# Controlled Depolymerization: Stimuli-Responsive Self-Immolative Polymers

Gregory I. Peterson,[†] Michael B. Larsen,[†] and Andrew J. Boydston*

Department of Chemistry, University of Washington, Box 351700, Seattle, Washington 98195-1700, United States

ABSTRACT: Self-immolative polymers (SIPs) are unique macromolecules that are able to react to multiple types of environmental influences by giving amplified response outputs. When triggering moieties installed at SIP chain ends are activated by their corresponding stimuli, a spontaneous head-to-tail depolymerization ensues, often involving multitopic release of small molecules. SIP designs have evolved a high degree of modularity in each of their functional components, enabling a broad range of utility and applications-driven tuning. In this Perspective, we summarize and discuss recent progress in this nascent area of research, including (i) synthesis of different types of SIPs, (ii) design and evaluation of triggering moieties, (iii) depolymerization mechanisms and kinetics, (iv) applications of SIPs, and (v) outlook and challenges facing the field.
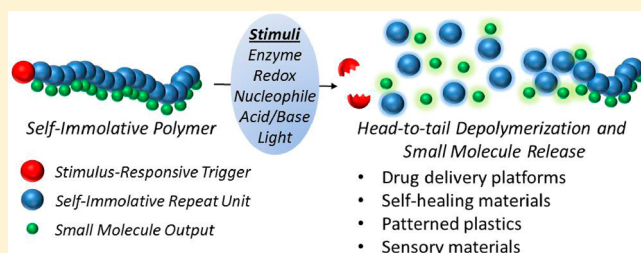
1. INTRODUCTION

Recent advances in the area of self-immolative polymers (SIPs) have drawn considerable attention toward the controlled deconstruction of macromolecular architectures. Excitement stems largely from the broad-reaching applications conceivable from these stimuli-responsive materials. A typical SIP ensemble comprises a kinetically stable polymer and a dormant chain end which responds to stimulus by triggering a head-to-tail depolymerization of the polymer main chain. The general design concept can be incorporated into complementary macromolecular structures, such as linear polymers and dendrimers, and adapted to facilitate release of small molecules pendant to the SIP main chain (Figure 1). The combination of selective and sensitive environmental responsiveness, spontaneous signal amplification, and diverse types of signal output has made SIPs an attractive and versatile new tool for applications-oriented research.

The origins of self-immolative macromolecules can be traced back to their small-molecule predecessors. In 1981, Katzenellenbogen developed a self-immolative "spacer" flanked by a triggering moiety and an "output" molecule (Figure 1A).[1] Many small-molecule variants have followed, and these developments have interlaced with evolving macromolecular designs to create a diverse assortment of self-immolative ensembles capable of selectively responding to myriad environmental influences. Transitioning from small molecules to oligomers, Scheeren and co-workers linked multiple spacers together in an iterative fashion and demonstrated a cascade of eliminations to release drug molecules from the terminus of the self-immolative scaffold (Figure 1B).[2] This idea was further expanded by three groups in 2003[3−5] with the development of self-immolative dendrimers comprising repeating branched self-immolative spacers (Figure 1C, representative example shown).[6] Since then, extensive research has been devoted to

the development of new self-immolative dendritic structures, with their linear counterparts (SIPs) only recently entering the scene. Much of the work toward self-immolative dendrimers,[7,8] SIPs,[9,10] or both[11−13] has been discussed in recent reviews.

Self-immolative polymers were developed by Shabat in 2008 and directly addressed challenges associated with dendritic analogues, specifically their time-consuming stepwise synthesis and steric limitations on the empirical number of output molecules they could possess.[14] In comparison, SIPs can be prepared via one-pot syntheses and can contain a number of output molecules that surpasses that of reported self-immolative dendritic structures (Figure 1D).[15] Within the context of this Perspective, we define a self-immolative polymer as having a linearly depolymerizing main chain of greater than 10 repeat units, although examples have been drawn from other self-immolative structures as well. While only recently established and their full potential yet unrealized, SIPs have already shown inspiring characteristics for multiple applications including sensory materials, drug releasing platforms, self-healing composites, and lithographic plastics. Herein, we offer an overview and assessment of SIPs, including their syntheses, triggers, depolymerization profiles, and applications.

