Perspective

Emerging Trends in the Chemistry of End-to-End Depolymerization

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ABSTRACT: Over the past couple of decades, polymers that depolymerize end-to-end upon cleavage of their backbone or activation of a terminal functional group, sometimes referred to as "self-immolative" polymers, have been attracting increasing attention. They are of growing interest in the context of enhancing polymer degradability but also in polymer recycling as they allow monomers to be regenerated in a controlled manner under mild conditions. Furthermore, they are highly promising for applications as smart materials due to their ability to provide an amplified response to a specific signal, as a single sensing event is translated into the generation of many small molecules through a cascade of reactions. From a chemistry perspective, end-to-end depolymerization relies on the principles of self-immolative linkers and polymer ceiling temperature (T_c). In this article, we will introduce the key chemical concepts and foundations of the field and then provide our perspective on recent exciting developments. For example, over the past few years, new depolymerizable backbones, including polyacetals, polydisulfides, polyesters, polythioesters, and polyalkenamers, have been developed, while modern approaches to depolymerize conventional backbones such as polymethacrylates have also been introduced. Progress has also been made on the topological evolution of depolymerizable systems, including the introduction of fully depolymerizable block copolymers, hyperbranched polymers, and polymer networks. Furthermore, precision sequence-defined oligomers have been synthesized and studied for data storage and encryption. Finally, our perspectives on future opportunities and challenges in the field will be discussed.

KEYWORDS: *depolymerization, self-immolative polymers, ceiling temperature, degradable, topology, sequence-defined*
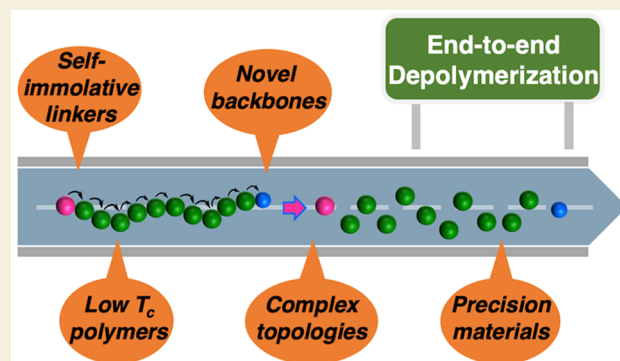
1. INTRODUCTION

Since the early days of macromolecular science, polymer chemists have largely focused on creating synthetic polymers with extraordinary performance, including durability and chemical resistance.[1] Such advances have generally been realized using definitions of performance in terms of function, while not necessarily accounting for adverse outcomes and sustainability.[1] As a result, an immense and growing accumulation of plastic waste is leading to a global plastics crisis and enormous materials value loss.[2] While enhanced waste management and recycling programs can provide an important contribution to addressing these pressing challenges, innovative polymers with degradability and sustainability embedded into their intrinsic properties can also play a vital role.[3,4] At the same time, suitably designed degradable polymers are also of great significance for advanced applications, such controlled drug delivery, tissue engineering, sensing, and transient materials.[5−7] To this end, the design of polymers whose degradation can be selectively actuated by external stimuli is of great interest.[4]

Over the past couple of decades, intrinsically degradable polymers that undergo end-to-end depolymerization, have garnered increasing attention.[8−10] A subset of such polymers,

sometimes referred to as "self-immolative" polymers (SIPs), are unstable in the absence of an end-cap and depolymerize upon cleavage of their backbone or end-cap. Another subset, sometimes referred to as intrinsically circular polymers (iCPs), are kinetically trapped and require heat and/or catalysis to activate depolymerization, even in their noncapped form. However, the boundary between SIPs and iCPs is not always clearly defined as some backbones considered as SIPs can be stabilized by quenching the polymerization catalyst[11] or through macrocyclization,[12,13] while others considered as iCPs can be depolymerized upon activation with stimuli under mild conditions.[14−16]
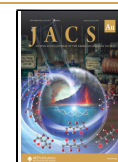
Intrinsically degradable polymers are gaining attention for chemical recycling as they allow monomers to be regenerated in an on-demand manner under relatively mild conditions.[8−10] Furthermore, they are highly promising as stimuli-responsive

materials for a variety of applications such as signal amplification, nanolithography, and controlled release, due to their ability to provide a selective and amplified response to a specific signal as a single sensing event is translated into the generation of many small molecules through a cascade of reactions.[8−10]

From a chemistry perspective, current designs of end-to-end depolymerizable polymer systems hinge on self-immolative linkers and the principles of equilibrium chain-growth polymerization, which can be quantified by ceiling temperature (T_c).[9] In this contribution, we will first introduce these chemical concepts. Then, we provide our perspective on recent exciting developments (Figure 1). For instance, depolymeriz-
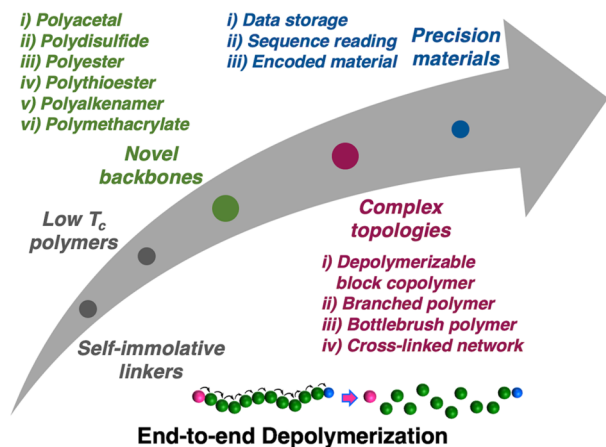

Figure 1. Emerging trends in the design of end-to-end depolymerization include developing novel depolymerizable backbones, creating complex architectures, and pursuing precision materials.

able polyacetals, polydisulfides, polyesters, polythioesters, and polyalkenamers will be discussed along with new approaches to depolymerize polymethacrylates. Progress has also been made on the topological evolution of depolymerizable systems including the introduction of fully depolymerizable block copolymers, hyperbranched polymers, and polymer networks. Furthermore, precision sequence-defined oligomers with programmed cascade depolymerization, akin to classic Edman degradation for peptide sequencing, have been synthesized and studied for data storage and encryption. Finally, future opportunities and challenges in the field will be discussed.

2. DESIGN PRINCIPLES OF END-TO-END DEPOLYMERIZATION

2.1. Self-Immolative Linkers

Self-immolative linkers are covalent systems designed to disassemble spontaneously after activation of a protective group from one terminus of the linker.[17] Originally developed as protecting groups for organic synthesis[18−21] and then for prodrug chemistry,[22−25] such linkers have found widespread use in prodrugs, sensing or imaging probes, and drug delivery systems.[26−28] Classic self-immolative linkers can be mainly categorized into electronic cascade elimination (e.g., 1,4-, 1,6-, and 1,8-elimination) (Figure 2ai) and intramolecular cyclization (Figure 2aii).[17] Both examples involve activation and consequent generation of nucleophilic groups, such as hydroxy, amino, or thiol groups, which are conjugated with or near a leaving group, followed by spontaneous reaction cascades to
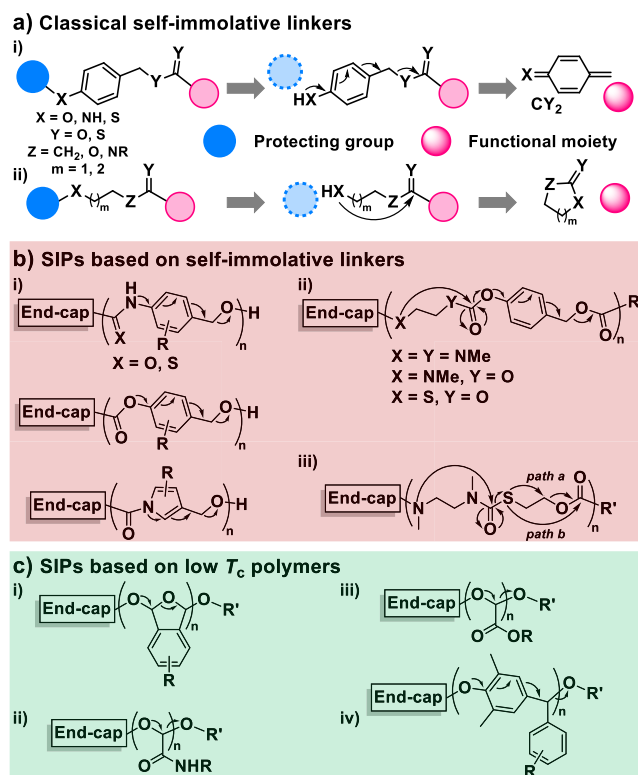

