Journal of Applied Polymer Science

REVIEW

Amplified Responses in Materials Using Linear Polymers that Depolymerize from End-to-End When Exposed to Specific Stimuli

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ABSTRACT: This review describes new types of smart materials that have the dual capabilities of responding to selective signals and providing an amplified response. Amplification arises from a signal-induced depolymerization reaction, where a single signaling event causes an entire polymer to convert to small molecules. When incorporated into a material, depolymerization of these polymers causes a change in shape, internal structure, or surfaces properties of the material. Moreover, the small molecules arising from depolymerization can play a role in the amplified response, particularly when they provide a secondary function (e.g., production of color or fluorescence). A brief overview of the current examples of linear depolymerizable polymers is provided, as are representative proof-of-concept applications of these polymers in the context of diagnostics and materials that remodel themselves and/or their surroundings. Together, these examples highlight the potential of this new class of polymers to provide unique and dramatic function to stimuli-responsive materials. © 2014 Wiley Periodicals, Inc. J. Appl. Polym. Sci. **2014**, *131*, 40992.

KEYWORDS: degradation; microfluidics; properties and characterization; stimuli-sensitive polymers

Received 18 April 2014; accepted 13 May 2014

DOI: 10.1002/app.40992

INTRODUCTION

Reagents that autonomously provide an amplified response to specific applied stimuli are rare, particularly when the reagents are capable of operating without the use of electronics or sources of power.[1–6] Even less common are polymeric reagents that possess these same capabilities, which is remarkable given the range of possible applications for such polymers.[7,8] Anticipated benefits of materials made from these polymers include materials that (i) provide responses to trace levels of specific stimuli with outputs that far exceed the intensity of the input signal; (ii) respond to applied stimuli more quickly than is possible without amplification; and (iii) are programmed to perform a function without user intervention. An emerging class of polymers holds promise for enabling these capabilities,[9–12] and thus presents an opportunity to begin investigating wide-ranging applications (Figure 1). This review focuses on this new type of polymer by describing both the structure/function relationships of a handful of polymers within this new class, as well as initial applications.

The defining feature of this new type of polymer is its ability to provide an amplified response by depolymerizing continuously and completely from end-to-end (or from wherever the initiation event originates in the polymer) in response to a specific stimulus (Figure 1).[9–12] The polymers contain two key design features. The first is a reaction-based detection unit[13,14] (often called an end-cap[15,16] or trigger[17,18]) that, in principle, may be located at either end of the polymer, in the middle of the polymer, or at multiple locations along the polymer chain. The reaction-based detection unit is a specific functionality that reacts selectively with a desired stimulus. The polymers can be designed to respond to different stimuli by altering the reaction-based detection units. The second design feature is a polymer backbone that is stabilized when attached to the reaction-based detection unit, but that becomes thermodynamically unstable upon cleavage of the detection unit from the polymer chain. Thus, the applied stimulus cleaves the detection unit from the polymer, which causes the polymer to depolymerize continuously and completely to reveal monomers or other small molecule products. The reaction-based detection unit provides the selectivity for the depolymerization reaction, while the depolymerization reaction itself creates the amplified response. Amplification may arise from release of many copies of a functional molecule, or from a change in the structure or surface properties of a material that contains the polymer.

The first example of a linear polymer that depolymerizes from end-to-end when a detection unit responds to a signal was reported in the primary literature in 2008[17–19]* and since then

*DuPont patented poly(acetals) that were terminated by light-responsive end-groups in 1978.[19] 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.

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Jessica Robbins earned her S.B. in Chemistry from the University of Chicago in 2007. She spent two years in industry as a petroleum chemist before joining the Phillips Group at Penn State in 2009. Her graduate work has focused on the design and synthesis of depolymerizable polymers for applications in point-of-care diagnostics. In Fall 2014, she will begin as an Assistant Professor of Chemistry at Coker College in Hartsville, SC.

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four additional classes have been described [Figure 2(a–e)]. This overall grouping of polymers has been given various names (self-immolative,[17] unzipping,[20] metastable[21]), but to better differentiate this type of polymer from other types of depolymerizable polymers and from other self-immolative reagents (e.g., prodrugs[22,23] and degradable dendrimers[24–32]), we now refer to them as CD_r polymers, which stands for continuous depolymerization after a reaction-based detection unit responds to a specific stimulus.[9] This nomenclature also differentiates this new class of linear depolymerizable polymers from polymers that continuously depolymerize when the backbone cleaves in response to a non-specific signal (e.g., hydrolysis) (these polymers are termed CD_b polymers).[33–38†] It further differentiates this class of polymers from those that degrade via fragmentation depolymerization reactions (FD polymers) in which reaction with one stimulus cleaves the polymer into two shorter polymers, but where additional reactions between the stimulus and the polymer are required to complete the degradation process (these polymers do not provide amplified responses).[39–45]

When compared to these other classes of depolymerizable polymers, CD_r polymers have a unique combination of attributes that make them desirable for use in a wide variety of settings. In fact, several proof-of-concept studies are already beginning to reveal these capabilities. For example, CD_r polymers have been used to make (i) stimuli-responsive, non-mechanical pumps[52,53]; (ii) micellar aggregates,[15] polymersomes,[54] and micro-[21,55] and nanocapsules[56] for controlled release applications; and (iii) shape-changing[50] and vanishing[51] plastics. They also have been used as signal amplification reagents in the context of point-of-care diagnostics.[46,57,58] However, only a fraction of possible applications have been explored thus far: additional opportunities exist in fields ranging from smart biomedical devices and materials, to new types of temporary or single-use materials, to new strategies for recycling plastics. Thus, the goal of this review is to highlight current examples of CD_r linear polymers, not only to demonstrate their existing capabilities, but also to inspire further development and application.

†Ref. 33 shows the use of CD_b polymers in the context of photolithography. For more recent examples of this class of polymer, see Refs. 34–38.

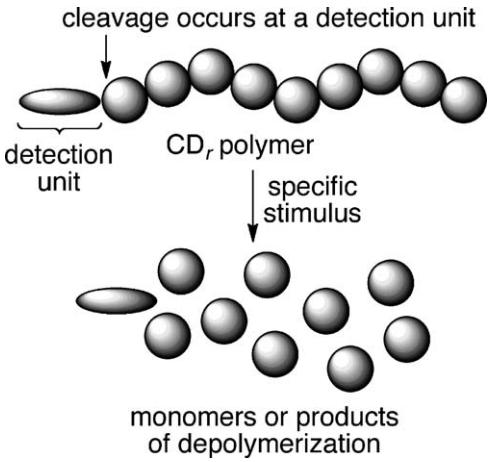


Figure 1. General depiction of a linear polymer that undergoes continuous end-to-end depolymerization when a reaction-based detection unit is cleaved from the polymer upon exposure to a specific stimulus (we call these polymers CD_r polymers).[9] A single detection event leads to complete depolymerization of the polymer, providing an amplified response.[10,11] The ellipse represents the reaction-based detection unit; the spheres depict repeating units within the polymer.

