GX-PAMAM) to initiate the ROP of BLG-NCA. The polymerizations demonstrated excellent controllability, yielding well-defined spherical polypeptides (GX-*g*-PBLG) (Figure 7b, c). These spherical polypeptides could achieve extremely high MWs while maintaining low MWDs. Notably, polymerization initiated by G5-PAMAM at $[M]_0/[I]_0$ of 3200 produced the highest MW of synthetic polypeptides ever reported (8.5×10^7 Da), surpassing the MW of the largest known protein, titin, (4×10^6 Da) by 20 times (Figure 7d). Similar to brush-like and hinged systems, polymerization in the dendritic system also exhibits two-stage kinetics. The use of racemic monomers significantly reduced the polymerization rate and broadened the MWD due to the disruption of α-helices. These results indicate that PAMAM-initiated NCA polymerization is also driven by α-helix-induced auto-acceleration. Additionally, other monomers including ZLL-NCA, γ-(4-propargyloxybenzyl)-L-glutamate *N*-carboxyanhydride (POBLG-NCA), and γ-(4-allyloxylbenzyl)-L-glutamate *N*-carboxyanhydride (AOBLG-NCA) were successfully used in PAMAM-initiated polymerizations to prepare unimolecular micelles bearing various functional motifs.

3.3 Crown ether catalyzed NCA ROP

We have demonstrated that CCP is a powerful strategy in brush-like, hinged, and dendritic systems. However, achieving rapid and controlled NCA ROP in linear systems remained challenging. In one study, we accidentally discovered that PEG could accelerate primary amine-initiated linear NCA ROP. This acceleration is likely due to PEG forming multiple hydrogen bonds, which facilitates the prior binding between the growing helical chain and the incoming monomer, a critical step in NCA ROP (Figure 8a) [74].

Inspired by this finding, we hypothesized that crown ether (CE), a cyclic analogue of PEG with a defined size, could similarly accelerate controlled linear polymerization in proper solvents [75]. Indeed, the presence of 18-crown-6 (18-C-6) significantly accelerated the linear ROP of BLG-NCA initiated by *n*-hexylamine in DCM, achieving 95% monomer conversion within 18 min. In contrast, without 18-C-6, only 75% monomer conversion was observed