Figure 2. (a) Representative self-immolative linkers involve either electronic cascade elimination or intramolecular cyclization. (b,c) Chemical structures of different classes of SIPs on (b) self-immolative linkers and (c) low T_c polymers.

liberate the desired compounds (Figure 2a).[17] Such self-immolative linkers generally involve the cleavage of C−O, C−N, and C−S bonds, which necessitates specific functional groups (e.g., hydroxy, amine, thiol, and carboxylic acid) within the desired compounds.[17] Notably, a recent development in acid-promoted C−C bond-cleaving 1,6-elimination expanded the scope of potential functional moieties.[29]

Inspired by self-immolative linkers, self-immolative oligomers[30] and dendrimers[31−33] were developed, followed by more synthetically accessible linear SIPs via step-growth polymerization.[34] To date, typical linear backbones based on self-immolative linkers include poly(benzyl carbamate),[34] poly(benzyl thiocarbamate),[35] poly(benzyl carbonate),[36] and poly(carboxypyrrole)[37] which solely rely on electronic cascade mechanisms (Figure 2bi), poly(carbamate-*alt*-carbamate),[38] poly(carbonate-*alt*-carbamate),[39] as well as poly-(thiocarbonate-*alt*-carbonate),[39] which are based on alternating cyclization and electronic cascade eliminations (Figure 2bii), and poly(carbamate-*alt*-thiocarbamate),[40] which capitalizes on sequential cyclizations (Figure 2biii). In all but the last example, the elimination cascades involve the loss of CO_2 or COS gas, rendering the depolymerization effectively irreversible. These SIPs based on self-immolative linkers generally exhibit relatively slow depolymerization kinetics, especially in nonpolar solvents or in the solid state.[8−10] However, chemical tuning of electron density, aromaticity, and substituents within these system can enable rapid depolymerization (e.g., complete depolymerization in seconds to minutes), as exemplified in poly(carboxypyrrole).[37] It is also notable that most iCPs contain cyclization spacers, reminiscent of classical self-immolative linkers, and their depolymerizations are thermo-

dynamically driven by the formation of stable cyclic products (Section 3), although the cyclization is not always spontaneous like that in SIPs.

2.2. Ceiling Temperature

Since the first report of the ceiling temperature (T_c) phenomenon for copolymerization of sulfur dioxide with olefins[41] and the subsequent thermodynamic description of the polymerization equilibrium,[42] it has been well documented that each polymerization system has a critical temperature at which the change in Gibbs free energy of polymerization (ΔG_p) is zero and the (de)polymerization is at equilibrium.[43,44] The thermodynamics of polymerization is described by $\Delta G_p = \Delta H_p - T\Delta S_p$, where T is the temperature and ΔH_p and ΔS_p are the polymerization enthalpy and entropy, respectively. Generally, polymerization is favored enthalpically ($\Delta H_p < 0$) and disfavored entropically ($\Delta S_p < 0$; due to loss of translational freedom by covalently connecting monomers together).[43,44] Below $T_c = \Delta H_p/\Delta S_p$, polymerization is favored and monomers will polymerize, while above T_c, depolymerization is favored (Figure 3). It should be noted
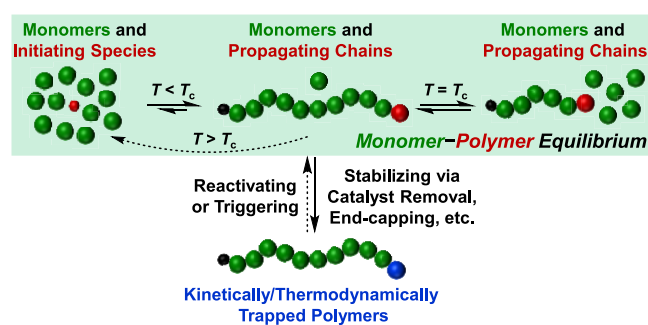

Figure 3. Schematic of representative monomer—polymer equilibrium for chain-growth polymerization and reversible stabilization/destabilization of propagating polymer chains.

that, in more rare cases, such as S$_8$, (Me$_2$SiO)$_4$, and large strainless macrocyclic monomers,[45] ΔS_p is positive due to the increase of conformational entropy. In these instances, polymerization occurs instead at temperatures above a critical temperature called the floor temperature.[43,44] However, such systems will not be the focus of this Perspective.

For a given polymerization system, in the absence of continuous perturbations to the equilibrium, such as the precipitation of polymer or removal of monomer by distillation, the T_c determines the temperature required for high yielding conversion of monomer to polymer or reversion of polymer to monomer.[43,44] However, polymer chains can be trapped kinetically through the removal or deactivation of a polymerization catalyst, making it possible to exploit low T_c polymers as useful materials under ambient conditions (Figure 3).[44,46] Reactivation of trapped chains back to the monomer—polymer equilibrium requires sufficient energy input or catalysis.[47] In addition, as the equilibrium in a chain polymerization is between monomers and propagating chains,[44] chains can be quenched through termination (e.g., cyclization, end-capping), a process that can provide thermodynamic and/or kinetic stabilization, as reactivation of the monomer-polymer equilibrium requires a bond cleavage. An early example of end-capping was the esterification of polyformaldehyde by Dupont.[44,46] Notably, when stimuli-responsiveness is embedded into end-capping agents, the

resulting stabilized end-capped polymers (i.e., SIPs), derived from low T_c polymers can undergo stimulus-mediated end-to-end depolymerization.[9,10,46] The more widely explored self-immolative backbones based on low T_c polymers are polyacetals including polyphthalaldehydes, polyglyoxylates, and polyglyoxylamides, (Figure 2ci—iii) as well as poly(benzyl ether)s (Figure 2civ).[9,10] Among these, polyphthalaldehydes exhibit rapid depolymerization in both nonpolar environments and in the solid state.[10]

3. RECENT DEVELOPMENTS IN DEPOLYMERIZABLE BACKBONES

Over the past decades, there have been considerable innovations in the design of novel self-immolative linkers in prodrug chemistry, profluorophore chemistry, and biorthogonal decaging chemistry.[27] In addition, many efforts have been directed toward the development of low or medium T_c polymers that can undergo chemical recycling to monomer for a sustainable circular plastic economy.[43,44] Thus, the chemical space to design end-to-end depolymerization systems based on self-immolative linkers or the principles of equilibrium polymerization has been greatly expanded. In this section, we highlight selected examples of emerging backbones that are promising for the creation of end-to-end depolymerization platforms. For more comprehensive overviews on polymers which can be chemically recycled into monomers, the readers are directed to excellent reviews that have examined their design and synthesis.[43,44,48]

3.1. Polyacetals

Low T_c polyacetals from diverse aldehyde monomers have been developed as end-to-end depolymerizable systems.[9,10] In a recent exciting contribution, the Coates group developed a well-controlled polymerization of the five-membered cyclic acetal, 1,3-dioxolane ($T_c \sim 13\ °C$ at 4.0 M), which is commonly employed as a green solvent, through a reversible-deactivation cationic ring opening process (Figure 4a).[49] In this method, a halomethyl ether initiator and an indium(III) bromide catalyst were used to access high molar mass poly(1,3-dioxolane), which exhibited a tensile strength comparable to some commodity polyolefins, such as isotactic polypropylene (iPP) and high-density polyethylene (HDPE) (Figure 4a). This approach was also applicable for other cyclic acetal derivatives, including 1,3-dioxepane, 1,3-dioxocane, 1,3,7-trioxocane, and $trans$-hexahydro-1,3-benzodioxole, indicating its versatility. Selective chemical recycling of poly(1,3-dioxolane) into monomer with a near-quantitative yield was achieved with a strong acid catalyst (e.g., camphorsulfonic acid, CSA or diphenylphosphoric acid, DPP) at elevated temperatures of 100—150 °C (Figure 4c). Very recently, the same group further developed a metal-free, economically friendly polymerization system to synthesize ultrahigh-molecular-weight (UHMW) poly(1,3-dioxolane) with molar masses greater than 1000 kg/mol, which demonstrated similar tensile properties to UHMW polyethylene (Figure 4a,b).[50]