2. SYNTHESIS OF SELF-IMMOLATIVE POLYMERS

2.1. SIPs from Condensation Polymerizations. Prior to the development of a true polymerization to achieve self-immolative polymers, discrete oligomers comprising linearly arranged self-immolative units were prepared by stepwise syntheses.[2,4,16] Oligomeric polyurethanes have been prepared
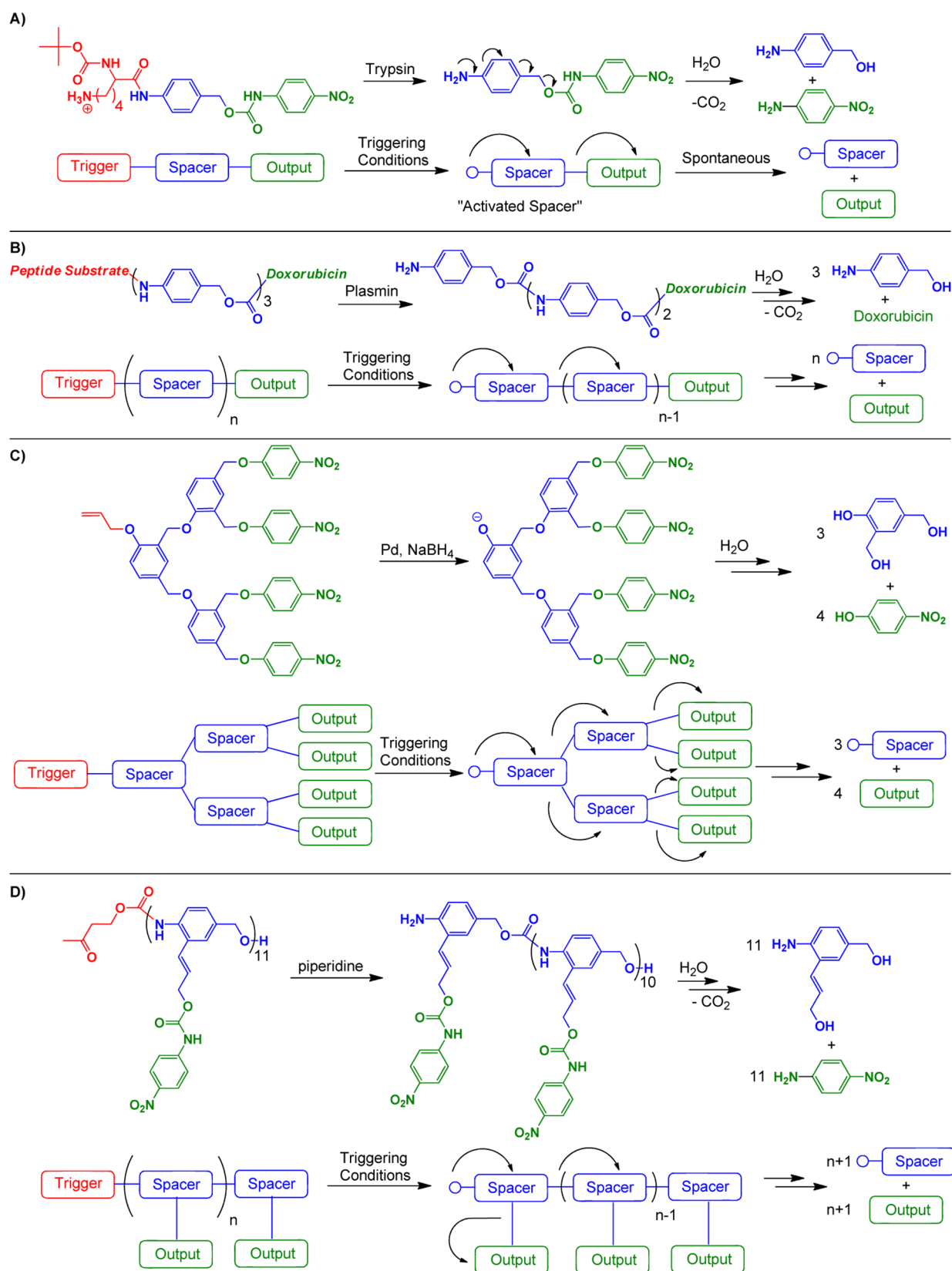
Figure 1. Specific examples and general models of a self-immolative (A) spacer, (B) oligomer/polymer, (C) G2 dendrimer, and (D) polymer with self-immolative side chains. Reproduced with permission from ref 15. Copyright 2008 Wiley-VCH Verlag GmbH & Co. KGaA.