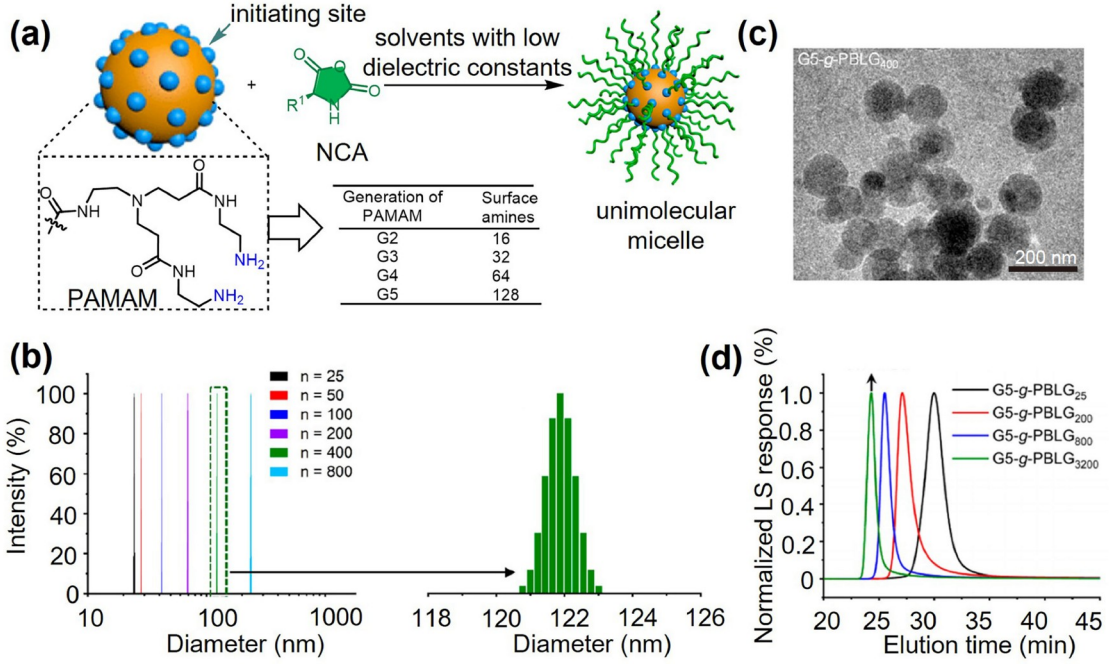

Figure 7 (Color online) (a) PAMAM-initiated cooperative covalent polymerization of BLG-NCA. (b) Size distributions of unimolecular micelles and the amplified DLS histogram of G5-*g*-PBLG$_{400}$. (c) Cryo-TEM image of G5-*g*-PBLG$_{400}$ unimolecular micelle in DMF (scale bar: 200 nm). (d) GPC traces of G5-*g*-PBLG with different MWs. Reproduced with permission from Ref. [73]. Copyright©2020, American Chemical Society.

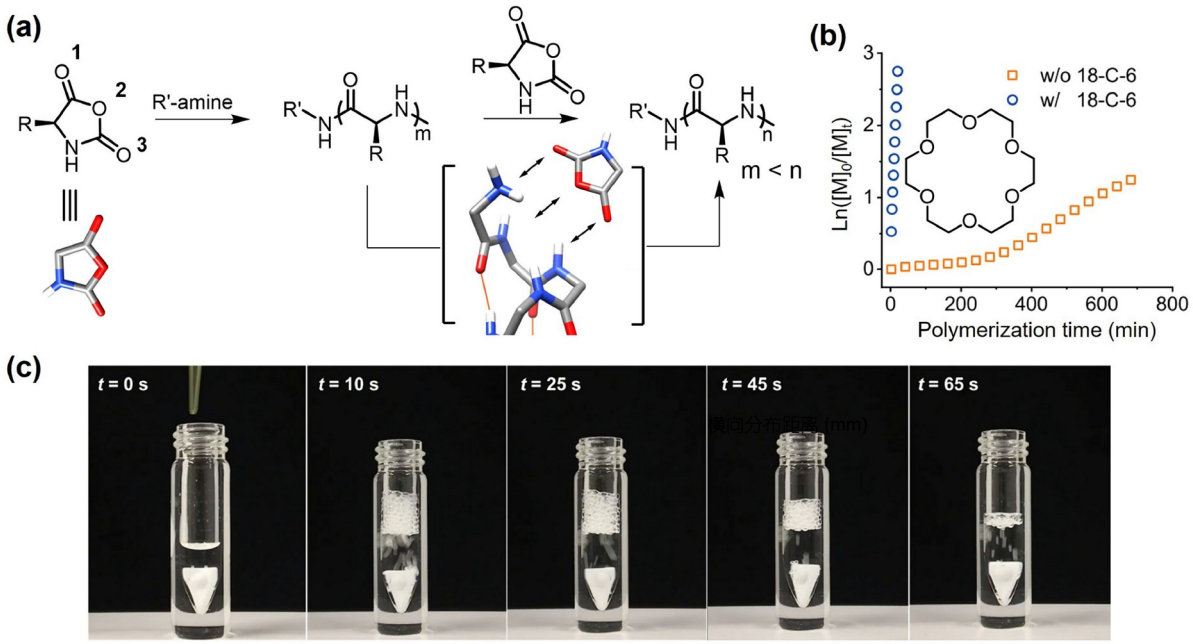

Figure 8 (Color online) CE-catalyzed linear polymerization of NCAs. (a) Proposed binding of NCA with the N-terminus of an α-helix. (b) The semi-logarithmic kinetic plot of polymerization of BLG-NCA initiated by primary amine in the presence and absence of 18-C-6 in DCM. (c) Images showing the rapid consumption of BLG-NCA accompanied by the rapid evolution of CO_2. Reproduced with permission from Refs. [74,75]. Copyright©2019, Nature Publishing Group.

after 12 h (Figure 8b). The reaction rate further increased with higher monomer concentrations. At $[M]_0$ = 400 mM, 95% conversion was reached within just 2 min, accompanied by vigorous CO_2 evolution (Figure 8c). Polymerizations catalyzed by other CEs and linear oligoethylene glycol were much slower, highlighting the crucial role of CE size and architecture in the acceleration process. Both experimental and theoretical studies confirmed that the presence of 18-C-6 brings the monomer and propagating chain end into closer proximity with more favorable geometry, aligning well with our initial hypothesis.