3.2. Polydisulfides

A disulfide is a dynamic covalent bond, which concurrently combines the features of robustness and dynamicity, and can be cleaved and reformed on demand.[51] Because of these features, polymers with disulfides as repeating units have garnered increasing attention as intrinsically dynamic smart materials.[51,52] Beginning with the synthesis of disulfide polymers via reaction between inorganic disulfides (e.g.,
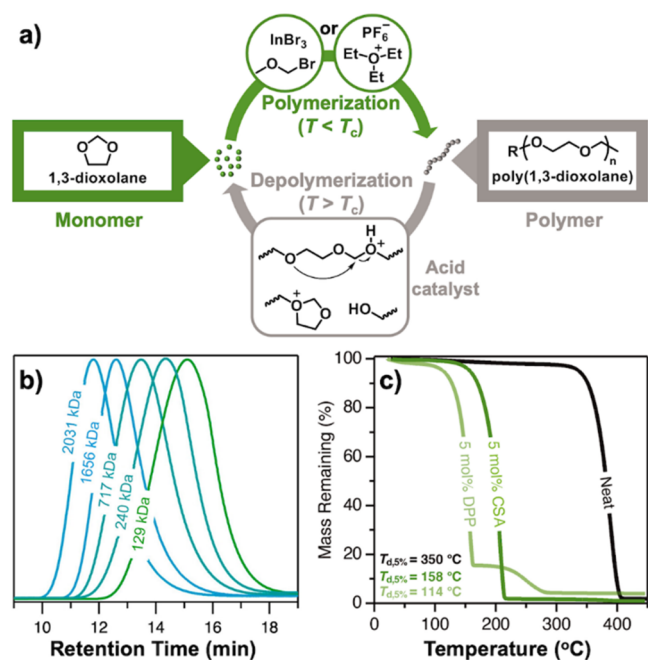
Figure 4. (a) Polymerization and depolymerization cycles for depolymerizable poly(1,3-dioxolane). (b) A metal-free polymerization approach accessed UHMW poly(1,3-dioxolane). (c) Thermogravimetric analysis of poly(1,3-dioxolane) in the absence and presence of 5 mol % acid catalysts, CSA and DPP. Panels (a) and (c) are adapted from ref 49. Copyright 2021 American Association for the Advancement of Science. Panel (b) is reproduced from ref 50. Copyright 2023 American Chemical Society.

Figure 5. (a) ROP approach to access dynamic and depolymerizable polydisulfides from cyclic disulfide monomers. (b) Architecture-controlled polymerization to cyclic and linear polydisulfides. (c) Releasable protein−polydisulfide conjugates. (d) Dual closed-loop polymerization−depolymerization to prepare supramolecular ionic networks and thermoplastic elastomers.

Na_2S_2) and organic dihalides in the 1920s,[53] a variety of polymerization methods including the oxidative polymerization of thiols, (co)polymerization of disulfide-containing monomers, and ring-opening polymerization (ROP) of cyclic disulfides, have been developed to access polydisulfides.[51,52] Notably, ROP of minimally strained cyclic disulfides can proceed via either anionic, cationic, or radical mechanisms, providing good control of the chemical structures of resulting polymers and their subsequent depolymerization behavior (Figure 5a).[52,54]

Inspired by elegant research on thiolate-initiated ROP of macrocyclic disulfides[55] or 1,2-dithiolanes[56,57] within liposome bilayers or on surfaces, Matile and co-workers reported cell-penetrating polydisulfides via ROP of guanidine-functionalized derivatives of lipoic acid and asparagusic acid.[58] Treatment with DL-dithiothreitol (DTT) led to degradation of the polydisulfides, and was believed to involve both end-to-end depolymerization and random thiol−disulfide exchange within the backbone.[58] Differences in the anionic ROP activity between derivatives of lipoic acid and asparagusic acid were also observed, implying substituent effects on 1,2-dithiolane ring strain.[58] Subsequently, Waymouth and Zhang compared the polymerization thermodynamics of methyl lipoate and the methyl ester of methyl asparagusic acid.[59] The standard ΔG_p^0 (23 °C) and T_c were determined to be about −0.2 kJ/mol and 30 °C, and 2.7 kJ/mol and −43 °C, respectively, for methyl lipoate and asparagusate, highlighting the structural effects of 1,2-dithiolanes on their (de)polymerization.

Moore et al. discovered an approach for controlling the architecture, molar mass, and dispersity of polydisulfides by modulating the nucleophilicity of initiators (Figure 5b).[60]
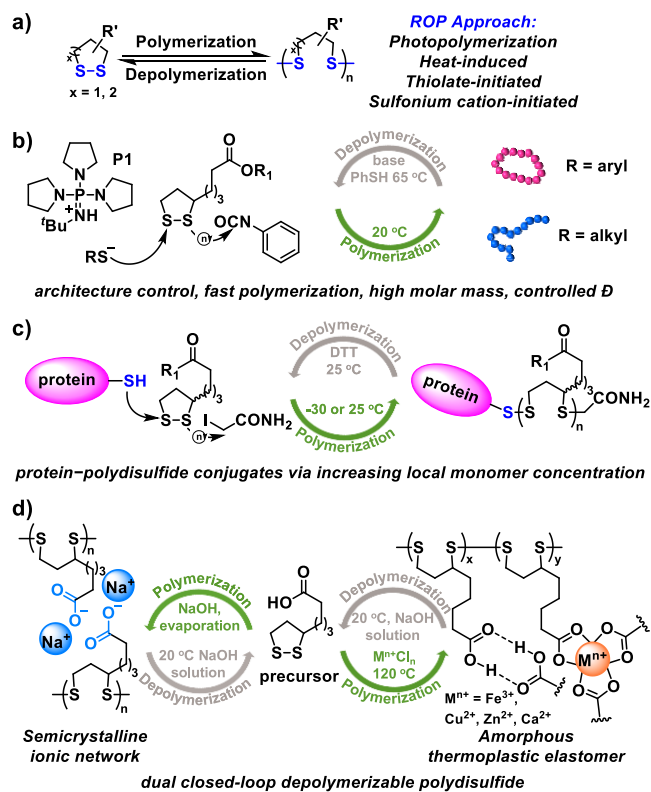
Cyclic polydisulfides were obtained with aryl thiol initiators for the polymerization of lipoates in the presence of organic bases at room temperature, while linear chains were achieved with alkyl thiol initiators. Furthermore, both cyclic and linear polydisulfides underwent efficient depolymerization at 65 °C to regenerate monomers in the presence of catalytic amounts of the initiator (i.e., PhSH) and the organic base (Figure 5b). ROP was further used to construct protein−polydisulfide conjugates using proteins bearing reactive cysteine residue as initiators and lipoates as 1,2-dithiolane monomers (Figure 5c).[61−63] Low polymerization temperature (−30 °C) or the aggregation of monomers was employed to increase the local monomer concentration, allowing for efficient polymerization at relatively low monomer concentrations (Figure 5c).[61−63] Moreover, native proteins could be recovered from the conjugates under mild reducing conditions (e.g., glutathione or thiol-containing proteins) via depolymerization (Figure 5c).[61−63]

Thermally initiated ROP of cyclic disulfide monomers via radical mechanisms has also been used to synthesize polydisulfides. For example, Qu, Tian, Feringa, and co-workers reported bulk polymerizations of lipoic acid derivatives upon heating (Figure 5d).[64−68] Furthermore, the resulting polydisulfides depolymerized to generate the corresponding monomers in aqueous NaOH[66] or polar organic solvents (e.g., N,N-dimethylformamide and dimethyl sulfoxide)[67] at room temperature. The same group also discovered that amphiphilic sodium lipoate could spontaneously form linear polydisulfides at high concentrations via a ROP process and

that the polymers underwent evaporation-induced interfacial self-assembly into a polymer ionic network (Figure 5d).[66,69] The supramolecular polydisulfide network could be efficiently depolymerized in aqueous NaOH to regenerate lipoates (Figure 5d).[66,69]

