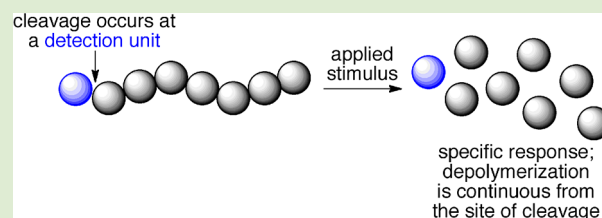


Continuous Head-to-Tail Depolymerization: An Emerging Concept for Imparting Amplified Responses to Stimuli-Responsive Materials

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ABSTRACT: Polymers that depolymerize continuously and completely from head-to-tail when a reaction-based detection unit is cleaved from the polymer provide both selective and amplified responses, a rare combination, to stimuli-responsive polymeric materials. This Viewpoint contextualizes this new class of depolymerizable polymers and outlines the key areas for growth and innovation.



Few stimuli-responsive polymeric materials have the ability to autonomously provide a change in property (i.e., color, structure, wettability, etc.) with a magnitude that is greater than the intensity of a specific applied stimulus.^{1,2} Mastering the ability to create such an amplified response has the potential to revolutionize the capabilities of stimuli-responsive materials, both by improving the rate and degree with which a material changes once exposed to a stimulus. Examples of polymeric materials that are capable of this type of response include microcapsules that release healing reagents when fractured due to mechanical stress,^{3,4} materials that swell and shrink as a Belousov–Zhabotinsky (BZ) reaction oscillates,^{5,6} or conjugated polymers for applications in sensing.^{7,8} Beyond these few examples, however, there is a need for general reagents, strategies, and design rules that enable amplified responses to various stimuli in a wide range of polymeric materials.

A new class of polymers holds promise for achieving these goals. These polymers depolymerize from head-to-tail (or from tail-to-head) continuously and completely when a specific functional group is cleaved from the polymer in response to a predefined stimulus.^{9–13} Ideally, these polymers are thermodynamically stable until the functional group (often called a reaction-based detection unit,^{14,15} an end-cap,^{16,17} or a trigger^{18,19}) is cleaved. Once the functional group is removed, the polymers depolymerize to generate monomers and additional small molecule products (Figure 1a). This depolymerization reaction occurs as a consequence of a single detection event, yet causes the entire polymer to revert to tens, hundreds, or thousands of monomers, depending on the length of the polymer.

In some applications, the products of depolymerization may serve a function or the process of depolymerization may simply change the structure, surface properties, or stability of a material in a way that is magnified relative to the input signal. Recent demonstrations of these polymers as stimuli-responsive materials include micro- and nanoscale capsules and micelles for controlled release applications,^{16,20–22} nonmechanical plastic pumps that turn on autonomously in the presence of an applied stimulus,^{15,23} shape-shifting plastics,^{24,25} and flow

control reagents (in the context of analyte detection in paper-based diagnostics).^{26–28}

Once the chemistry for this class of polymers is developed further, however, the applications could be substantially broader and may include new plastics that are easily recycled,^{29–37} new materials for biomedical applications, or new types of self-healing materials. These are just a few of many possible uses; the applications could be vast and diverse.

Classifying depolymerizable polymers: Before discussing the details of this new class of polymers, we offer some context and definitions. Depolymerization is a term that has been used in the literature to describe a number of processes in polymer chemistry that differ substantially from one another in terms of mechanism, selectivity, and degree of amplification. For example, the process of continuous head-to-tail depolymerization after selective removal of a detection unit (the focus of this Viewpoint) is distinct from polymers that depolymerize continuously when the backbone of the polymer degrades in response to a nonspecific signal (e.g., poly(1,2-glycerol carbonates); Figure 1b).^{34,36} In this latter case, the backbone cannot be altered easily to change the signal to which the polymer responds, whereas, in theory, polymers that contain detection units can be tuned quite easily by simply changing the composition of the detection unit. Likewise, polymers that depolymerize continuously after cleavage of a detection unit differ substantially from polymers that degrade by cleaving multiple times at random positions in a polymer backbone (e.g., via hydrolysis; Figure 1c)³⁹ or even at well-defined locations in response to specific signals (Figure 1d).^{40,42,43} The polymers in these latter examples split in two after each reaction without propagation of the cleavage event.