It is worth noting that the obtained polypeptides had significantly higher MW than anticipated, likely due to the slow primary stage as described in Section 2.1. By using α-helical PBLG as macroinitiators instead of small molecular amines, it was possible to bypass the first stage and directly engage the rapid second-stage polymerization kinetics. This approach greatly improved the controllability, resulting in well-defined polypeptides ($Đ$ < 1.1). The CE-catalyzed polymerization strategy also proved for various NCA monomers including γ-ethyl-L-glutamate NCA (ELG-NCA), POBLG-NCA, and ZLL-NCA.

4 Controlled synthesis of polypeptides in oil-water system

The CCP provides a simple, rapid, and controlled method for preparing well-defined polypeptides. However, ultrapure NCA monomers are essential to prevent inhibition and chain termination caused by trace amounts of acidic or electrophilic impurities. The purification process for NCA monomers, whether through repetitive recrystallization or column chromatography under anhydrous conditions, is tedious and challenging. In contrast, protein production in ribozyme is highly efficient and precious, despite the complexity of the cytoplasm. The efficiency is due to the peptidyl transferase center (PTC) of a ribozyme providing a highly regulated microenvironment that excludes numerous competing species from reaching the catalytic center. The amino groups of the substrates remain uncharged, ensuring an amidation rate 10^5 to 10^7 folds higher than that of a non-catalyzed reaction [76,77].

Drawing inspiration from natural protein synthesis, we designed a water-in-oil emulsion system to mimic the segregation capability of ribozymes [78]. This design logically extends our previously reported dendritic initiator (zero-dimension initiators placed in close proximity) [73] and polymeric initiator (one-dimension initiators placed in close proximity) [67] initiated polymerization settings. In this emulsion system, assuming the initiation starts from the oil/water interface, the NCA polymerization can be treated as a two-dimensional initiator placed in proximity proximity-initiated setting. Given that NCA hydrolysis takes hours to complete, we hypothesized that the CCP could be rapid enough so that the competitive water-induced NCA hydrolysis

would become negligible. To implement this initiator design, an amphiphilic macroinitiator, PEG-*b*-PBLG, was used as both a surfactant to stabilize the emulsion and a 2-dimensionally initiator placed in close proximity. The hydrophobic helical PBLG block protrudes into the oil phase, while the PEG is anchored at the oil/water interface. This setup established a cooperative macrodipole that accelerates polymerization in a controlled manner, outpacing water-induced side reactions. Since NCA is an organic molecule that largely remains in the organic phase during polymerization, while impurities from the NCA preparation step are primarily acidic or charged residues, we hypothesized that when non-purified NCA monomers are added to the emulsion, the hydrophilic impurities would be rapidly extracted into the water phase, resulting in *in situ* purification of the NCA monomers (Figure 9a). If such polymerization setting is sufficiently robust, polymerization could proceed well with these *in situ* purified NCAs, thereby circumventing the tedious NCA pre-purification step, one of the key bottlenecks of NCA ROP chemistry [78]. This method, termed as Segregation-Induced Monomer-Purification and initiator-Localization promoted rate-Enhancement (SIMPLE) polymerization, showed promising results.

SIMPLE polymerization of non-purified BLG-NCA in water/DCM emulsion exhibited accelerated kinetics, with monomer conversion exceeding 99% within 20 min, showing negligible difference from that of purified BLG-NCA. The resulting polypeptide had anticipated MW and narrow MWD ($Đ$ = 1.06), indicating excellent controllability and remarkable impurity tolerance of SIMPLE polymerization. Conversely, polymerizations initiated by either hydrophobic PBLG-amine or hydrophilic PEG-amine under identical conditions were much slower, demonstrating the importance of the amphiphilic PEG-*b*-PBLG initiator anchored at the interface (Figure 9b). Not surprisingly, polymerization of non-purified BLG-NCA in anhydrous DCM exhibited much slower kinetics, with monomer conversion below 15% and poor controllability after 12 hours of polymerization (Figure 9c). SIMPLE polymerization is also applicable to other non-purified NCA monomers, and the living polymerization behavior enables the synthesis of well-defined block copolypeptides (Figure 9d). Mechanism studies revealed that the rapid kinetics and good controllability are due to the α-helix-induced auto-acceleration. It is worth noting that other rationally designed initiators, including the brush-like initiators of PNB (Figure 5) and tris(2-aminoethyl) amine, can also initiate polymerization to synthesize well-defined polypeptides with diversified topologies.