In another example, Daasbjerg et al. reported a mechanical solid-state polymerization to access linear poly(DTT) end-capped with pyridyl disulfides from DTT and 2,2′-dithiodipyr-idine as an activating reagent.[70] The hydroxyl groups from the DTT repeat units could be further functionalized with diverse carboxylic acids through esterification.[71,72] Notably, end-capped poly(DTT)s underwent rapid (i.e., within minutes) and complete end-to-end cyclization-driven depolymerization upon the introduction of a stoichiometric amount of DTT relative to the end-caps, in the presence of triethylamine. Intriguingly, redox-active anthraquinone-functionalized poly-(DTT) could be electrochemically depolymerized, represent-ing a promising triggering strategy.[72]

3.3. Polyesters

Polyesters, including poly(L-lactide) (PLLA) and poly(ε-caprolactone) (PCL), are technologically important degradable polymers, which can be readily produced via either polycondensation or ROP of cyclic esters and lactones.[73] The latter method provides a powerful route to control the chemical structure of polyesters, such as their molar mass, dispersity, and tacticity.[73] Moreover, the well-documented (de)polymerization equilibrium for low-strain lactones enables the development of chemically depolymerizable polyesters (Figure 6a).[73,74] Previous studies have successfully demon-strated the end-to-end depolymerization of melted PCL in the presence of catalyst,[75] oligolactide in a mixture of acetonitrile and phosphate buffered saline,[76] as well as PLLA in specific solvents.[77] Recent research efforts have led to the development of several polyester systems which are promising for achieving end-to-end depolymerization under mild conditions.[44,78]

There are several examples of clearly observed monomer–polymer equilibria during ROP of five-membered and six-membered lactones.[79−81] For example, Hillmyer and co-workers developed an efficient biobased route to the six-membered lactone, β-methyl-δ-valerolactone, which could be polymerized into a depolymerizable polyester.[81,82] In follow-up work, the same group further systematically examined the effect of n-alkyl substituents on the polymerization thermody-namics and kinetics of substituted δ-valerolactone mono-mers.[83] The enthalpy and entropy of polymerization were significantly affected by the substituent position, but both were largely insensitive to the n-alkyl length.

In another nice contribution, γ-butyrolactone, previously considered as "non-polymerizable", was efficiently polymerized by ROP under optimized reaction conditions (i.e, low temperature, high monomer concentration, and suitable solvent) with potent catalysts.[14,84,85] The resulting poly(γ-butyrolactone) (PGBL) and poly(α-methylene-γ-butyrolac-tone) could be depolymerized back into their monomers, in quantitative yield, via thermolysis or chemolysis under mild conditions (e.g., room temperature) using catalysts.[14,84,85] Moreover, fluoride-triggered end-to-end depolymerization of silyl ether end-capped poly(2,4-disubstitued γ-butyrolactone) at physiological temperature (i.e., 37 °C) was described, although the degradation was relatively slow and incomplete.[86]

As revealed above in the ROP of 1,2-dithiolanes, different substituents and substitution patterns on minimally strained
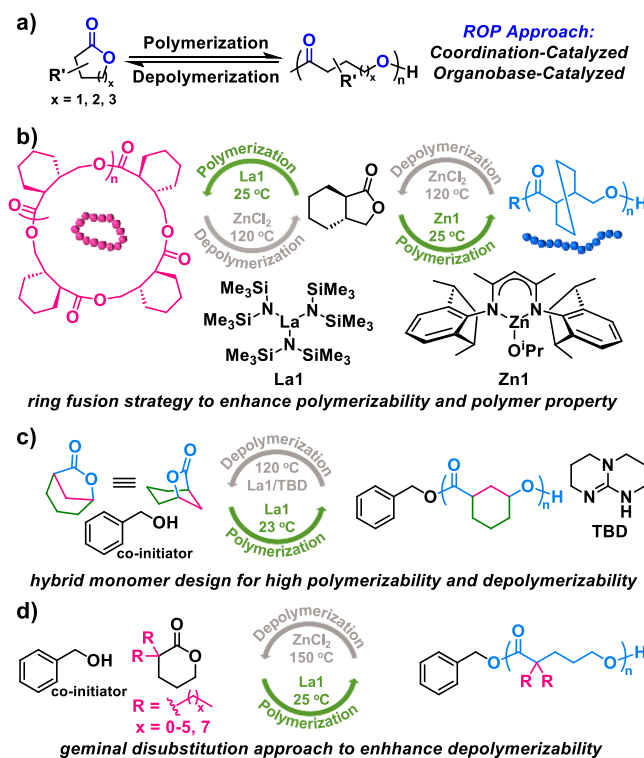
Figure 6. (a) Monomer–polymer equilibrium in ROP of low strain cyclic lactones with appropriate substituents. (b) Ring fusion strategy to unify polymerizability and performance for γ-butyrolactone. (c) Structural hybridization between high strain, high T_c ε-caprolactone and low strain, low T_c γ-butyrolactone to address the dilemma between polymerizability and depolymerizability. (d) Geminal disubstitution strategy to enhance the depolymerizability of high-strain lactones.

lactones can strongly affect the thermodynamics of their polymerization. Structural modifications were applied to γ-butyrolactone by Chen and co-workers to avoid the undesirable low-temperature polymerization conditions and improve the physical and mechanical properties of the resulting polymers.[87] In particular, 3,4-*trans*-cyclohexyl-ring-fused and 4,5-*trans*-cyclohexyl-ring-fused γ-butyrolactone monomers were designed, which could be readily polymerized at room temperature under solvent-free conditions (Figure 6b).[80,87−89] Furthermore, the resulting polymers could be depolymerized back to their corresponding monomers in quantitative yield in the presence of catalysts with heating (Figure 6b).[87−89] However, the catalytic depolymerization conditions were much harsher than for PGBL, implying a trade-off between polymerizability and depolymerizability.[14,87−89]

To address the trade-off between polymerizability and depolymerizability, an emerging hybrid monomer design strategy was proposed by the Chen group (Figure 6c).[90] For example, structural hybridization between high T_c ε-caprolactone and low T_c γ-butyrolactone generated a [3.2.1]-bicyclic lactone, 6-oxabicyclo[3.2.1]octan-7-one, which ex-hibited both high polymerizability and depolymerizability (Figure 6c).[91] In this design, polymerization proceeded via the ring-opening of the high T_c substructure at room temperature, and the depolymerization occurred through ring closing to form the low T_c substructure (Figure 6c). Furthermore, the resulting polymer could be completely depolymerized and converted into monomer in the presence

of La1 or 1,5,7-triazabicyclo[4.4.0]dec-5-ene (TBD) catalyst, although it required higher temperature (i.e., 120 °C) compared to that for PGBL (Figure 6c). Notably, this hybrid strategy[92] has also been exploited to access chemically recyclable nylons[92] and achieve orthogonal (de)polymerization of a lactone/olefin hybrid.[93]

Altogether, the aforementioned ring fusion and hybrid monomer design approaches can be considered to increase the ring strain of an extremely low T_c monomer, aiming to balance the (de)polymerizability and performance properties. An alternative approach to achieve depolymerizability is to decrease the ring strain from high T_c monomers via monomer redesign.[44] In this context, a geminal disubstitution strategy based on the well-known Thorpe–Ingold effect has been successfully applied to enhance the depolymerizability of polyvalerolactones[94] (Figure 6d) and polyhydroxyalkanoates.[95] More importantly, these chemically recyclable polymers exhibited excellent mechanical properties that were comparable with or superior to HDPE.[94,95]

3.4. Polythioesters

Compared to polyesters, the ROP of thiolactones to prepare polythioesters is in an earlier stage of development.[44] However, polythioesters are of significant interest for depolymerization as they are expected to have more dynamic properties due to the increased lability of the thioester bond compared to its ester analog.[44] In this context, the Bowman group created dynamic and responsive DNA-mimicking polythioesters via the ROP of bicyclic deoxyribose-fused 6-membered thiolactones (Figure 7a).[96,97] These metastable uncapped polythioesters underwent complete depolymerization into monomers under dilute conditions in the presence of N,N-diisopropylethylamine (DIPEA), while end-capped polythioesters were stable under identical conditions (Figure 7a). Moreover, the dynamic rearrangement of polythioesters via thiol-thioester exchange was demonstrated by depolymerization of the polymers in the presence of free thiolate and coalescence of polythioesters with different molar masses or chemical compositions.[96,97] This fused or bridged ring strategy was also employed by the Lu[15] and Chen[98] groups to design polythioesters that could be depolymerized in the presence of catalysts at room temperature (Figure 7b).