All of these polymers can be classified loosely as depolymerizable polymers based on the IUPAC definition of the term⁴⁴ since eventually, after enough reactions with a stimulus, they degrade into monomers or small molecule

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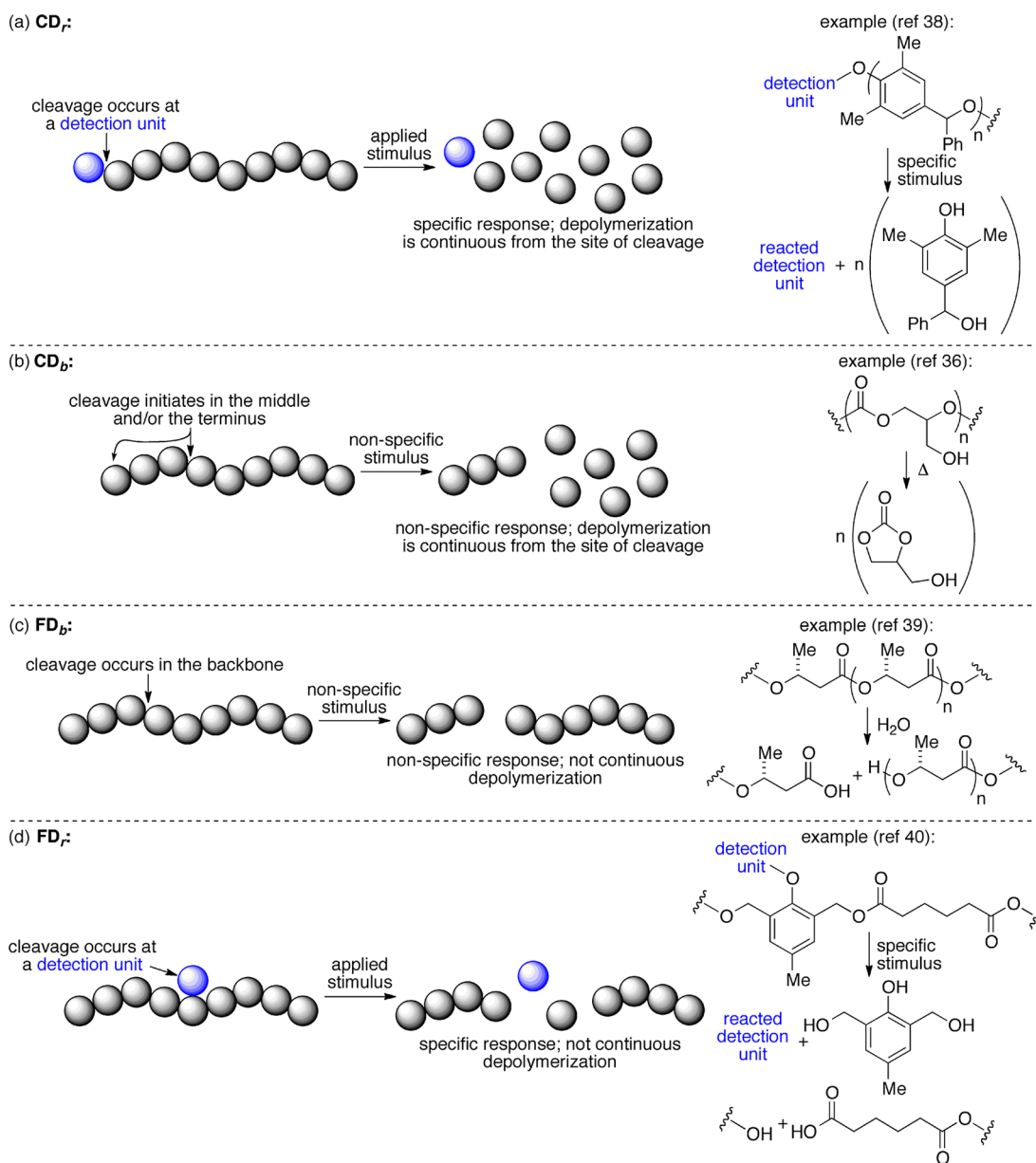


Figure 1. General classes of depolymerizable polymers. Example members of each class are depicted on the right side of the figure. The gray spheres represent monomers. The class of polymers represented in (a) are the subject of this Viewpoint. These polymers provide continuous depolymerization after a reaction-based detection unit is cleaved from the polymer. Thus, we refer to them as CD_a polymers. Some early literature has referred to these polymers as self-immolative,¹⁸ which is a term commonly associated with prodrugs.⁴¹

products. In Figure 1, we propose a classification and nomenclature scheme to differentiate these classes of polymers from one another and to better define the corresponding research areas.