The synthesis of well-defined multiblock copolypeptide holds significant potential for the development of protein-mimicking biomaterials due to their unique self-assembly properties, which are encoded by precisely controlled blocks [79–81]. However, conventional synthetic methods face considerable challenges, particularly in controlling polymerization kinetics and managing the accumulation of impurities. These issues severely limit the achievable block length and number, hindering the development of advanced materials [42,82]. SIMPLE polymerization offers a solution

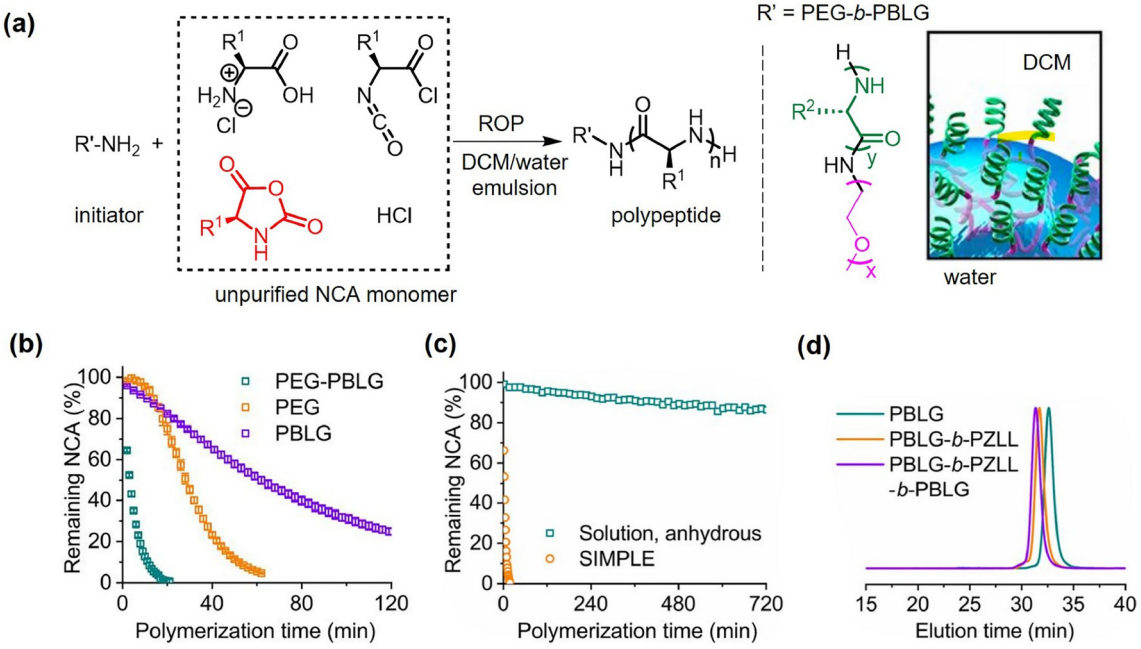

Figure 9 (Color online) SIMPLE polymerization of NCA. (a) The illustration of SIMPLE polymerization strategy. (b) Conversion of purified BLG-NCA monomers in water/DCM emulsion initiated by different macroinitiators. (c) Conversion of non-purified BLG-NCA in SIMPLE polymerization and conventional polymerization in anhydrous DCM. (d) GPC traces of homopolypeptide and block copolypeptides. Reproduced with permission from Ref. [78]. Copyright©2019, Proceeding of National Academy of Sciences.