CURRENT CLASSES OF CD_r POLYMERS

Designing and synthesizing CD_r polymers is a non-trivial exercise, particularly as the polymers are primed to depolymerize unless the reaction-based detection unit is in place. Moreover, seemingly orthogonal qualities are needed: fast rates of depolymerization (i.e., complete depolymerization in seconds) are attractive, but so too is stability (i.e., chemical and thermal stability) in the absence of a specific stimulus. The design challenges also include polymers that are capable of depolymerizing in the solid state to impart specific and amplified responses to solid-state materials. This latter issue requires not only polymers that are capable of depolymerizing in non-polar environments (the polymers themselves are often relatively non-polar),[14] but also strategies for displaying the reaction-based detection units at the solid–liquid or solid–gas interface between the material and the surrounding medium (this interface is where the detection unit will encounter the stimulus in most situations).[53] Additional design features of CD_r polymers that require further exploration include issues of compatibility with certain materials, interfaces, or environments, and issues related to the properties of the products of depolymerization (e.g., if they are volatile, toxic, or inert).

For now, the key challenge in this emerging area has been establishing guidelines for how to design stable polymers that are capable of depolymerizing cleanly, predictably, and continuously in response to a specific signal. Three of the five current classes share related depolymerization mechanisms: that is, formation of quinone- or azaquinone-methide intermediates. These polymers include poly(benzyl carbamates) [Figure 2(a)],[14,17,18,46,54,57–59] poly(benzyl ethers) [Figure 2(b)],[47] and polymers that depolymerize via alternating intramolecular cyclization/quinone methide elimination reactions [Figure 2(c)].[15,48,49,56] The two other classes offer unique mechanisms of depolymerization from one another as well as from the first three classes of polymers: they depolymerize via intramolecular cyclization reactions [Figure 2(d)][16] or acetal chemistry [Figure 2(e)].[50–53,55] There is vast chemical space yet to be explored.

The five current classes of CD_r polymers display remarkably different depolymerization rates and stabilities (in the absence of the signal). They also vary substantially in the ease with which they are prepared and with which they can be manipulated to fabricate responsive materials. New polymers will add to this diversity. Thus, before discussing the current applications of CD_r polymers, we first offer brief descriptions of the chemistries of the polymers themselves.

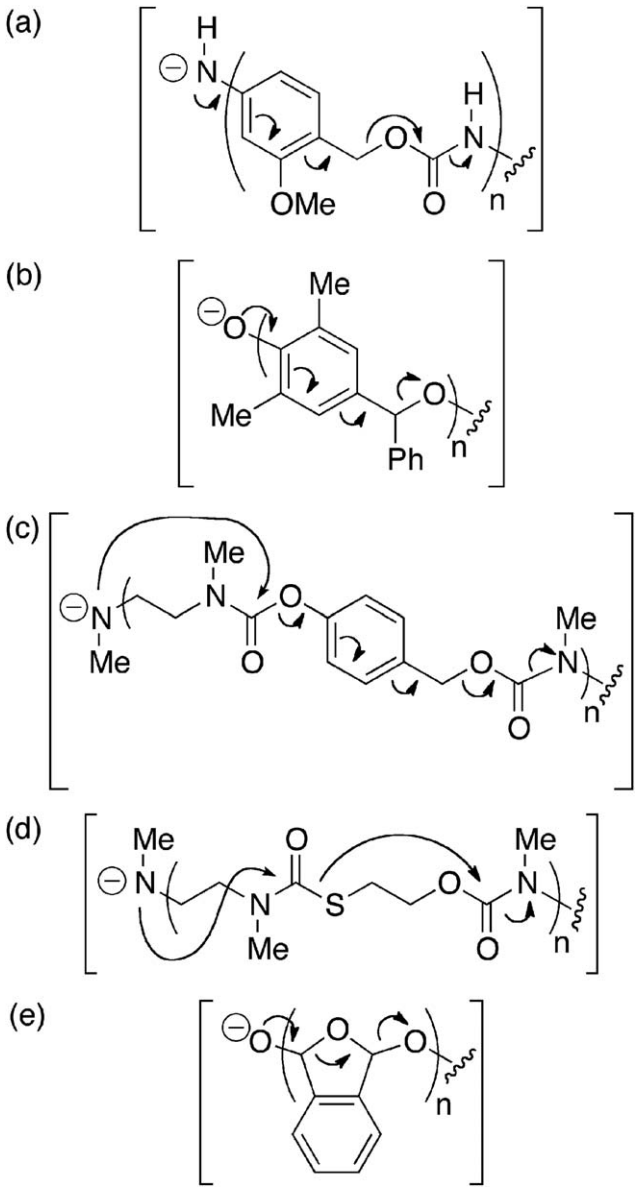


Figure 2. Representative members of the five current classes of CD_r polymers. The polymers are depicted as they might exist after cleavage of the reaction-based detection unit. These polymers are (a) a poly(benzyl carbamate),[17,46] (b) a poly(benzyl ether),[47] (c) a polymer that depolymerizes via alternating cyclization/quinone methide elimination reactions,[15,48,49] (d) a polymer that depolymerizes entirely through cyclization reactions,[16] and (e) poly(phthaladehyde).[50,51]

Poly(benzyl carbamates)

Poly(benzyl carbamates) [Figure 2(a)] were the first examples of linear CD_r polymers to be reported in the literature.[17‡] The polymers typically contain fewer than 20 repeating units (due to solubility issues),[§] and are synthesized by condensation polymerization from a monomer that contains both a masked aromatic isocyanate and a benzylic alcohol (the two functional groups are positioned *para* to one another on the aromatic ring of the monomer).[17] A reaction-based detection unit is installed by terminating the polymerization reaction with an appropriately functionalized alcohol.