There are four general categories of polymers in Figure 1. Two defining characteristics between these four classes are (i) whether the polymers contain reaction-based detection units to provide selectivity in the response to a stimulus and (ii) whether the polymers depolymerize continuously or via repetitive fragmentation processes. Two of the categories depolymerize *continuously*^{45,46} once a reaction occurs between the stimulus and the polymer, and hence provide substantial signal amplification for each detection event. The other two categories are *fragmentation* processes whereby reaction with the stimulus breaks the polymer into two smaller polymer fragments that must undergo additional reactions with the

stimulus to continue converting the polymers into monomers or other small molecule products.

Thus, the nomenclature given in Figure 1 is based on the mechanism of depolymerization and whether the polymer includes a specific detection unit to enable selective and tunable responses to specific stimuli. For example, the class of polymers in Figure 1a contains one or more reaction-based detection units and provides continuous depolymerization once the stimulus selectively cleaves the reaction-based detection unit from the polymer.⁴⁷ We refer to these polymers as CD_a polymers. Using similar descriptors: Figure 1b shows polymers that are capable of continuous depolymerization once a nonspecific cleavage event occurs in the backbone of the polymer (CD_b); Figure 1c depicts polymers that undergo fragmentation depolymerization when the backbone cleaves nonspecifically (FD_b); and Figure 1d describes a second class of

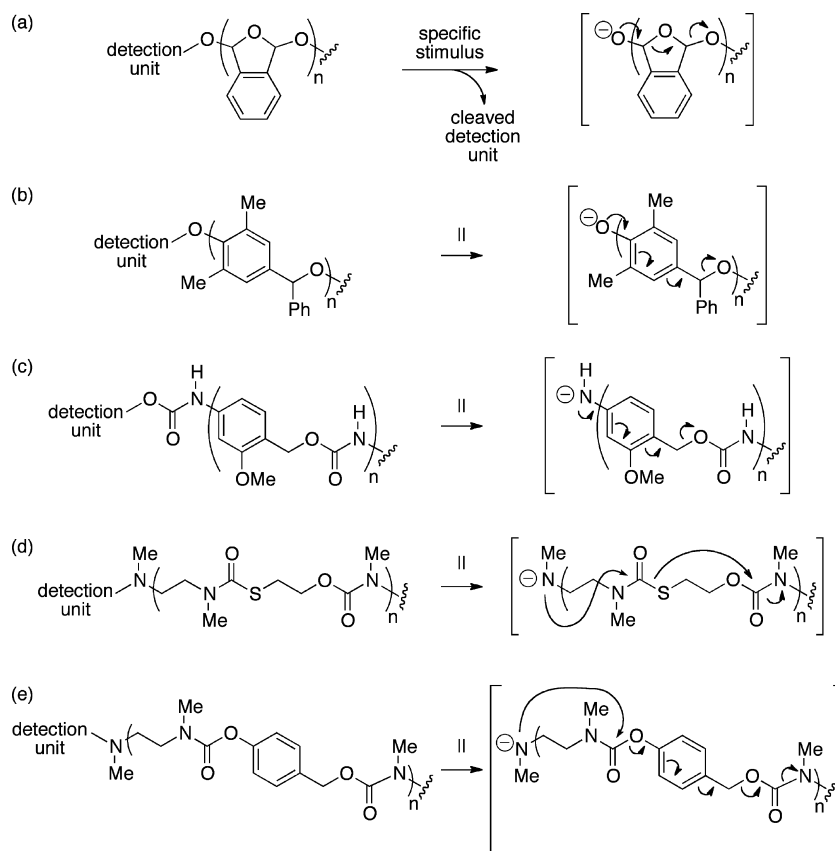


Figure 2. Representative examples of the current classes of CD_r polymers and their mechanisms of depolymerization. Structural variants of these examples have been reported for the poly(benzyl carbamates)^{18–20,68} (c) and cyclization/quinone methide elimination polymers (e).^{66,67}