to these challenges. In a subsequent study, we applied SIMPLE polymerization to synthesize a series of block copolypeptides (Figure 10) [83]. The high-end-group fidelity achieved through this method ensured the liveness of the propagating chains, which is crucial for constructing multiblock architectures. Notably, SIMPLE polymerization enabled the synthesis of unprecedented 20-block copolypeptide (DP = 10 for each block), with well-defined structures ($Đ$ = 1.07) (Figure 10a). The polymerization was completed within 5 h and over 97% of the end groups remained active, suggesting the potential for reaching even higher block numbers. Moreover, the versatility of SIMPLE polymerization was further demonstrated by synthesizing a series of ABCDE pentablock copolypeptides, derived from five different NCA monomers (Figure 10b). The reaction completed within 1 h despite the longer block length (DP = 25), and the resulting copolypeptides possess well-defined structures ($Đ$ < 1.1).

While expanding the application scope of SIMPLE polymerization, we encountered challenges with certain NCA monomers prepared using a high phosgene feeding ratio (> 1.5 equiv.) or through multistep reactions, which resulted in poorly defined products. Upon analyzing these polymerization systems, we discovered that a significant number of macroinitiators were quenched at the beginning of polymerization by hydrophobic impurities, such as the phosgene derivatives, present in the non-purified monomers (Figure 11a) [84]. We hypothesized that small molecular amines could serve as scavengers (amine scavenger, AS) to eliminate these amine-active impurities without introducing additional side reactions. This is because the polymerization initiated by AS is too slow to compete with the rapid kinetics of SIMPLE polymerization (Figure 11b). To test this concept, we introduced *n*-hexylamine as an AS into the SIMPLE polymerization of non-purified BLG-NCA. The reaction exhibited significantly improved MW control ($Đ$ = 1.16) compared to the polymerization under identical conditions without AS ($Đ$ = 1.66) (Figure 11c). The entire process was completed within 3–4 h, and gram-scale polypeptide syntheses were achieved with excellent control over MWs (Figure 11d). Notably, non-purified NCA monomers synthesized via both the Fuchs-Farthing method (phosgenation of amino acids) and Leuchs method (reaction between *N*-alkoxycarbonyl α-amino acids and halogenating reagents)

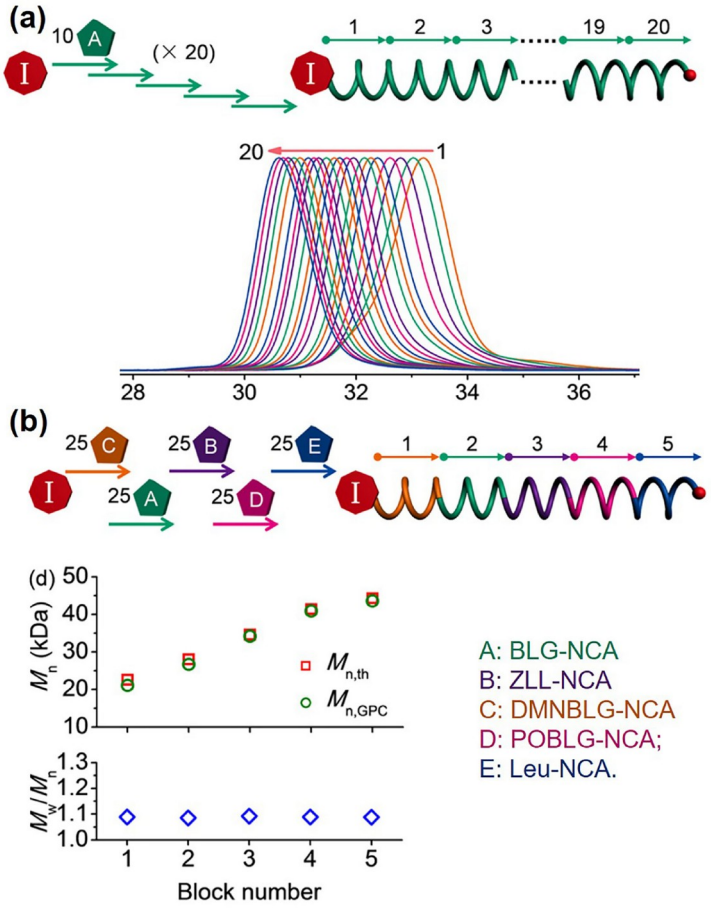

Figure 10 (Color online) Synthesis of multiblock copolypeptides through SIMPLE polymerization. (a) Synthesis of 20-block copolypeptides through sequential addition of BLG-NCA monomers. (b) Synthesis of ABCDE pentablock copolypeptides and the evolution of MW and MWD after the polymerization of each block. Reproduced with permission from Ref. [83]. Copyright©2019, American Chemical Society.