Depolymerization requires cleavage of the reaction-based detection unit, followed by repetitive and sequential decarboxylation and 1,6-azaquinone methide elimination reactions [Figure 2(a)]. Complete depolymerization requires minutes to many hours, depending on the electronics of the repeating unit,[14] the length of the polymer,[¶] and the polarity of the environment,[14] where highly polar environments favor formation of azaquinone methide and, therefore, depolymerization.[14]

Poly(benzyl ethers)

Depolymerizable poly(benzyl ethers) [Figure 2(b)] are prepared via anionic polymerization of a stabilized quinone methide monomer, such as 2,6-dimethyl-7-phenyl-1,4-benzoquinone methide.[47**] The polymerization procedure gives polymers with polydispersity index values (PDI) of 1.1–1.8. The length of the polymer is tuned easily by adjusting the quantity of initiator, with accessible lengths exceeding 2000 repeating units.[47] Electrophilic reagents are used to terminate the polymerization reaction and introduce a reaction-based detection unit.

Rapid depolymerization at room temperature is possible with these polymers (e.g., complete depolymerization within seconds to minutes), although base is required to achieve these rapid response times, as are polar solvents (dielectric constant $[\varepsilon] \geq 36$).[47] The time required for complete depolymerization is surprisingly short compared to poly(benzyl carbamates), even in low polarity solvents such as dichloromethane ($\varepsilon = 8.9$) (hours time scale).[47] Complete depolymerization in nonpolar solvents such as tetrahydrofuran ($\varepsilon = 7.6$) requires days,[47] whereas current poly(benzyl carbamates) do not appear to depolymerize substantially under neutral conditions in environments of polarity this low.[14] Additionally, the poly(benzyl ethers) are robust relative to several other classes of CD_r polymers, showing no background degradation in response to water, mild base, acid, or when heated at modest temperatures.[47] In fact, thermal decomposition in the solid state occurs only at temperatures exceeding ~190°C (this value is for a 124 kDa [M_n] version of the polymer shown in Figure 2(b) with an acetate group at the terminus as the end-cap).[60]

Cyclization Depolymerization

Two classes of CD_r polymers depolymerize through cyclization reactions: one proceeds through a combination of cyclization and 1,6-quinone methide elimination reactions [Figure 2(c)],[15,48,49,56] while the other proceeds exclusively through cyclization reactions [Figure 2(d)].[16] Both classes of polymers are prepared via step growth polymerization, which has yielded polymers up to several hundred repeating units.[56] Different functionalities have been used to connect repeating units in the backbones of the polymers, including carbonates, carbamates, thiocarbonates, or thiocarbamates, with tunable rates of depolymerization being achieved by varying the arrangement of these functionalities.[48] For example, the time to complete depolymerization in water–acetone mixtures (pH 7.4) at 37°C ranges from 30 days to 1–2 h,[16,48] although the likelihood of non-specific background hydrolysis becomes more prevalent for the faster derivatives if used in aqueous environments.

Poly(phthalaldehydes)

The final class of CD_r polymers is poly(phthalaldehyde) (PPA) that contains a reaction-based detection unit on either end of the polymer, or on both ends [Figure 2(e)].[50–53,55] These polymers typically are prepared via low temperature (−78°C) anionic cyclopolymerization of 1,2-aromatic dialdehydes (a reaction-based detection unit can serve as the initiator), followed by quenching of the reaction by addition of an electrophilic reagent, which oftentimes is a reaction-based detection unit.[51,61–63††] PDI values range from 1.1 to 2.6, different length polymers are readily accessible, and long polymers (exceeding 1000 repeating units) can be prepared.

Depolymerization of PPA is exceedingly rapid (seconds time scale) once the reaction-based detection unit is exposed to a specific applied stimulus.[50] Moreover, rapid depolymerization is possible in polar and nonpolar environments, and, importantly, in the solid state.[50,51] Rapid depolymerization of PPA likely is the consequence of the low ceiling temperature (T_c) of the polymer: without a stabilizing reaction-based detection unit, the ceiling temperature of the polymer is −40°C, whereas when functionalized with a reaction-based detection unit, the polymer remains stable up to ~150°C.[64] This rapid rate of depolymerization is balanced, however, with stability issues when the polymer is exposed to mild acid or base.[63,65] This polymer highlights the orthogonal challenges associated with designing polymers for stability, but also for rapid depolymerization.[62,63,66–72‡‡]

[‡]The first structures of depolymerizable linear poly(benzyl carbamates) were inspired by previous studies in the context of prodrugs[22] as well as later work in the context of degradable dendrimers.[27]

[§]Polymers up to ~100 repeating units have been reported,[21] but only in situations where functionality is appended to each monomer that enhances the solubility of the polymer during polymerization.

[¶]This point was made both in the context of a polymer that depolymerizes via alternating cyclization and quinone methide elimination reactions[49] and in depolymerizable poly(benzyl carbamates),[14] but unpublished observations indicate that it is a general trend among CD_r polymers.

[**]McGrath has demonstrated poly(benzyl ether) dendrimers and oligomers, which are prepared in a step-wise procedure, rather than through a polymerization reaction.[24,25,30–32]

[††]Cationic polymerization conditions also provide PPA derivatives, although recent work has revealed that these conditions provide cyclic polymers (that do not contain reaction-based detection units) rather than linear polymers that contain reaction-based detection units.[63]

[‡‡]PPA and PPA derivatives that do not contain reaction-based detection units also have been explored recently, including as macrocyclic polymers,[63,66] as supramolecular polymer nanoparticles and networks,[67] as resists for nanoprobe lithography,[62,68–70] as depolymerizable mechanophores,[71] and as degradable block copolymers.[72] The earliest use for PPA was as a photoresist that depolymerized in response to photoacids.[64]