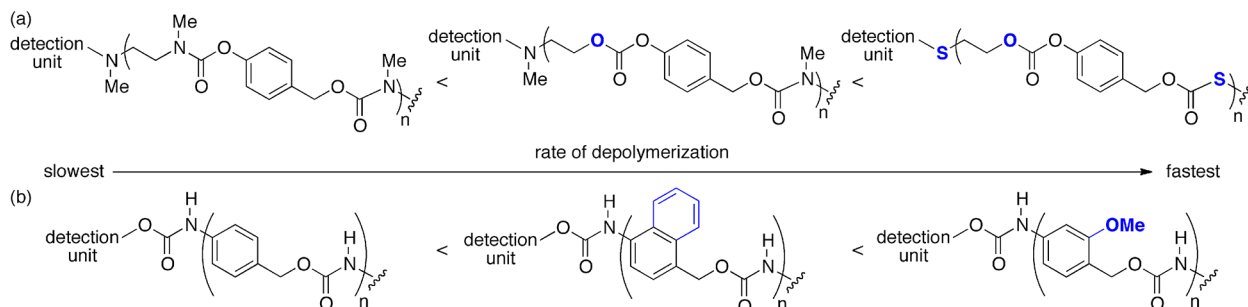


Figure 3. Examples of modifications (blue portions) to two classes of CD_r polymers to increase the rate of depolymerization. Changing heteroatoms in the polymer backbone in (a) accelerates the rate of depolymerization, but also likely increases the prevalence of nonspecific background depolymerization (via hydrolysis) for long-term applications.⁶⁶ (b) Altering the level of aromaticity in each repeating unit and/or increasing the electron density of each repeating unit enhances the rate of depolymerization of poly(benzyl carbamates).^{68,71}

polymers that undergo fragmentation depolymerization, but when a reaction-based detection unit is cleaved selectively by a specific signal (FD_r). The requisite designs for each class of polymers are unique and warrant their own focus; some of this material has been discussed in recent reviews.⁴⁸ Moreover, it is worth noting that some current, and likely some future, polymers will depolymerize via combinations of mechanisms. Current examples of this situation include FD_r polymers that also degrade via hydrolysis (FD_b).^{49–51} We suggest combining descriptors for these situations, for example, $FD_{r/b}$. Identifying the emerging areas of research in depolymerizable polymers: A representative survey of the literature from January 1, 2008 to January 15, 2014 reveals that FD_b polymers are by far the most studied of depolymerizable polymers (i.e., 95% of the 1723 publications in the area of depolymerizable polymers

during this time period).⁵² FD_b polymers are prevalent in the literature, in part, because they were identified first, but also because of their potential for creating degradable materials for biomedical applications,⁵³ as well as their applicability in the area of biodegradable plastics.⁵⁴ CD_b polymers are the second most commonly studied (3% of publications), while publications on CD_r and FD_r polymers each represent only 1% of the total work in the area of depolymerizable polymers (i.e., 18 and 14 publications, respectively). These latter two classes are the newest types of depolymerizable polymers, having been reported only in the past 6 years.^{55,64}

The limited number of studies concerning CD_r and FD_r polymers, however, belies their potential: they offer a level of tunability and selectivity that is not easily achieved using CD_b and FD_b polymers. CD_r polymers, in particular, are attractive