by activation of a benzyl alcohol chain end via installation of a nitrophenyl carbonate and subsequent coupling with amino-benzyl alcohols to extend the chain by one repeat unit (Scheme 1A).[2] This method requires long reaction times and chromato-graphic separation for each step but is useful for synthesizing well-defined oligomers with three or fewer repeat units.

Scheme 1. Stepwise Synthesis of Self-Immolative Oligomeric Structures Comprised of (A) Urethane and (B) Benzyl Phenyl Ether Linkages[a] (Reproduced with Permission from Ref 18. Copyright 2012 The Royal Society of Chemistry)
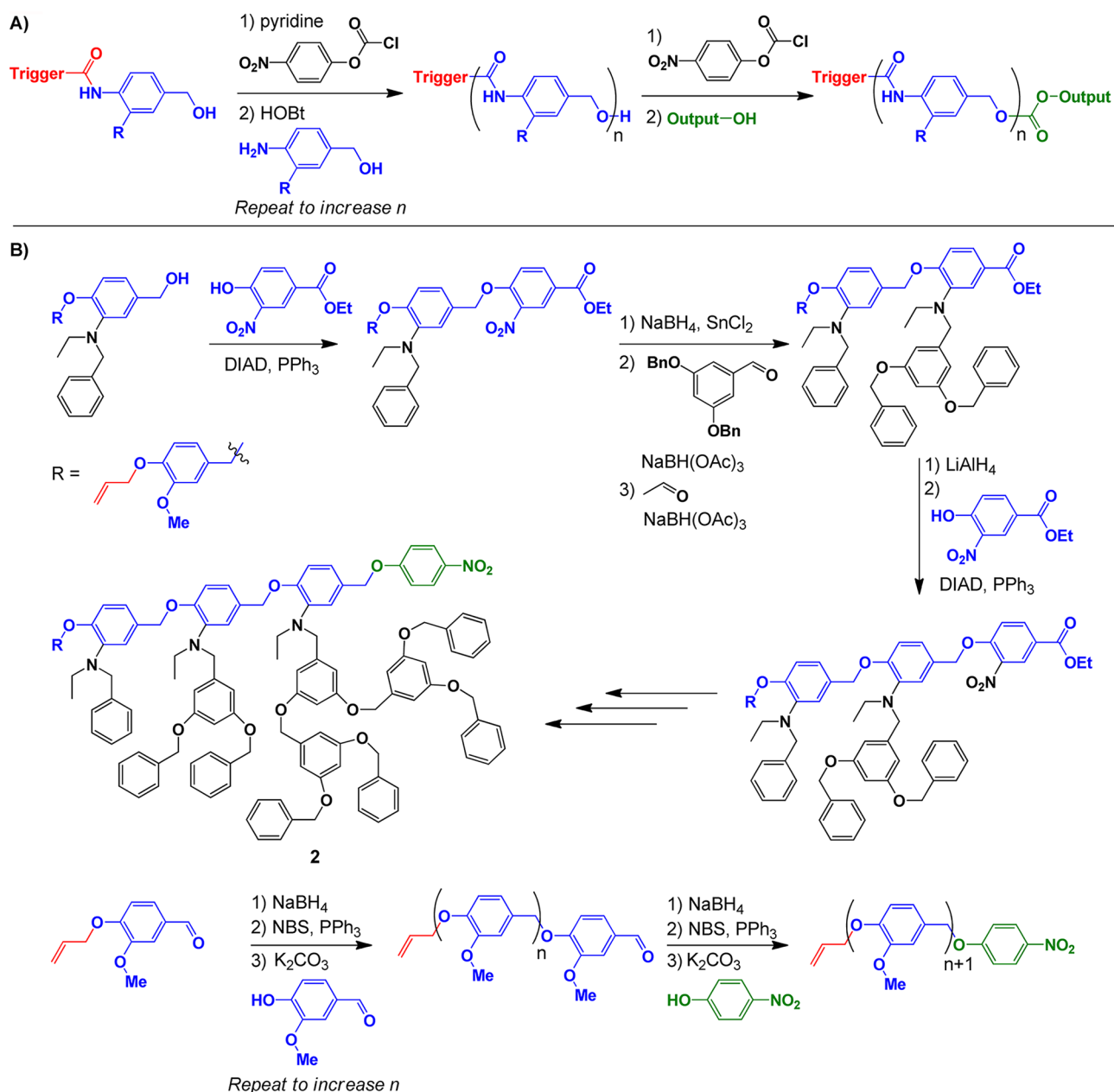
[a]The DP of oligomers is equal to the number of times the chain extension cycle is conducted.