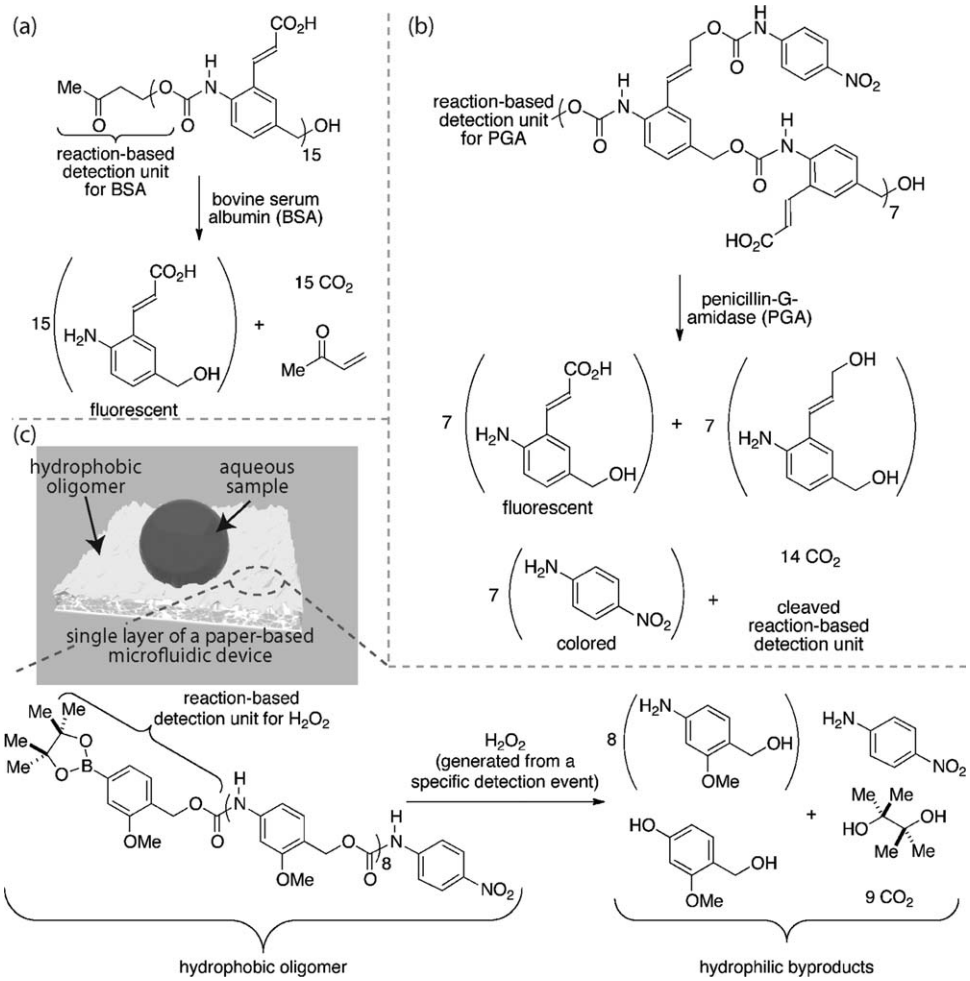


Figure 3. Applications of CD_r polymers in diagnostics. (a) Depolymerization provides fluorescent products,[17] or (b) fluorescent and colored products (via a comb polymer).[18] (c) Hydrophobic CD_r polymers cover a layer of paper and serve as flow control reagents in paper-based diagnostics.[46,57,58] The polymers operate by altering the wetting properties of the paper (hydrophobic to hydrophilic) upon depolymerization in response to hydrogen peroxide (the hydrogen peroxide is generated in a separate detection event in the paper-based microfluidic device).

APPLICATIONS OF CD_r POLYMERS

Given that CD_r polymer chemistry is in the early stages of development, many of the applications outlined in the following sections are not yet perfect solutions to a problem. They do, however, highlight the unique capabilities of CD_r polymers, suggest future applications, and hopefully inspire the development of new classes of CD_r polymers with alternative properties.

Diagnostics

CD_r polymers display a unique collection of properties, of which the most useful is the ability to respond autonomously to a specific signal both selectively and with an amplified response. The reaction-based detection units play a key role in this duality, but they also enable a single class of CD_r polymer to be altered (by switching one reaction-based detection unit for another) to make the same polymer backbone responsive to more than one kind of stimulus.[47,50] This ability to mix-and-match reaction-based detection units offers a convenient and unique way to create a variety of stimuli-responsive materials from the same polymer backbone, where the only difference between polymers is the functionality of the reaction-based detection unit.[50] This ability to alter the signal that a CD_r polymer responds to, in combination with the features of selectivity and sensitivity (i.e., amplified response), leads naturally to the use of CD_r polymers in diagnostics applications.

Colorimetric and Fluorescent Signal Amplification. One of the most logical strategies for using CD_r polymers in diagnostics is to design a polymer that is colorless or non-fluorescent, but where the small molecule products arising from depolymerization are colored or fluorescent. In this scenario, a polymer with 1000 repeating units would provide, in theory, 1000× signal amplification when the reaction-based detection unit responds to a single copy of an analyte. Although this level of performance has yet to be achieved, two depolymerizable poly(benzyl carbamates) have established the validity of the idea [Figure 3(a,b)].[17,18]

In the first example [Figure 3(a)], a non-fluorescent poly(benzyl carbamate) oligomer (15 repeating units) depolymerized to fluorescent products when the reaction-based detection unit (4-

hydroxy-2-butanone) was exposed to the enzyme bovine serum albumin (BSA).[17] Depolymerization of this oligomer in pH 7.4 phosphate buffer over the course of 10 h provided a distinct increase in fluorescent signal that demonstrated the efficacy of signal amplification via analyte-induced depolymerization.

The second example [Figure 3(b)] is a comb-polymer that contains two repeating units: one generates fluorescent small molecules upon depolymerization [similar to the example in Figure 3(a)] in response to the enzyme penicillin-G-amidase (PGA), while the second repeating unit releases a colored reporter molecule in a subsequent post-depolymerization reaction.[18] Ultimately, these two examples demonstrate that, with appropriate designs, the repeating units can serve secondary functions beyond forming covalent bonds within the polymer backbone.

Amplification in Paper-Based Microfluidic Devices. The unique attributes of CD_r polymers also can be used in a non-spectroscopic diagnostic application. Rather than relying on the production of colored or fluorescent products upon depolymerization, this second strategy relies on the designed change in hydrophobicity of a CD_r polymer once it depolymerizes (i.e., a hydrophobic polymer converts to hydrophilic small molecules).[46,57,58] For example, certain types of depolymerizable poly(benzyl carbamates) are hydrophobic relative to wet paper, and therefore can be used as analyte-responsive switches when incorporated into three-dimensional paper-based microfluidic devices [Figure 3(c)].[46,57,58] In this scenario, inclusion of a hydrophobic poly(benzyl carbamate) CD_r polymer into a hydrophilic region of paper causes a decrease in flow rate as an aqueous sample wicks through the region. In the presence of a specific analyte, however, the polymer depolymerizes and converts to hydrophilic small molecules. Consequently, the region of paper that contains the CD_r polymer switches wetting properties from hydrophobic to hydrophilic, which allows the sample to wick through the hydrophilic paper with a rate that depends on the concentration of the analyte. This difference in wicking rate means that different samples reach the end of a hydrophilic region of paper at different times, which provides the readout for an assay. This time-based approach has been used to create quantitative assays for small molecules (e.g., H_2O_2),[46] enzymes,[57] and inorganic ions (Pb^{2+} and Hg^{2+}; 1 ppb detection limits).[58] In each case, the analyte-induced depolymerization reaction provides both selectivity and sensitivity to the assay. In fact, the level of sensitivity that is possible using this strategy is striking, particularly as poly(benzyl carbamates) with only eight repeating units are needed to achieve femtomolar detection limits for enzymes (the limit of detection is dependent on chain length[46]), with assay times under 30 min.[57]

Encapsulation

CD_r polymers have been used in a number of contexts other than diagnostics, one of which is nano and micron-scale capsules for controlled release applications (Figure 4).[15,21,54–56] In this context, CD_r polymers offer not only a unique mechanism for release of the encapsulated contents (via continuous end-to-end depolymerization of the polymers that make up the capsule walls), but they also provide a level of selectivity and tunability (via the reaction-based detection units) that is difficult to achieve using other types of polymers.[12] These two attributes of selectivity and sensitivity, in principle, should provide capsules with the ability to release their contents in response to trace levels of specific applied signals.