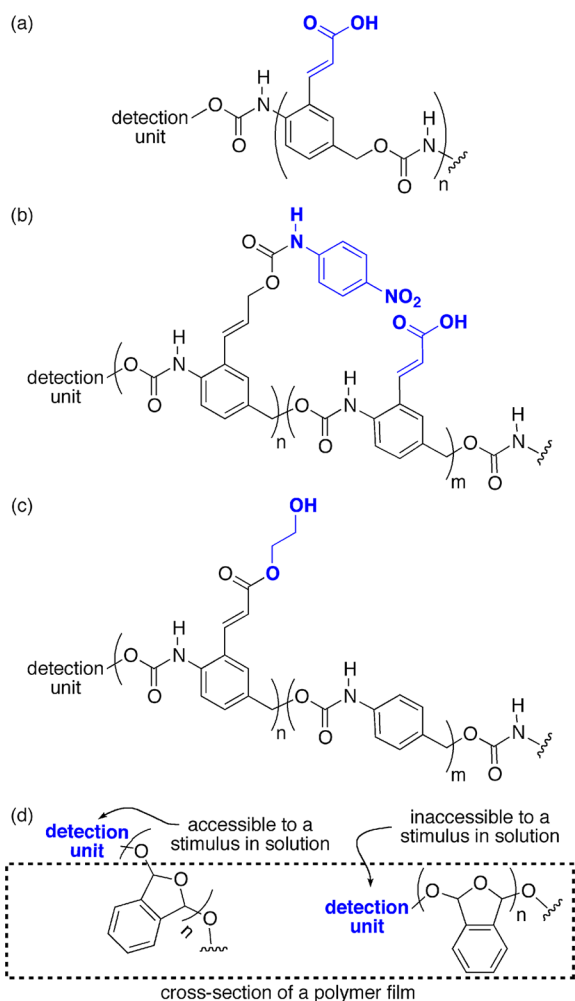


Figure 4. Examples of structural modifications (blue portions) to CD_r polymers that improve their function. (a) Each repeating unit becomes fluorescent upon depolymerization.¹⁸ (b) One repeating unit releases *p*-nitrophenol upon depolymerization, while the other becomes fluorescent.¹⁹ (c) Additional functional groups provide handles for cross-linking polymers.²⁰ (d) The detection unit can be modified to increase the likelihood that it is displayed at the solid–liquid interface of a solid-state material.¹⁵

for use in stimuli-responsive materials due to their ability to provide an amplified response (in addition to a specific response) to a signal as a result of the continuous depolymerization mechanism. The remainder of this Viewpoint focuses on CD_r polymers, including the basic and applied science that must be developed to expand, explore, and employ this emerging class of polymers.

There are currently five classes of CD_r polymers: polyacetals (Figure 2a),^{15,22–25} poly(benzyl ethers) (Figure 2b),³⁸ poly(benzyl carbamates) (Figure 2c),^{18–20,26–28,85} polymers that undergo depolymerization via intramolecular cyclization reactions (Figure 2d),¹⁷ and polymers that depolymerize via alternating intramolecular cyclization/quinone methide elimination reactions (Figure 2e).^{16,21,66,67}

Although the exact properties of an ideal CD_r polymer will depend on the application, desirable attributes for most applications include rapid rates of depolymerization, tunable rates of depolymerization, chemical and physical stability (until the detection unit is cleaved), the ability to be manipulated easily, the ability to form materials with useful bulk properties,

and efficient and scalable syntheses that provide access to large quantities of the polymers with predictable and tunable lengths.

None of the five current classes of polymers provide all (or even most) of these capabilities: some are slow to depolymerize,⁶⁸ while others are prone to background degradation when removed from neutral conditions.^{24,25,69} The ability of these polymers to rapidly depolymerize in the solid state also is rare^{15,22,24,25} (although critical for many applications in the context of smart materials), and the products of depolymerization often provide little to no additional function. Additional physical organic studies in conjunction with the development of new, efficient polymer chemistry should provide access to other classes of polymers that overcome current limitations and further reveal the potential of CD_r polymers for use in stimuli-responsive materials. The following sections outline the recent advances in CD_r polymers that are moving the field forward.