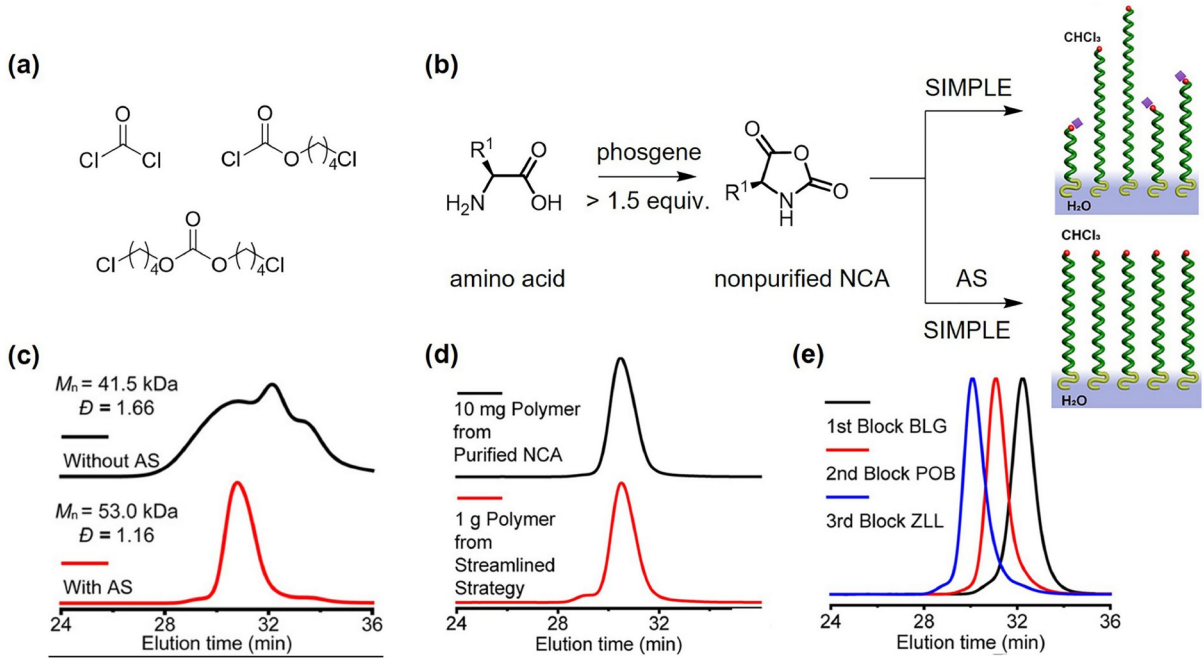

Figure 11 (Color online) Streamlined synthesis of polypeptides through refined SIMPLE polymerization. (a) Presumable hydrophobic impurities in non-purified NCA monomers. (b) SIMPLE polymerization with or without AS. (c) GPC traces of polypeptides synthesized via SIMPLE polymerization with or without AS. (d) GPC traces of polypeptides synthesized via SIMPLE polymerization at the scale of 10 mg and 1 g. (e) GPC traces of triblock copolypeptides, DP = 50 for each block. Reproduced with permission from Ref. [84]. Copyright 2020, American Chemical Society.

were compatible with the streamlined SIMPLE polymerization, demonstrating the good tolerance to diversified hydrophobic impurities. This refined SIMPLE polymerization was also applied to various non-purified NCAs, enabling the synthesis of copolypeptides with complex chemical compositions (Figure 11e). By eliminating the need for tedious purification, isolation, and storage processes of NCA monomers, the refined SIMPLE polymerization removed the technical barrier in the synthesis of polypeptides, streamlining the process and expanding its potential applications.