To date, five capsules have been reported using three different CD_r polymers: one based on poly(phthalaldehyde),[55] two using poly(benzyl carbamates),[21,54] and two more using polymers that alternate between cyclization and quinone methide elimination reactions[15,56] [Figure 4(a)]. The resulting capsules range in size (from ~150 μm-diameter[55] to 150 nm-diameter[56]) and physical structure (i.e., core–shell microcapsules[21,55] to polymersomes[54] to micellar aggregates[15]). For the most part, the capsules have in common the ability to respond to select stimuli and release their contents,[§§] but the rates of release differ dramatically between the examples and do not always correlate logically with the solution-phase rates of depolymerization of the parent polymers [Figure 4(a)].[¶¶] Moreover, the rates of release likely depend substantially on the polarity of the surrounding medium,[14] the polarity within the capsule wall, the concentration (or intensity) of the applied signal, the thickness of the capsule wall,[55] and the length of the polymer that is used to create the wall.[55] Consequently, the capsules are difficult to compare quantitatively. The current capsules do, however, demonstrate the feasibility of encapsulation using CD_r polymers.

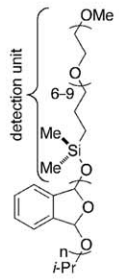
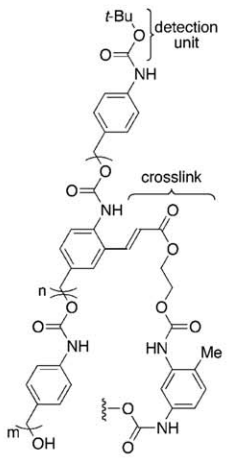
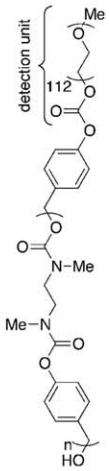
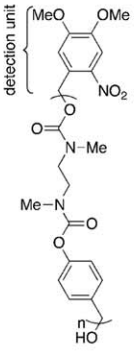
As these studies move forward, more information must be obtained about the behavior of the polymers and the capsules before the advantages of these capsules can be realized fully. For example, a better understanding of the effects of depolymerization on the morphology of a capsule wall is necessary to improve the design and response properties of the capsules, and to control how well the capsules balance mechanical stability with a desired rate of release. Currently, signal-induced morphological changes have been imaged clearly in only two examples of micron-scale capsules, both before and after exposure to a desired stimulus [Figure 4(b−e)].[21,55] These two capsules are made from different polymers [Figure 4(a)], and reveal substantially different changes in surface structure when exposed to the stimulus. In one case [Figure 4(b,c)], the capsules develop pinholes to release the encapsulated contents,[55] whereas in the other case [Figure 4(d,e)], the capsules shrivel and/or crack.[21]

As further comparisons are made to relate changes in surface structure and depolymerization, it also will become increasingly important (from a basic science perspective) to identify specific factors that contribute to wall rupture, including whether depolymerization plays a dominant or secondary role. Factors that may affect wall rupture include (i) swelling of the polymer, (ii) changes in the solubility and wettability of a polymer after

[§§]The exception is the micellar aggregate,[15] which, in its current form, lacks a reaction-based detection unit that allows it to respond to signals other than water.

[¶¶]It is unlikely that direct correlations between solution-phase depolymerization rates and rates of release will be observed due to two factors: (i) differences in the polarity of the environment in which a polymer depolymerizes between solution phase and a solid-state capsule; and (ii) contributions from mechanisms other than depolymerization that may give rise to release of the contents of the capsule.

(a)

	polymer	 (ref 55)	 (ref 21)	 (ref 15)	 (ref 56)
characterization of the polymers	M_n (kDa)	54	17[b]	29	38
	number of repeating units	400	93	89	146
	initiating signal	F^-	H^+	H_2O	350 nm light
	solvent	63:1 THF-aqueous buffer (pH 7.1)	1:1 TFA-CH_2Cl_2	D_2O, 37 °C	4:3 acetone-buffer (pH 7.4)
	time to complete depolymerization of the polymer (h)	5	no available data[c]	650	600
characterization of the particles	type of particle	core-shell microcapsule	core-shell microcapsule	micellar aggregates	polymeric nanoparticle
	method of fabrication	double-emulsion microfluidic flow focusing with solvent evaporation	emulsification polymerization	coacervation	internal phase separation with solvent evaporation
	average diameter of the particles (μm)	155	5 to 40	<0.1 to 0.3	0.151
	thickness of the shell wall (nm)	tunable from 100 to 1800	no available data	not applicable	no available data
	initiating signal	50 mM F^-	acid[b] (4 M HCl)	H_2O	350 nm light
	solvent	aqueous buffer (pH 7.1) with 17% THF and 2.5% EtOAc	10% EtOH in aqueous HCl	H_2O (pH 7.4)	3:4 buffer (pH 7.4)-MeCN
	time to 50% release of the encapsulated contents (h)	62[a]	~15	24	0.08

[a]The shell wall thickness was 1800 nm.
[b]This polymer responds to acid, but a second polymer (and the corresponding microcapsule) was also demonstrated to respond to base (ref 21).
[c]The polymer depolymerizes, but insufficient data is available to estimate the time required to reach complete depolymerization.