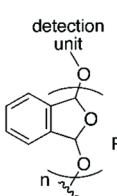
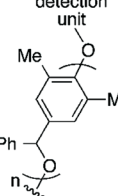
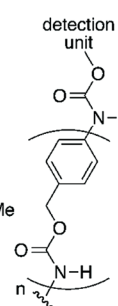
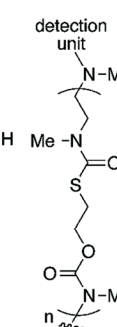
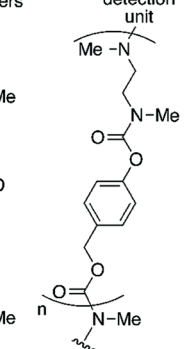
Increasing the rate of depolymerization: Fast rates of depolymerization are desirable for many applications, yet they depend on the type of polymer, the mechanism of depolymerization, and typical reaction parameters such as temperature and the polarity of the solvent (if any). In many cases (particularly when used as a stimuli-responsive material), the polymers will exist predominantly in the solid state and will operate, ideally, at ambient temperatures. Therefore, the rate of depolymerization will depend entirely on the structure and design of the polymers, not on solvation or temperature effects. Of the current CD_r polymers, polyacetals such as poly-(phthalaldehydes) (Figure 2a) depolymerize most quickly (depolymerization occurs within seconds) and are one of the few polymers that are capable of depolymerizing completely and rapidly in the solid state.^{24,25} However, the acetal backbone makes them susceptible to nonspecific degradation from stimuli such as acid.⁶⁹ The other current CD_r polymers have depolymerization times⁷⁰ ranging from minutes (Figure 2b)³⁸ to days (Figure 2d),¹⁶ depending on the polymer and the depolymerization conditions.

In some cases, it is possible to accelerate the rate of depolymerization by tailoring the backbone of the polymers (while retaining the core motifs). For example, by changing select functional groups (e.g., carbamates to carbonates) in the polymer depicted in Figure 2e, complete depolymerization in water–acetone mixtures occurs within several hours versus several days for the parent polymer (Figure 3a).⁶⁶ Similarly, modifying the aromaticity and the electronics of the aromatic rings in the repeating units of the poly(benzyl carbamates) (Figure 2c) reduced the time required for complete depolymerization from 6 h to 65 min in a 7.2:1.8:1 DMSO–water–dioxanes mixture (Figure 3b).^{68,71}

Additional studies aimed at modulating the rates of depolymerization would substantially enhance the capabilities and versatility of the current class of CD_r polymers, and even may expand the scope of polymers that are capable of depolymerizing in the solid state. Of course, modifications to accelerate the rate of depolymerization must be balanced with efforts to minimize the possibility of nonspecific background depolymerization caused by hydrolysis, thermal degradation, or other factors. Studies on accelerating the rate of depolymerization should therefore include results both for the rate of the desired and undesired reactions to provide a balanced view on the performance and stability of the polymers.

Modifications that provide additional performance: CD_r polymers often provide function when the polymer is part of

Table 1. Roadmap of Desirable Properties for CD_r Polymers^c

		general classes of current CD _r polymers				detection unit
categories	properties					
stability	thermal		(38)			
	chemical		(38)			
accessibility	scalable synthesis	(25)	(38)			
	tunable M _n	(25)	(38)	(26)		
	compatible with various detection units	(25)	(38)			
versatility	generalizable to access variants of the polymers			(18-20)		(66)
	compatible with post-polymerization modifications	(69) ^b		(20)		
depolymerization rate	modifiable to ensure access of the detection units at the solid-liquid interface	(15)				
	rapid in solution ^a	(24)	(38)			
	rapid in the solid state ^a	(24)				
	rapid in polar and non-polar environments ^a	(24)				
products of depolymerization	tunable			(68,71)		(66)
	all are gases					
	inert				(17)	
	nontoxic					(21)
	water soluble			(18)		
	monomers (recycling)	(24)	(38)			
	provide signal			(18,19)		
	perform function	(23)		(65)		
	quantitative yields	(24)	(38)			(16)

^aWe define “rapid” loosely as complete depolymerization in seconds to minutes. ^bA poly(phthalaldehyde) derivative that lacked responsive detection units was used to demonstrate this capability. ^cRecent studies have touched upon only a selection of these properties (as identified by the references provided in parentheses in the blue sections), while the gray regions reflect examples of unmet needs.

a material (e.g., nonmechanical plastic pumps initiated by depolymerization).^{15,23} Other functions, however, are achieved by the monomers that are revealed upon depolymerization. For example, Figure 4 shows examples of exploratory efforts to enhance the properties of CD_r polymers by incorporating repeating units that provide fluorescent (Figure 4a) or colored monomers (Figure 4b) upon depolymerization or that enable release of a pendant small molecule (Figure 4b).^{18,19} Likewise, appended functional handles provide opportunities for cross-linking polymers, which has been used to make more complex polymeric structures (e.g., microcapsules) (Figure 4c).²⁰

Clearly only a fraction of possible modifications have been explored. As such, this area of CD_r polymers is one with

substantial opportunities for rapid development, particularly since advances in function do not necessarily require the discovery of new classes of CD_r polymers.