Alternatively, a geminal disubstitution strategy was applied to high T_c thiolactone monomers to enhance depolymerizabiity of the corresponding polymers (Figure 7c).[99,100] The geminal disubstitution site proved to be important, as substitution led to changes in conformation of the thiolactones, leading to unpredictable shifts in T_c.[100] On the other hand, direct O-to-S substitution from lactones emerged as another promising approach to access depolymerizable polythioesters (Figure 7d).[16,101−105] For example, diverse low-strain dithiolactones bearing different side chains were synthesized and then polymerized into polythioesters with molar masses up to 100.5 kg/mol, which could undergo efficient thermolysis or catalytic depolymerization at room temperature to regenerate monomers.[16]

In another recent interesting contribution, irreversible ROP of biomass-derived thionolactones was discovered, which proceeded at industrially relevant temperatures of 80−100 °C to produce high-molar-mass polythiolactones (Figure 7e).[104,105] Computational studies revealed that the selective irreversible ROP of γ-thionobutyrolactones was thermodynamically driven by S/O isomerization during the ring-opening
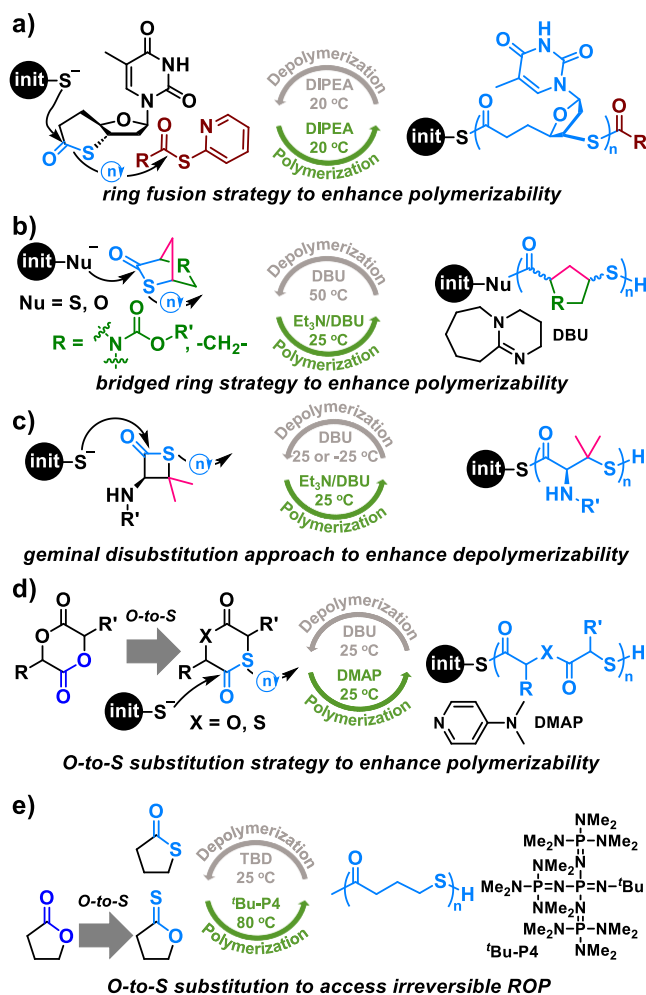

Figure 7. (a) Fused and (b) bridged ring strategy to increase ring strain of thiolactones. (c) Geminal dimethyl substitution to enhance depolymerizability of β-thiolactones. (d,e) Structural conversion of lactones to (d) thiolactones or (e) thionolactones to synthesize depolymerizable polythioesters.

process. Notably, poly(γ-thionobutyrolactone) with a high molar mass up to 162.6 kg/mol could undergo depolymerization within only 15 s upon treatment with 0.2 mol % of TBD at room temperature, quantitatively converting into γ-thiobutyrolactone, a structural isomer of the initial monomer, although at a relatively low concentration.

3.5. Polyalkenamers

Ring-opening metathesis polymerization (ROMP), driven by the relief of ring strain, has been widely used to synthesize polyalkenamers from cyclic olefins.[106] However, for low-strain cyclic olefins, equilibrium ROMP can be easily accessed, presenting an excellent opportunity to design depolymerizable systems, such as polypentenamers from cyclopentene monomers.[107] Furthermore, bottlebrush polymers with polycyclopentene backbones underwent quantitative end-to-end depolymerization in the presence of second- and third-generation Grubbs catalysts (G2 and G3).[108] In another interesting study, Feist and Xia described ROMP of a low ring strain 2,3-dihydrofuran monomer under ambient conditions with good control over molar mass (Figure 8ai).[109] The resulting poly(2,3-dihydrofuran)s underwent acid-catalyzed backbone degradation through hydrolysis of the enol ether but could also

Depolymerization for carbon–carbon backbones

a) Ene/yne metathesis depolymerization

i)

depolymerizable and acid-degradable poly(enol ether)

ii)

ring fusion strategy for higher depolymerizability

iii)

X = variable substitutions

enyne metathesis cascade-triggered depolymerization

b) Polymethacrylates

i)

azobisisobutyronitrile (AIBN)

ii)

R = Me, ^{n}Bu, PhCH$_2$, HOCH$_2$CH$_2$, CF$_3$CH$_2$, (CH$_3$)$_2$NCH$_2$CH$_2$, CH$_3$(OCH$_2$CH$_2$)$_{11}$

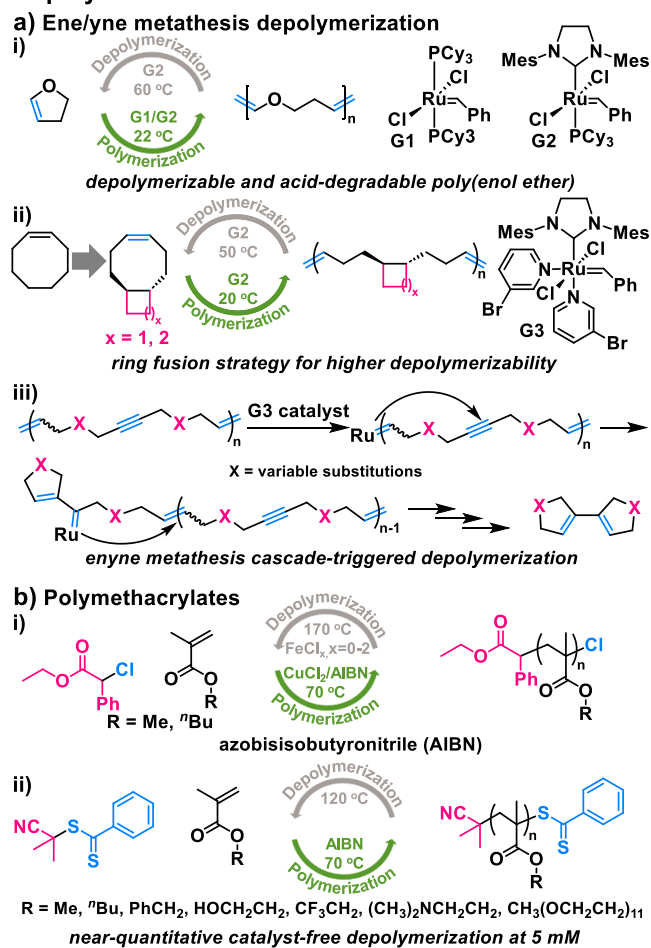*near-quantitative catalyst-free depolymerization at 5 mM*

Figure 8. (a) Depolymerization systems via ene/yne metathesis cyclization for (i) depolymerizable, acid-degradable poly(2,3-dihydrofuran), (ii) ROMP polymers from fused cyclooctenes, and (iii) enyne polymers. (b) Controlled depolymerization of polymethacrylates under moderate conditions via reversing (i) ATRP or (ii) RAFT process.

be recycled to monomer via depolymerization with the G2 catalyst (Figure 8ai).