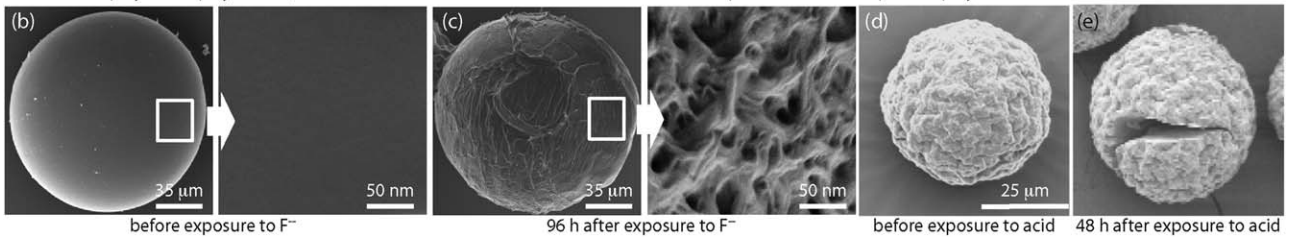


Figure 4. Examples of four of the five stimuli-responsive capsules made from CD_r polymers. The excluded example is a polymersome that was made using a poly(benzyl carbamate).[54] This example was published during the proofs stage of this review, and therefore details of this polymersome can be found in Ref. 54. (a) Comparisons of four capsules made using three different CD_r polymers.[15,21,55,56] Two of the capsules were imaged before and after exposure to their respective stimuli (b−e). The capsules in (b) and (c) were made using fluoride-responsive PPA, where (b) shows SEM images of the capsules before exposure to fluoride, and (c) shows the capsules 96 h after exposure.[55] The capsules in (d) and (e) were made using cross-linked poly (benzyl carbamates), where (d) shows the capsule before exposure to acid, and (e) shows the capsule 48 h after exposure.[21] (Portions of this figure are reproduced from Refs. 21 and 55 with permission from the American Chemical Society.)

cleavage of the reaction-based detection unit (this is a particularly important consideration when oligomers are used instead of polymers), (iii) background degradation of the polymer, and, of course, (iv) depolymerization. In the existing examples, a combination of factors may lead to release of the encapsulated contents, thus depolymerization may not be acting alone. With these caveats, however, the first examples of CD_r polymer-based capsules are encouraging, particularly when viewed in light of the envisaged attributes of such capsules.[12]

Materials that Remodel Themselves

Most types of smart materials (e.g., shape memory materials[73] or hydrogels[74]) are capable of switching between physical conformations or states (typically two states[73]), whereas CD_r polymers should enable smart materials that remodel themselves multiple times depending on the number of polymer/reaction-based detection unit pairs that are incorporated into the material.*** More specifically, it should be possible to use a single CD_r polymer to build a material, but to vary the reaction-based detection units that are attached to the CD_r polymer in different locations of the material. In this situation, the backbones of the polymers are identical in composition; the only difference between portions of the material is the reaction-based detection unit. This arrangement enables portions of a material to respond via depolymerization to one signal, while another section of the material could respond to a different signal. The different sections of the material, however, would seamlessly blend with one another, as the identical polymer backbones will preclude phase segregation of the polymers.

Shape-Changing Materials. This ability to selectively depolymerize one portion of a material over another should be useful in a variety of fabrication processes, including for creating porous materials.[75,76†††] It also should be useful in settings where the plastic must change shape or surface properties to enable a new function.[50] A conceptual form of this latter behavior is depicted in Figure 5(a), in which a macroscopic piece of patterned plastic responds to fluoride and changes its shape from a rectangular piece of plastic to a rectangular piece of plastic that contains a circular hole [Figure 5(b,c)].[50] The plastic is made from two different versions of PPA that differ only in the reaction-based detection unit. In this example, the change in shape does not lead to a change in function, but it does illustrate the potential for creating macroscopic shape-shifting plastics using CD_r polymers that differ only in the composition of the reaction-based detection unit.

Vanishing Plastics. Similarly, CD_r polymers enable "vanishing" plastics in which the plastic converts to small molecules only

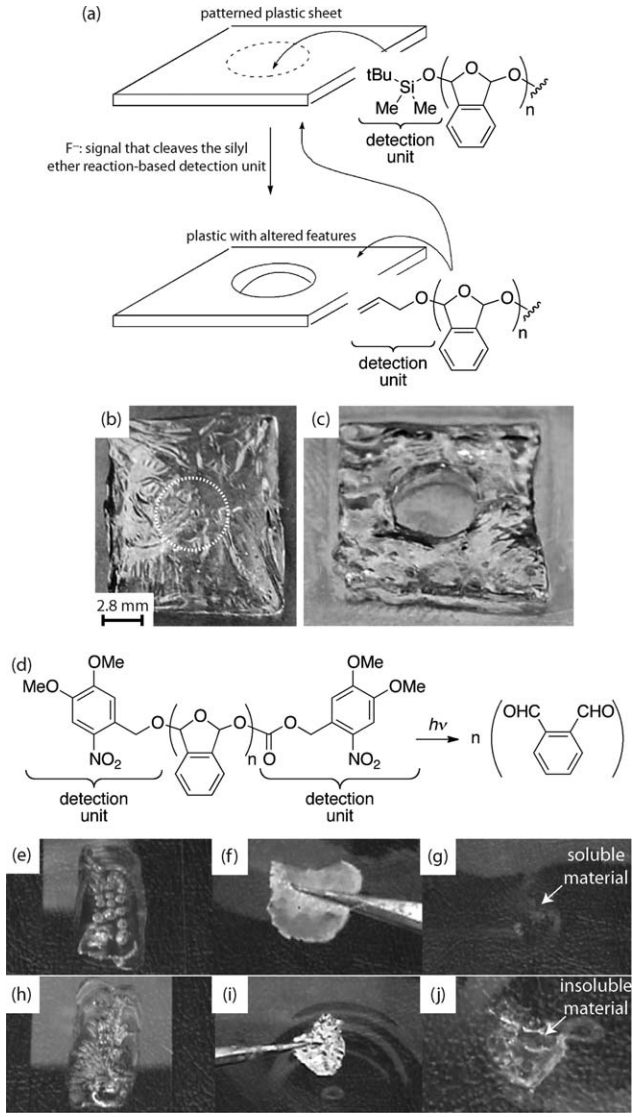


Figure 5. Shaping-shifting[50] and vanishing plastics[51] made from CD_r polymers. (a) Schematic of a pre-patterned macroscopic piece of plastic made from two versions of PPA that differ only in the composition of the detection unit. One detection unit responds to fluoride, while the other does not, which gives rise to a change in shape of the plastic when exposed to fluoride.[50] (b) Image of the patterned plastic before and (c) 15 min after exposure to fluoride in 20 : 6 : 3 EtOAc–phosphate buffer (pH 7.1)–THF. The dotted line in (b) indicates the approximate location of fluoride-responsive PPA. (d) PPA that contains light-responsive detection units on both ends of the polymer.[51] (e) A film of this polymer was exposed to broad-spectrum UV light (250–600 nm) for 10 min, which yielded a yellow material (f) that is the same color as the 1,2-benzenedicarboxaldehyde monomer.[51] (g) This yellow material was readily soluble in ethyl acetate, whereas the polymer is not. For comparison, the monomer is soluble in ethyl acetate. (h–j) A control PPA polymer that lacks UV-responsive detection units was used in a similar sequence of experiments, yielding a colorless (i) and insoluble (j) material after exposure to UV light.[51] (Portions of this figure are reproduced from Refs. 50 and 52 with permission from the American Chemical Society.)