Similarly, oligomers containing benzyl phenyl ether linkages prepared by Mitsunobu couplings[17] or S_N2 reactions of phenoxides and benzyl halides[4,18] have been reported (Scheme 1B) and provide access to self-immolative structures that do not require decarboxylation during depolymerization.

As a more direct route to SIPs, Shabat developed a one-pot Sn(IV)-catalyzed polymerization of "blocked isocyanates", yielding polyurethanes with degrees of polymerization (DPs) reaching ca. 20 within 15 min at 110 °C (Scheme 2A).[14] This polymerization was shown to be successful with monomer 1 as well as with monomers containing functionalized side chains, which renders the polymer capable of releasing small molecules from the side chain during depolymerization (monomer 2)[15] or displaying a "turn-on" response by imparting fluorogenic properties to the repeat units upon depolymerization

(monomer 3).[14] It has also been shown that after polymerization the esters on the side chains of monomer 3 can be converted to carboxylic acids to increase the water solubility of the polymer.[14,15,19] Trigger installation was accomplished by adding a nucleophilic alcohol or amine to the reaction mixture after polymerization had ensued. The end-capping agent was found to react selectively with the phenyl carbamate chain end to cease polymerization and install functional groups bearing reactivities specific to triggering depolymerization at a later time.

Complementary to benzyl alcohol-based SIP main chains, Gillies has achieved condensation polymerizations of carbamate- and thiocarbamate-based monomers for the production of two different classes of SIPs (Scheme 2B).[20,21] For the synthesis of each, AB-type monomers were prepared that