As discussed in section 3.3, an alternative approach to designing depolymerizable systems is to reduce the ring strain of high-strain monomers. Wang and co-workers screened a variety of ring-fused cyclooctenes by installing different sized rings at the 5 and 6 positions, including both *cis* and *trans* isomers.[110] The *trans*-cyclobutane-fused cyclooctenes (*t*CBCO) with diverse substituents were excellent candidates, and ROMP was then used to synthesize their corresponding polymers (Figure 8aii). These *t*CBCO polymers all underwent >90% depolymerization with G2 catalyst to regenerate monomers, although a low polymer concentration was required and unlike the bottlebrush polycyclopentenes which depolymerized from the termini, random chain cleavage initiated the depolymerization mechanism.[108] Notably, the *cis*-to-*trans* alkene isomerization within *t*CBCO was used by the same group to increases the ring-strain, enabling high-driving-force ROMP at lower monomer concentrations to access the same depolymerizable *t*CBCO polymers.[111] In follow up work, a structure–thermodynamic relationship for *trans*-cyclobutane, *trans*-cyclopentane, and *trans*-five-mem-

bered cyclic acetal fused cyclooctenes was revealed, shedding light on the design of chemically and catalytically depolymerizable polyalkenamers.[112]

Recently, Wang and co-workers employed the concept of "locked degradability"[113,114] to synthesize a polymer which could be mechanochemically activated into poly(2,3-dihydrofuran).[115] An unsaturated polyether containing cyclobutane-fused tetrahydrofuran in each repeat unit was prepared. Mechanical force-induced cycloreversion of each cyclobutene in the backbone generated three repeat units of poly(2,3-dihydrofuran), which could be depolymerized into 2,3-dihydrofuran in the presence of G2 catalyst, although a complete cycloreversion was not achieved.

In a different approach, Niu and co-workers reported polymers with enyne metathesis cascade-triggered depolymerization (Figure 8aiii).[116] Polymers containing optimized 1,6-enyne motifs were prepared via both polycondensation and iterative exponential growth approaches. Importantly, these enyne polymers showed excellent stability in strong acid, base, nucleophiles, and at elevated temperatures but underwent efficient and complete depolymerization into 1,1′-bicyclopentene derivatives upon activation by a G3 catalyst (Figure 8aiii).

3.6. Polymethacrylates

With the exception of some examples of polyalkenamers, all of the depolymerizable systems discussed above in section 3 contained heteroatoms within the polymer backbones. Furthermore, most of the depolymerizations involved were thermodynamically driven by cyclization reactions. In contrast, the design of depolymerizable polymers formed by addition across a C−C π bond, such as HDPE and *i*PP, poses a substantial challenge due their generally higher hydrolytic and thermodynamic stability.[43] Nevertheless, over the past several years, it has been demonstrated that some specific C−C backbones, such as poly(methyl methacrylate) (PMMA) (T_c of 205 and 296 °C at 1.0 and 9.35 M (bulk), respectively), prepared by controlled polymerization can be depolymerized under moderate conditions, presenting exciting opportunities for further innovations.[117] This depolymerizability arises from the high-fidelity end-group functionality achieved through polymerization techniques including atom transfer radical polymerization (ATRP) and reversible addition−fragmentation chain-transfer (RAFT) polymerization.[117]

Matyjaszewski and co-workers explored the catalyzed solution depolymerization of chloride-capped poly(oligo-(dimethylsiloxane) methacrylate) bottlebrushes, poly(n-butyl methacrylate) (PBMA), as well as PMMA, which were synthesized via ATRP, in the presence of copper or iron catalyst at 170 °C (Figure 8bi).[118−120] Alternatively, high end-group fidelity of RAFT polymers were also leveraged to achieve depolymerization by the Gramlich[121] and Anastasaki groups.[122] High yield (up to 92%) and catalyst-free depolymerizations of various linear, cross-linked, and functional polymethacrylates (e.g., PMMA, PBMA, and poly(oligo-(ethylene glycol) methyl ether methacrylate) were achieved at 120 °C via the generation of terminal radicals upon reversible cleavage of the RAFT end-group, although low concentrations of polymer (i.e., 5 mM of repeating units) were required (Figure 8bii).[122] Subsequently, photoassisted and photo-catalyst-accelerated depolymerization of PMMA at 100 °C were further developed.[123,124] It is important to note that such advances are inaccessible for commercial PMMA, which is prepared by conventional free radical polymerization. The
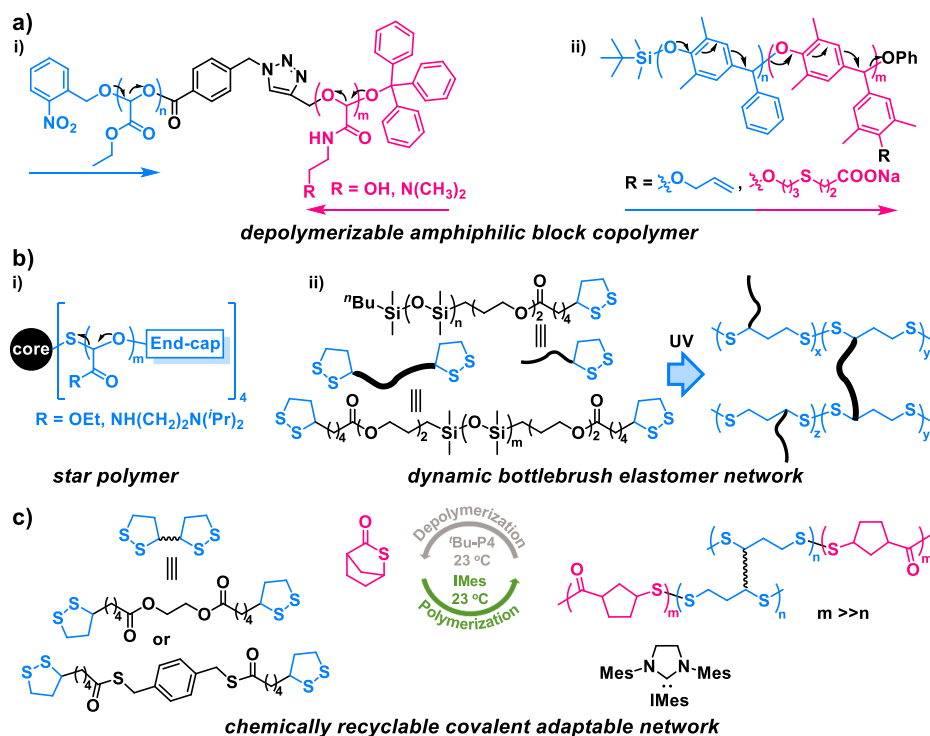
Figure 9. (a) Fully depolymerizable amphiphilic block copolymers via (i) coupling of orthogonally depolymerizable blocks and (ii) sequential polymerization and postpolymerization functionalization. The arrows show the direction of triggered depolymerization. (b) Representative branched depolymerizable systems include (i) 4-arm star polyglyoxylate and polyglyoxylamide with acid-responsive end-caps and (ii) dynamic polydisulfide bottlebrushes as elastomers. (c) Covalent adaptable networks derived from thiolactones and cyclic disulfide cross-linkers with complete chemical recyclability.

incorporation of halogen or RAFT end-group would also compromise other properties such as thermal and chemical stability.[122] Moreover, compared to well-established pyrolysis depolymerization of PMMA, in which up to 98 wt % MMA can be regenerated at 450 °C using a fluidized bed process,[43,125] the recycling efficiency has been relatively low for depolymerization of PMMA prepared via both ATRP and RAFT approaches. Thus, ongoing efforts are underway to further improve the depolymerization conditions and efficiency,[126−128] expand monomer scope, and find niche applications for depolymerizable polymers synthesized via controlled polymerizations.