***Remodeling using CD_r polymers is not currently reversible, whereas shape memory materials and other types of materials that switch states often are reversible.

†††Poly(lactic acid) has been used as a sacrificial material to create microporous structures in poly(dimethyl siloxane).[75,76] In this case, the poly(lactic acid) degrades via thermal processes in the presence of a Lewis acid rather than reaction of a reaction-based detection unit with a specific signal (the polymer lacks a reaction-based detection unit). The concept of using depolymerization to create three-dimensional materials with interesting architectures is applicable to future applications of CD_r polymers.

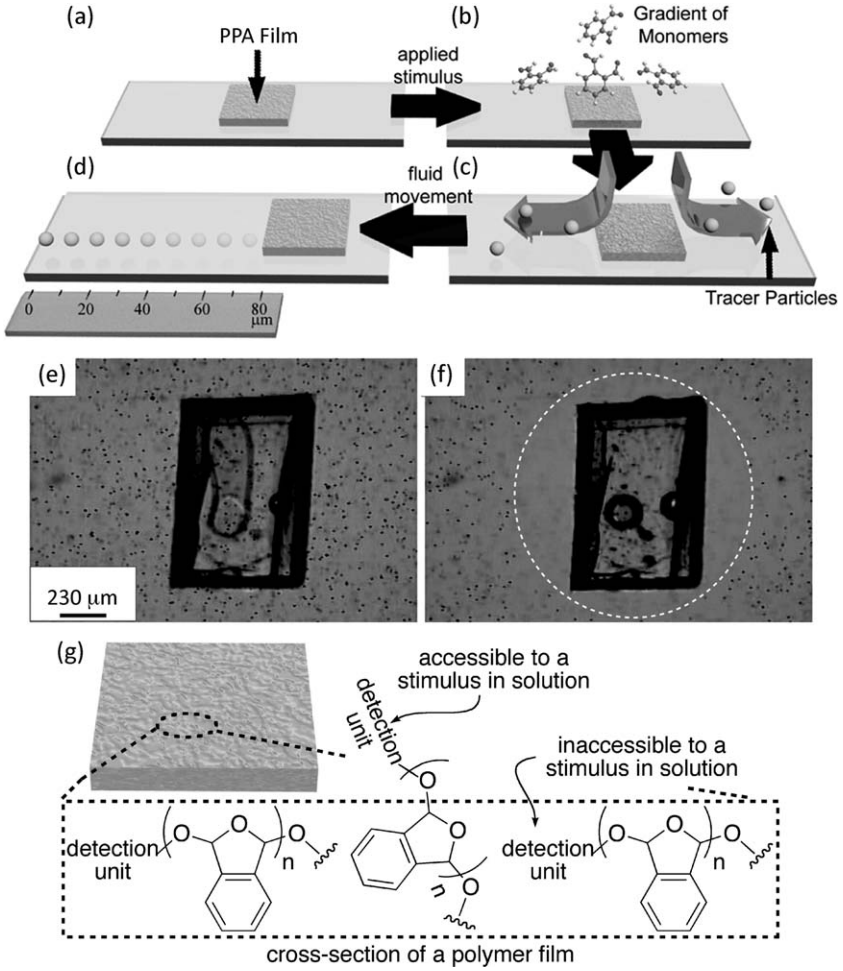


Figure 6. Non-mechanical plastic pumps made from films of PPA, where the polymer contains a reaction-based detection unit that is specific for a signal in solution.[52,53] (a)−(d) Graphical representation of the operation and characterization of the PPA pump.[53] (a) A PPA film (gray square) on a glass slide (light gray rectangle) is immersed in a solution that contains the stimulus. (b) Reaction of the stimulus with the detection units at the solid–liquid interface between the PPA film and the surrounding solution leads to surface polymerization, predominantly on the top of the film. (c) The surrounding fluid moves from above the film towards the film, and then away, as indicated by the curved arrows. Poly(styrene) tracer particles (6 μm diameter spheres) are used to track the speed of the fluid, which is measured as depicted in (d). (e, f) Photographs of a PPA film that responds to fluoride: (e) before and (f) ~17 min after exposure to 0.1*M* fluoride in water.[52] The black dots are the poly(styrene) tracer particles and the white dotted line in (f) depicts the approximate boundary of an exclusion zone that is created as a result of the signal-induced pumping. (g) A film made from a CD_r polymer that depicts the issue of accessibility of the detection unit at solid–liquid or solid–gas interfaces.[53] (Portions of this figure are reproduced from Refs. 53 and 52 with permission from the American Chemical Society and John Wiley & Sons, respectively.)

when exposed to a specific signal.[51] This type of plastic could be useful in a variety of scenarios, including attempts to minimize the accumulation of plastic waste in the environment.[77] Figure 5 illustrates this capability using PPA that is modified with a UV light-responsive reaction-based detection unit [Figure 5(d)].[51] In this scenario, a PPA plastic film on a glass slide [Figure 5(e)] is exposed to UV light, which causes the plastic to turn yellow (the color of the dialdehyde monomer) [Figure 5(f)]. The remaining material is soluble in ethyl acetate (the monomer is soluble in ethyl acetate, while the polymer is not) [Figure 5(g)]. A control polymer [PPA with an end-cap that does not respond to UV light; Figure 5(h−j)] does not turn yellow when exposed to UV light [Figure 5(i)], and remains insoluble in ethyl acetate [Figure 5(j)], demonstrating that the photochemically induced depolymerization reaction is selective for PPA that contains an appropriate reaction-based detection unit.

Materials that Remodel Their Environment

The capabilities of materials made from CD_r polymers are not limited to materials that remodel themselves; materials that remodel (or alter) their surroundings are possible as well.