5 Summary and outlooks

We aimed to develop new strategies for simplified, controlled NCA polymerization and to deepen our understanding of the unprecedented mechanisms in NCA chemistry. Alongside efforts to create novel metal or organocatalysts for NCA polymerization, we identified and successfully elucidated two distinct mechanisms that govern polypeptide chain self-propagation without relying on complex catalysts. The use of a simple chemical structure like TMS effectively regulates the activity of the polypeptide amine end group and controls the ring-opening process of NCA monomers through the TMS-CBM mechanism [18,19]. While applying TMS-CBM mediated NCA polymerization to prepare hybrid brush-like copolypeptides, we serendipitously discovered the new mechanism of α-helix-induced auto-acceleration. This mechanism dramatically increases the polymerization rate, surpassing side reactions including moisture-induced NCA hydrolysis and eliminating the need for stringent anhydrous operation [67]. The bio-inspired SIMPLE polymerization is another tremendous progress that enables the use of non-purified NCA monomers for streamlined polypeptide synthesis [78]. Anyone who has basic synthetic skills can prepare well-defined polypeptides without technical barriers by following the protocols of SIMPLE chemistry.

Despite these advancements, several questions remain unanswered. (1) What is the mechanism of α-helix-induced auto-acceleration? Although the dominating role of cooperative macrodipole has been supported by substantial circumstantial evidence, direct proof and a detailed description of the mechanism are still needed. (2) What is the limit of auto-acceleration effect? SIMPLE polymerization enables the synthesis of polypeptides with extremely high MWs and unprecedented block numbers. However, it is still unclear whether there is a critical MW at which the auto-acceleration effect diminishes. Addressing these questions could provide deeper insight into the mechanism and guide the further development of polymerization strategies.

Besides our research, the field of controlled NCA ROP has witnessed other exciting advances. Deming's pioneering work revived the vitality of NCA polymerization [11,85,86], while Schlaad and colleagues [15,16] introduced hydrochloride salts to suppress side reactions, achieving nearly

monodisperse polypeptides; Hadjichristidis and his team [26,29,31,87,88] employed tailor-designed amine initiators, hydrogen-bond catalysts, or vacuum conditions to achieve rapid, controlled NCA polymerizations; Liu *et al*. [17,20,35] reported ultrafast NCA polymerization catalyzed by lithium salts, acetates, and cationic catalysts; Tao *et al*. [24] advanced in anionic ROP of NCAs; Lu *et al*. [89] even utilized water to facilitate the highly controlled ROP of proline NCA, a particularly challenging polymerization for conventional system. Recently, Lu and his team [90] reported a much-simplified synthetic strategy for NCA monomers, further removing the technical barriers and expanding the library of amino acid building blocks. The same team also developed a high-throughput strategy for diversifying high-MW polypeptides [91]. Additionally, Ling and colleagues [92,93] provided theoretical explanations for NCA polymerizations through density-functional theory (DFT) calculations.

Benefiting from these collective efforts, polypeptide materials with well-defined structures have become more accessible. Future breakthroughs in NCA polymerization are expected to focus on the following directions. (1) Achieving rapid, controlled polymerization in multicomponent systems. This advancement would not only be beneficial for cost reduction and scale expansion in industrial polypeptide production, but also offer insights into the natural origin of proteins and their connection with NCA chemistry. The success of SIMPLE polymerization in emulsion systems marks a promising start in this field. Additionally, open-air NCA polymerization with simple catalysts or initiators could eventually lead to water-phase polypeptide synthesis. (2) Preparation of monodispersed and sequence-controlled polypeptide. Natural proteins have precise peptide sequences and monodispersed MWs, ensuring their specific spatial structures. Combining improved polymerization technologies and advanced separation strategies may address this challenge and produce "perfect" polypeptides with distinct MW, potentially competing with solid-phase peptide synthesis (SPPS) and synthetic biology for bioactive molecules and therapeutics. Although achieving sequence control in NCA chemistry remains challenging, it would represent a paradigm shift if realized. (3) Developing AI-assisted, automated high-throughput polypeptide synthesis. As research in laboratory NCA chemistry progresses, there will be increased interest in computation NCA polypeptide chemistry and AI-assisted material design, mechanism elucidation, and automated synthesis. It will dramatically accelerate the exploration and profoundly impact the research field of synthetic polypeptides.

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Conflict of interest The authors declare no conflict of interest.

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