4. EVOLVING TOPOLOGIES OF DEPOLYMERIZABLE SYSTEMS

Since the introduction of depolymerizable oligomers and dendrimers based on self-immolative linkers, depolymerizable systems have experienced a topological evolution from linear and cyclic polymers to complex architectures including block copolymers, bottlebrush copolymers, star polymers, hyperbranched copolymers, as well as networks.[129] In this section, we will provide an overview of selected recent examples to highlight the unique features of each macromolecular topology. For a comprehensive discussion of this emerging subfield, readers are referred to recent review articles.[27,129]

4.1. Fully Depolymerizable Block Copolymers

Taking advantage of the amplified stimulus-triggered degradation of SIPs, block copolymers bearing SIPs as the hydrophobic blocks and poly(ethylene glycol) (PEG) or polyacrylamide as the hydrophilic blocks have been constructed as self-assembling amphiphiles for biomedical applications.[9,10,27]

However, after SIP depolymerization, the nonresponsive, hydrophilic PEG or polyacrylamide blocks would still exist.[9,10,27] Fully depolymerizable block copolymers, where each block is depolymerizable, have been far less developed. In this context, Liang and Gillies recently presented fully self-immolative diblock copolymers via coupling of hydrophilic, acid-responsive polyglyxoylamides with hydrophobic, photosensitive poly(ethyl glyoxylate) by copper-catalyzed azide–alkyne cycloaddition (CuAAC) reactions (Figure 9ai).[130] Orthogonal depolymerization of each block was achieved as acid led to selective depolymerization of the polyglyxoylamide block, and UV light resulted in depolymerization of the poly(ethyl glyoxylate) block (Figure 9ai). In another contribution, Kim and co-workers reported fully depolymerizable poly(benzyl ether)-based diblock copolymers by living polymerization with sequential additions of two different monomers, followed by end-capping (Figure 9aii).[131] After partially functionalizing one block with pendent carboxylic acids, the resulting polymer amphiphiles self-assembled into micelles in aqueous media. Head-to-tail complete depolymerization of the polymer amphiphiles occurred after removal of a single capping moiety, leading to the dissociation of the micelles without any polymeric residues (Figure 9aii).

4.2. Star, Hyperbranched, and Bottlebrush Copolymers

Star polymers are branched macromolecular architectures with linear arms radiating from a central core.[132] Gillies, Such, and co-workers reported the synthesis and degradation of starshaped self-immolative poly(ethyl glyoxylate)s derived from tetrathiol cores with acidic pH-responsive end-caps (Figure 9bi).[133] Ethyl esters of the hydrophobic poly(ethyl glyoxylate)

arms were also transformed into amides, affording cationic star polymers with accelerated depolymerization rates (Figure 9bi).

Hyperbranched polymers possess globular and highly branched structures with a large number of peripheral groups.[134] Liu and co-workers described the facile preparation of hyperbranched SIPs using a one-pot AB$_2$ polycondensation method, followed by sequential functionalization.[135] Using the hyperbranched SIP platform, different functions including phototriggered intracellular release of peripheral conjugated drugs, intracellular delivery and reductive milieu-triggered plasmid DNA release, fluorescent and colorimetric sensing of H$_2$O$_2$, and ultrasensitive detection of pathologically relevant antigens were explored.

Highly branched bottlebrush polymers with either depolymerizable backbones or side-chains have also been developed.[129] Recently, Bates and colleagues introduced a light-mediated grafting-through polymerization approach to synthesize dynamic bottlebrush elastomers with a polydisulfide backbone (Figure 9bii).[136] Specifically, α-lipoic acid-functionalized polydimethylsiloxane macromonomers and cross-linkers were subjected to UV irradiation in a solvent-free manner, resulting in the formation of bottlebrush polymers, including elastomers (Figure 9bii). Importantly, the high concentration of disulfides along the bottlebrush backbone enabled dynamic exchange in response to UV light, imparting self-healing and reprocessing capabilities. Moreover, the stimulus-actuated depolymerization of the bottlebrush backbones could be achieved using heat, reducing agents, or bases. In another interesting study, the Bai group developed a method for the accelerated fabrication of polypeptides and related hybrid materials from depolymerizable poly(benzyl ether)-backbone bottlebrush polymer precursors.[137] Bottlebrush polymers were synthesized via a grafting-from approach using poly(benzyl ether)s with multiple side-chain amine groups. Free polypeptide side-chains could be efficiently generated by depolymerizing the poly(benzyl ether) backbones upon treatment with strong acids (e.g., HCl), simultaneously unmasking highly reactive benzhydrylium motifs for subsequent functionalization.

4.3. Networks

Networks prepared by the chemical cross-linking of depolymerizable polymers provide stimulus-mediated degradation for controlled structural transformations and property tuning.[129,138] In this context, the Gillies group reported the construction of hydrogels from self-immolative dendrons with photoresponsive focal points.[139] Two different generations of dendrons with alkyne moieties at their peripheries were cross-linked with 4-arm PEG-azides via CuAAC, leading to self-immolative hydrogels with distinct physical and degradation properties. Very recently, we further constructed self-immolative hydrogels from phototriggered depolymerizable poly(ethyl glyoxylate) and 4-arm PEG-azides via CuAAC.[140] The hydrogel degradation could be turned on and off repeatedly through alternating cycles of UV irradiation and dark storage. Similar cycles could also be used to control the release of the physically encapsulated anti-inflammatory drug celecoxib.

In another example by the Bowman group, depolymerizable polythioesters with norbornene-functionalized side chains were reacted with 8-arm PEG-thiols through a thiol–ene photoclick reaction.[141] The resulting hydrogel networks were depolymerized by activating the terminal uncapped thiols of the

polythioester backbones by increasing the pH and temperature. In another study, Bowman and co-workers prepared organogels from allyl-functionalized polyphthalaldehyde copolymers and tetrathiols through thiol–ene photopolymerization.[142] These cross-linked networks were depolymerized upon exposure to various chemical or physical stimuli. Very recently, Kim and co-workers reported reprocessable thermoset networks as smart adhesives from graft copolymers containing a polynorbornene backbone and depolymerizable furan-functionalized poly(benzyl ether) side chains with bismaleimide cross-linkers.[143] Reversible Diels–Alder cross-linking chemistry made the thermosets reprocessable via covalent bond exchange. In addition, triggered end-to-end depolymerization of the poly(benzyl ether) arms led to cleavage of multiple cross-links, resulting in the rapid on-demand debonding.

As discussed briefly in section 3.2, coordination complexes between metal ions and organic ligands have been used to construct dynamic networks.[64−66,71] The reversible formation of coordination complexes rendered self-healing properties,[64,65] reprocessability,[66] and on-demand release.[71] On the other hand, by combining acylhydrazone-based dynamic covalent chemistry with depolymerizable polydisulfides, Qu, Tian, Feringa, and co-workers presented a chemically recyclable cross-linked polymer network via a one-pot solvent-free method from an acylhydrazine-bearing α-lipoic acid derivative and aldehyde cross-linkers.[67] Notably, acylhydrazone moieties not only functioned as dynamic cross-linking points but also acted as supramolecular multiple hydrogen bonding units, providing a cross-linked network with high mechanical robustness, toughness, and adaptability. Moreover, these networks could be dissociated and depolymerized by using small molecule nucleophiles in DMSO. However, this dynamic material exhibited creeping and flowing properties at high temperatures. Alternatively, the Chen group reported the construction of covalent adaptable networks based on depolymerizable polythioesters by ring-opening copolymerization of a bridged thiolactone monomer with α-lipoic acid-derived small molecule cross-linkers (Figure 9c).[144] These cross-linked, semicrystalline polythioester networks featured both dynamic disulfide bonds and intrinsic crystallinity and depolymerizability, generating an adaptable system that exhibited not only reprocessability and crystallinity-restricted creep but also complete chemical recyclability to the initial monomer by catalyzed depolymerization in solution or bulk (Figure 9c). Moreover, the properties of these adaptable networks could be readily tuned by changing the feed ratio of thiolactone monomer and cross-linkers.