Scheme 2. Synthesis of (A) Polyurethanes and (B) Cyclization Elimination SIPs that are Prepared by Condensation Polymerizations (Reproduced with Permission from Ref 21. Copyright 2010 Wiley Periodicals, Inc.)
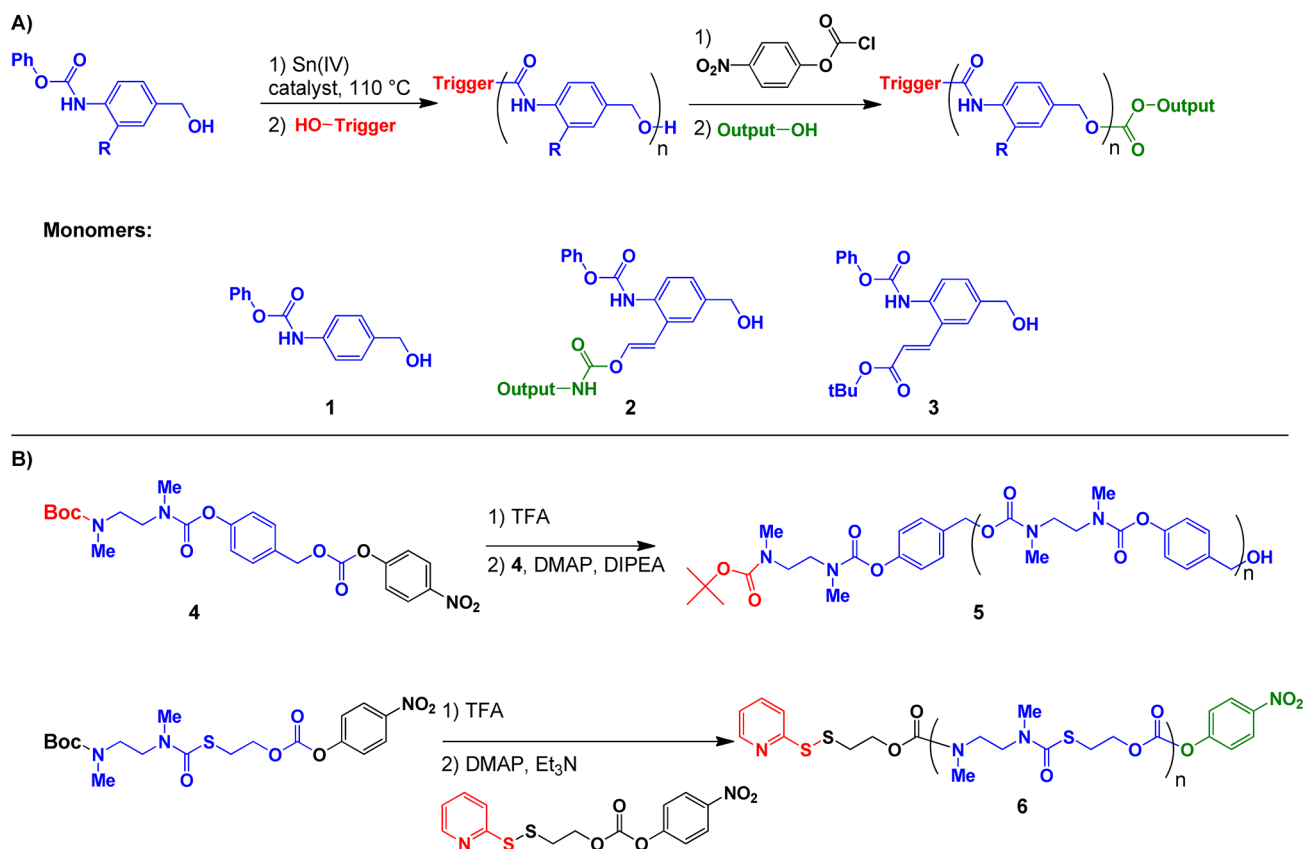
featured an electrophilic *p*-nitrophenyl carbonate end group and a Boc-protected amine at opposite termini. To avoid coupling of the end groups during and after deprotection, the amine was maintained as the protonated ammonium salt. Then, upon addition of DMAP and Et$_3$N, polymers were obtained with M_n values ranging from 1.8 to 17 kDa. Triggering moieties were incorporated at the polymer chain ends by conducting the polymerizations in the presence of a small amount of protected monomer. In this way, the same protecting group used to prepare the monomers also functioned as the triggering moiety, though this is not expected to be an inherent requirement and other triggers could likely be incorporated. The nitrophenyl end group was hydrolyzed from polymer **5** during the workup but was retained in polymer **6** as a usable reporter molecule for monitoring depolymerization (see section 5.1). Conceivably, the polymer terminus could be modified for application-specific outputs, and the aryl groups of the benzyl alcohol repeat units could be functionalized to facilitate side-chain release.