Chemistry of the detection unit in CD_r polymers: The chemistry of the detection unit is critical for the success of CD_r polymers. The most generalizable and useful polymers will be those that enable facile incorporation of a variety of detection units so that the stimulus to which the polymer responds can be changed. Selectivity in the response of the detection unit for one stimulus over all others also is important, as are tunable rates of reaction between the detection unit and the stimulus.

The detection unit also must be accessible to the stimulus, which is a particularly important consideration for applications

in which the detection event occurs at the interface of a CD_r polymer in the solid-state and a stimulus in a liquid or gaseous phase. In fact, it is likely that strategies to achieve a high level of accessibility will be as critical for achieving rapid solid-state responses as the design of polymers that depolymerize quickly in the solid state. A step toward this goal was reported recently in the context of poly(phthalaldehydes), where varying the polarity of the detection unit improved its accessibility to a stimulus at the solid–liquid interface and, therefore, the rate of the response (Figure 4d).¹⁵

Stimuli such as light and heat are capable of penetrating a solid material, and therefore there may be certain applications where surface accessible detection units are not crucial. However, even with this type of stimulus, there likely will be cases where the light (or other forms of electromagnetic radiation) will not easily penetrate the material or where heating the bulk material is not an attractive option. Surface-accessible detection units will become important once again for achieving a response with a desired rate and selectivity, as well as for providing spatial control over where the response occurs in the material.

Future directions for CD_r polymers: The emerging field of CD_r polymers is currently in an exploratory phase with a handful of first generation polymers and a few demonstrations of proof-of-concept applications. The area is gaining traction and is set for rapid growth as the potential of this class of polymers becomes increasingly apparent. However, new examples of CD_r polymers are needed to realize this potential fully, as are improvements upon existing designs. Moreover, studies that fine-tune and optimize existing polymers so that they excel in specific applications will begin to showcase the unique attributes of CD_r polymers.

With these basic and applied research goals in mind, we offer Table 1 as a summary of current capabilities and unmet needs in the area of CD_r polymers. The table is based upon attributes that we envisage will be useful for certain applications, but clearly other attributes could be added to the list. Some of the topics in the table have been touched upon (blue regions in Table 1), while others have yet to be explored (gray areas). Moreover, the performance characteristics provided in the table are qualitative and will depend significantly on the context in which the polymer is used. One of the most challenging aspects in designing future CD_r polymers will be to create polymers that simultaneously display several (or even many) of the properties listed in the table.

Finally, formulation of CD_r polymers into materials remains an unexplored, but equally critical, aspect of this research area, as does the subsequent evaluation and tuning of the properties of the materials. The ability to tune a class of CD_r polymers easily to obtain several types of bulk materials will be a valuable capability as this field moves from proof-of-concept studies to more applied materials science.

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Notes

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(45) Polymers that depolymerize continuously have been called self-immolative polymers in some literature (e.g., ref 18), since some of the early designs were based on small molecule linkers and short dendrimers in the controlled release literature.

(46) Continuous, head-to-tail depolymerization also has been referred to as polymer unzipping (ref 44). However, this term is commonly used to describe the disassembly of supramolecular systems and biopolymers as well. See, for example: Tamm, M.; Nechaev, S. *Phys. Rev. E* **2008**, *78*, 011903-1–011903-12.

(47) In principle, the reaction-based detection unit could be located on either end of the polymer, on repeating units within the polymer, or as a combination of the two scenarios.

(48) For an overview on the field of FD_b polymers, see: *Degradable Polymers and Materials: Principles and Practice*, 2nd ed.; Khemani, K., Scholz, C., Eds.; ACS Symposium Series 1114; American Chemical Society: Washington, DC, 2012. For a review on CD_b polymers in the context of photolithography, see: Ito, H.; England, W. P.; Ueda, M. *J. Photopolym. Sci. Technol.* **1990**, *3*, 219–233. Since FD_r polymers also represent an emerging field of research, there is currently no comprehensive review on this class of polymer.