5. PRECISION SEQUENCE-DEFINED DEPOLYMERIZABLE OLIGOMERS

Inspired by the precise synthesis of natural biomacromolecules like DNA and proteins, unnatural precision sequence-defined polymers have emerged as biomimetics with advanced functions.[145] For example, they can serve as alternative information storage media due to their chemical diversity and durability.[145] To this end, the development and use of sequencing methods to decipher the sequence information is of great significance.[146] In this aspect, controlled end-to-end depolymerization provides an appealing approach to achieve facile data decryption, similar to the stepwise Edman degradation for protein sequencing (Figure 10a).[146]

In seminal work, Anslyn et al. presented a self-immolative sequencing method to decode sequence-defined oligour-
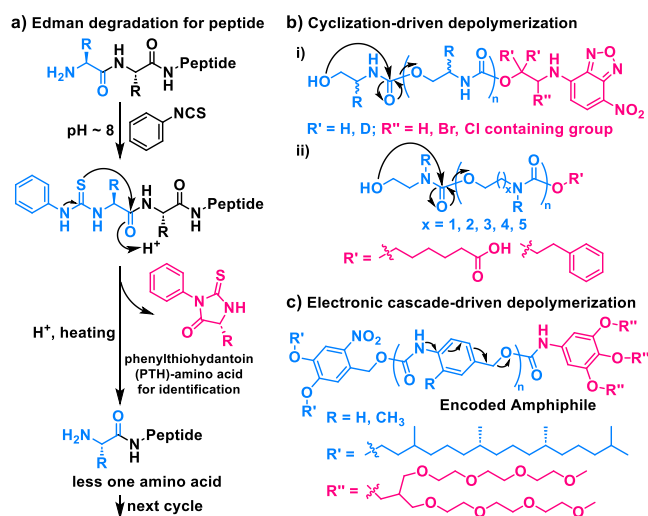
Figure 10. (a) Chemical reaction cycle used in the Edman degradation to stepwise remove one amino acid per cycle from a peptide. The released PTH moiety is used for the sequential identification of the terminal amino acid. (b,c) Sequence-defined oligomers featuring end-to-end depolymerization under specific conditions based on (b) cyclization and (c) electronic cascade elimination.

ethanes via a controlled and iterative depolymerization (Figure 10bi).[147] A terminal β-alcohol facilitated a thermodynamically favorable but kinetically slow cyclization that released a 2-oxazolidinone and a new alcohol that was available for the next cyclization event, under basic conditions at 70 °C. Importantly, the sequence information on heptamers or octamers could be decoded by a single liquid chromatography/mass spectrometry (LC/MS) run. The design of these sequence-defined, depolymerizable oligourethanes was inspired by cyclization-driven depolymerization of PGBL derivatives. In follow-up research, the self-immolative sequencing method was further applied to encrypt and decrypt molecular information in mixtures of sequence-defined oligourethanes by using different isotope labels, greatly expanding data storage capacity (Figure 10bi).[148,149]

Lutz and co-workers described sequence-defined N-substituted oligourethanes with chemically tunable depolymerization kinetics (Figure 10bii).[150] An increase in the spacer length (i.e., ethyl to hexyl) between the terminal alcohol group and the neighboring urethane led to decreased depolymerization rates under basic conditions at room temperature. Moreover, the lack of cyclization for the hexyl spacer was used as a stopper to interrupt depolymerization at a predetermined chain site, enabling the erasure and repair of the sequence information. The controlled depolymerization of such sequence-defined N-substituted oligourethanes was further explored by the Du Prez group to decipher monomer sequence by either LC/MS or electrospray ionization (ESI)-MS (Figure 10bii).[151] Notably, the application of these sequence-defined oligourethanes as anticounterfeiting tags was demonstrated by their physical incorporation into a cross-linked polyurethane material.

Liu and co-workers reported sequence-encoded polymeric amphiphiles comprising self-immolative oligo(benzyl carbamate)s with the 2-nitrobenzyl moiety as a photo-responsive trigger and a discrete PEG dendron (Figure 10c).[152,153] After UV irradiation, end-to-end cascade depoly-

merization occurred and sequence information within the oligo(benzyl carbamate) could be directly decoded from matrix-assisted laser desorption/ionization–time-of-flight (MALDI–ToF) MS at a specific incubation interval.[152] Moreover, direct sequence information reading could also be accomplished with a MALDI tandem mass spectrometry (MS/MS) technique, which was attributable to the combination of high-affinity binding of alkali metal ions (i.e., Na⁺) with PEG dendrons for ionization and selective but random cleavage of benzyl-carbamate linkages under MS/MS conditions.[153] Furthermore, digital micelles self-assembled from such precisely encoded amphiphiles were exploited as novel polymeric biomaterials for high-throughput label-free MS imaging and quantification *in vitro* and *ex vivo*.[153] It should be noted that all of the described precision sequence-defined depolymerizable oligomers would undergo end-to-end degradation along with data decryption, generating small molecule fragments that could not be directly repolymerized.

6. CONCLUSIONS AND OUTLOOK

In this Perspective, we have briefly introduced self-immolative linkers and monomer–polymer equilibria as the foundations of current depolymerizable systems, including those that are unstable in the absence of an end-cap, often referred to as self-immolative polymers, as well as depolymerizable systems that are stable in the absence of end-caps but can be activated to depolymerize in the presence of a catalyst and/or mild heating. Subsequently, we highlighted emerging trends in the chemistry of end-to-end depolymerization, including the introduction of new depolymerizable backbones, the creation of complex architectures, and the pursuit of precision information-containing macromolecules.

Currently, there is rapidly expanding interest in degradable polymers and chemically recyclable polymers for a circular plastic economy. This interest is accompanied by innovations and applications of click chemistry and bio-orthogonal chemistry to enable access to complex functional materials. Furthermore, the bioinspired creation of precision polymers as structural and functional mimics of natural macromolecules is a rapidly growing pursuit. Therefore, we envision that the field of end-to-end depolymerization will continually expand in the next decade to allow for next-generation polymeric materials with embedded on-demand degradability. For instance, releasable bioconjugates bearing cell-penetrating polydisulfides have emerged as promising delivery systems for biologics.[154] However, it is worth noting that these emerging trends are still in their infancy, and there still exist many opportunities and challenges to be explored.

First, most of the depolymerization studies for the examples discussed in this Perspective were conducted under well-controlled laboratory conditions from as-synthesized and purified polymers. A complete analysis of stabilities of promising depolymerizable systems is required, as minor structural changes either on the backbone or side-chain would affect the depolymerizability as manifested by the strong influence of geminal disubstitution on T_c.[94] Moreover, any undesirable degradation imparted by hydrolysis, acid, base, light irradiation, or oxidation for real applications would possibly result in alterations from the as-designed depolymerization pathways.[155] Moreover, high-efficiency and facile methodologies to incorporate functional moieties including responsive end-caps into depolymerizable backbones without compromising depolymerization capability requires more

efforts.[156] On the other hand, other depolymerizable systems that are not discussed here, including polycarbonates,[43] polyamides,[92] polyurethanes,[157] and polysaccharides,[158] also show widely attainable properties and depolymerizations.

Second, the creation of depolymerizable materials with different architectures is driven by topology-dependent properties, such as stability, thermal properties, and depolymerizability.[60,87] Different topologies also differ with respect to their synthesis, functionalization, and depolymerization pathways.[129] On the basis of emerging depolymerizable backbones and click reactions, complex functional materials can be attainable.[130,159] Notably, controlled solid-state or solution self-assembly of fully depolymerizable block copolymers could possibly accelerate the fabrication of nanoporous separation membranes and simplify their end-of-life management.[160] In addition, the properties of cross-linked networks or thermosets consisting of depolymerizable chains or cross-links could be easily tuned on demand as advanced biomaterials[161] or dynamic materials.[136,144]

Third, programmed end-to-end depolymerization for sequence-defined oligomers has proven to be advantageous to decode information that is encoded in their primary sequences.[147,150,151,153] So far, the reported studies primarily involved urethane backbones, which combine adequate stability and chemically tunable fragmentation in comparison to ester, thioester, or disulfide linkages. Thus, there is still ample space for the exploration of new backbones for sequence-defined polymers with structural integration in the use and optimization of depolymerization kinetics for decoding. In this aspect, end-capping of reactive termini of sequence-defined polymers and catalyst-assisted depolymerization could be examined. Furthermore, sequence-defined polymers with chemically diverse functional groups combined with on-demand depolymerization behavior are also promising for use as tags or libraries to discover therapeutics and biochemical ligands.[162]

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The manuscript was written through contributions of all authors. CRediT: **Zhengyu Deng** conceptualization, writing-original draft; **Elizabeth R. Gillies** conceptualization, writing-review & editing.

Notes

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