Non-Mechanical Pumps. Typically, this remodeling of the environment occurs through the action of the products of depolymerization, as illustrated in the first example in Figure 6(a−d).[52,53] In this example, films made from poly(phthalaldehyde) CD_r polymers operate as non-mechanical pumps[78,79]

when immersed in a solution and exposed to a specific stimulus [Figure 6(a−d)].[52,53] The stimulus cleaves reaction-based detection units that are located predominantly on the surface of the film, which gives rise to surface depolymerization. The resulting 1,2-benzenedicarboxaldehyde monomers create a concentration gradient near the surface of the film, which causes the water above the film to move down towards the film and then radially away. In effect, the selective depolymerization reaction induces the movement of the surrounding fluid, hence the analogy to a pump. The consequence of the signal-induced pumping is that the film creates an exclusion zone [Figure 6(e,f)] by pumping away 6 μm-diameter poly(styrene) tracer particles, which are used as markers for measuring pumping speeds.[52] As might be expected, the CD_r polymer-based pumps move the surrounding fluid with speeds that depend on the concentration of the applied signal,[52,53] but they also are likely dependent on the rate of depolymerization of the CD_r polymer.

An important feature that affects the pumping speed is the accessibility of the reaction-based detection units to the signals in the surrounding solution [Figure 6(g)].[53] In fact, this issue of accessibility of the detection unit at the solid–liquid interface likely is critical in most solid-state materials made from CD_r polymers. A recent demonstration highlights this point: by tuning the length of CD_r polymers as well as the polarity of the reaction-based detection unit, it is possible to substantially alter the accessibility of the detection unit at the solid−liquid interface in CD_r polymer pumps as well as the corresponding pumping speed when the pumps are exposed to a specific stimulus.[53] Shorter CD_r polymers increase the density of the detection unit per area of polymer film (and, hence, increase the pumping speed), while polar detection units favor arrangement of the detection units at the solid–water interface rather than being buried in the hydrophobic film.[53]

Selective Labeling of Proteins. The products of depolymerization can be used in other ways to modify their environment as well. An example is the purposeful alkylation of nucleophilic residues on the surface of an enzyme that initiates depolymerization of a water-soluble CD_r polymer (Figure 7).[59] In this case, the polymer contains a reaction-based detection unit that is a substrate for a target enzyme. In the presence of the enzyme, the reaction-based detection unit is cleaved, and the polymer depolymerizes to reveal electrophilic azaquinone methides.[80] These azaquinone methides alkylate residues on the enzyme, thus leading to selective fluorescent labeling of the enzyme that initiated the depolymerization reaction (Figure 7).[59]

Additional Comments. These two examples (pumps and fluorescent labels) demonstrate only a fraction of possible scenarios for how a CD_r polymer (or a material made from a CD_r polymer) may be capable of modifying its surroundings. Clever designs of repeating units will lead to new types of functional small molecules upon depolymerization, which ultimately will give rise to new classes of stimuli-responsive materials. In comparison, the vast majority of current stimuli-responsive materials (in general) are designed to alter themselves but to have little effect on their surroundings,[7,8] so this dual capability of CD_r polymer-based materials to alter themselves and their surroundings is a unique and underdeveloped attribute of this class of polymers.

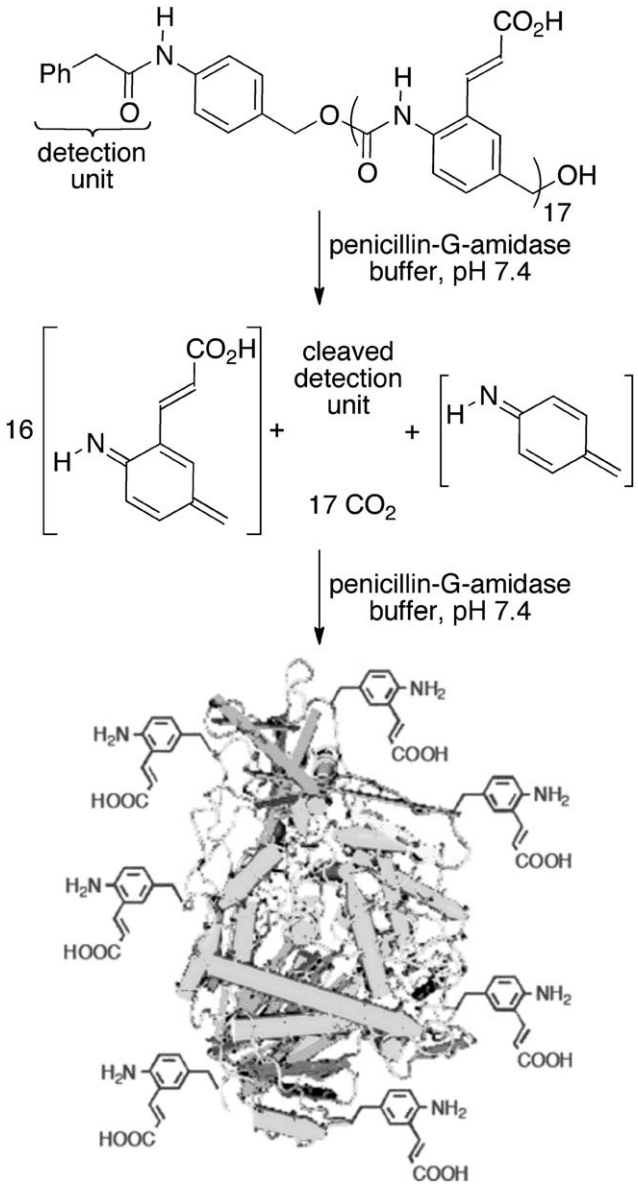


Figure 7. An example of a CD_r polymer that covalently modifies an enzyme after the enzyme reacts with the detection unit on the polymer.[59] In this case, the azaquinone methide products of depolymerization are electrophilic, and thus react with nucleophilic functionality on the enzyme that induces depolymerization. The products of this labeling reaction are fluorescent, resulting in a fluorescent enzyme. Moreover, the labeling reaction shows selectivity for the target enzyme over other proteins in solution. (A portion of this figure is reproduced from Ref. 59, with permission from the American Chemical Society.)

CONCLUSIONS AND FUTURE DIRECTIONS

CD_r polymers are an emerging class of linear polymers that selectively respond to specific applied signals by depolymerizing continuously and completely from end-to-end. This depolymerization reaction provides an amplified response, either by changing the properties of a material, or by changing the

surrounding environment, or, sometimes, by doing both. These types of response properties are in contrast to traditional polymers, which are designed to be robust and to last indefinitely. As such, CD_r polymers may be uniquely useful in creating the new types of dynamic, stimuli-responsive, smart materials that are needed as we move into an era in which we demand more from plastics than simply serving as a static object.

ACKNOWLEDGMENTS

The authors' work in this area currently is supported by NSF (CHE-1150969), and, in part, by the Semiconductor Research Corporation and the Defense Threat Reduction Agency (HDTRA1–13-1–0039). The authors thank Gregory G. Lewis for assistance with creating images for Figure 3.

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