(49) Mejia, J. S.; Gillies, E. R. *Polym. Chem.* **2013**, *4*, 1969–1982.

(50) de Gracia Lux, C.; Almutairi, A. *ACS Macro Lett.* **2013**, *2*, 432–435.

(51) de Gracia Lux, C.; Olejniczak, J.; Fomina, N.; Viger, M. L.; Almutairi, A. *J. Polym. Sci., Part A: Polym. Chem.* **2013**, *51*, 3783–3790.

(52) The following procedure and considerations were used for the literature survey: A series of Web of Science topic searches were performed for articles dating from January 1, 2008 to January 15, 2014 based on the search terms “depolymerization”, “self-immolative polymer”, “degradable polymer”, “biodegradable polymer”, and “polymer unzipping”. The resulting papers were categorized as describing FD_b , FD_r , CD_b , or CD_r polymers based on the mechanism of depolymerization described in the main text of the Viewpoint. Reviews, corrections, and conference proceedings were omitted from the analysis. We also did not include papers that concentrated on (i) depolymerization of biopolymers (e.g., chitosan, cellulose, lignin, DNA); (ii) degradation and stimuli-responses through mechanisms other than depolymerization; or (iii) polymers with a backbone in which the repeating units were linked by noncovalent bonds. We

further excluded articles that used depolymerizable polymers, but that did not show degradation in the paper. Additionally, we did not include articles that focused on (i) polymer pyrolysis; (ii) laser-induced polymer fragmentation for MALDI analysis; (iii) high-temperature thermal depolymerization (unless a paper dealt with strategic thermal depolymerization in the context of a specific application, such as thermal probe lithography or polymer recycling); or (iv) low molecular weight dendrimers or oligomers.

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(55) The chemistry of several of the current classes of CD, polymers builds on earlier discoveries in prodrugs (ref 41) and on depolymerizable/self-immolative dendrimers (refs 56–63).

(56) Li, S.; Szalai, M. L.; Kevitch, R. M.; McGrath, D. V. *J. Am. Chem. Soc.* **2003**, *125*, 10516–10517.

(57) Szalai, M. L.; Kevitch, R. M.; McGrath, D. V. *J. Am. Chem. Soc.* **2003**, *125*, 15688–15689.

(58) de Groot, F. M. H.; Albrecht, C.; Koekkoek, R.; Beusker, P. H.; Scheeren, H. W. *Angew. Chem., Int. Ed.* **2003**, *42*, 4490–4494.

(59) Amir, R. J.; Pessah, N.; Shamis, M.; Shabat, D. *Angew. Chem., Int. Ed.* **2003**, *42*, 4494–4499.

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(62) Polaske, N. W.; Szalai, M. L.; Shanahan, C. S.; McGrath, D. V. *Org. Lett.* **2010**, *12*, 4944–4947.

(63) Kevitch, R. M.; Shanahan, C. S.; McGrath, D. V. *New J. Chem.* **2012**, *36*, 492–505.

(64) DuPont patented poly(acetals) that were terminated by light-responsive end-groups in 1978: Chambers, W. J.; Foss, R. P. U.S. Patent 4,108,839, August 22, 1978. However, the concept of creating polymers that contain reaction-based detection units for a variety of stimuli was not generalized in the literature until 2008.

(65) Weinstein, R.; Baran, P. S.; Shabat, D. *Bioconjugate Chem.* **2009**, *20*, 1783–1791.

(66) Chen, E. K. Y.; McBride, R. A.; Gillies, E. R. *Macromolecules* **2012**, *45*, 7364–7374.

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(68) Robbins, J. S.; Schmid, K. M.; Phillips, S. T. *J. Org. Chem.* **2013**, *78*, 3159–3169.

(69) Kaitz, J. A.; Moore, J. S. *Macromolecules* **2013**, *46*, 608–612.

(70) The time for complete depolymerization will depend on the length of the polymers, as shown in ref 67.

(71) The studies in ref 68 focus on tuning and increasing the rate of azaquinone methide elimination for oligomeric model systems, but the concepts can be extended to longer oligomers and polymers, as shown in refs 26–28.