2.2. SIPs from Addition Polymerizations. To our knowledge, poly(phthalaldehyde) (PPA) is the only reported SIP that can be prepared via addition polymerization. This has been achieved by anionic and cationic polymerizations of 1,2-benzenedicarboxaldehyde.[22,23] The polymerization requires low temperatures, as the ceiling temperature of the polymer is −40 °C. PPA produced via cationic polymerization was found to be thermally stable up to 150 °C in the solid state, whereas the product of anionic polymerization reverts almost instantaneously after isolation of the polymer if the end groups are not capped.[24] Polymerizations typically required 10−14 days and yielded polymers with molecular weights ranging from

20 to 30 kDa with PDIs of 1.1−1.3 (Scheme 3A).[25] With addition of catalyst **7**, the reaction time was decreased to 2 h and yielded polymers with molecular weights of 70 kDa and PDIs of 1.6 (Scheme 3B).[26] While PPA has traditionally been depolymerized by acid-catalyzed hydrolysis initiated at random sites within the polymer main chain,[27] Phillips has developed end groups with functionalities that allow for selective triggering of head-to-tail depolymerization (see section 4.3).[25,28]

3. STIMULI-RESPONSIVE TRIGGERS

Designing SIP triggers to be selectively responsive to specific stimuli enables chemists to utilize the general function of SIPs to address diverse applications. Multiple trigger designs have been reported, with key examples described in Table 1. Although not all of the triggers presented have been used in linear polymeric systems, the modular nature of the triggering component should facilitate incorporation of triggers reported for oligomeric or dendritic structures into linear SIPs. The primary reactivity observed for essentially all known triggering moieties is the unmasking of an electron-rich functional group in response to a specific stimulus that is compatible with the SIP main chain and output units. In many cases, cleavage of the triggering group liberates a carbamate or carbonate which undergoes subsequent decarboxylation to reveal an amine or hydroxyl group, respectively (entries 2, 4, 14−16, and 18). Alternatively, some systems achieve direct conversion of the trigger into an electron-donating moiety without an intermediate decarboxylation step (entries 1, 3, and 5−13). Currently, there are ~20 distinct trigger/stimulus combinations

Scheme 3. Anionic Polymerization of Phthalaldehyde and Capping of the Resulting Polymer (A) without a Catalyst and (B) with a Phosphazene Catalyst
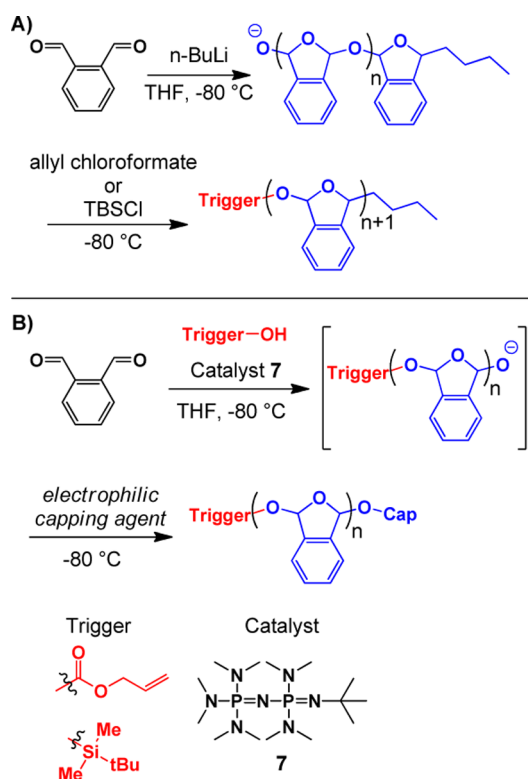
that have been reported, and they can be conveniently grouped according to the type of stimulus required for their activation. These classes consist of enzyme, redox, nucleophile, acid/base, and photomediated cleavage.

3.1. Enzyme-Mediated Cleavage. Enzymatic substrates (Table 1, entries 1−6) were the first reported triggers in systems capable of multiple elimination events.[2] Research in this area is strongly motivated by the potential applications of SIPs in biological systems. Triggering by biological agents that are native (entries 1, 5, and 6)[2,29,30] or foreign (entries 2−4)[14,15,19,31−41] to human physiology has been achieved. Using linear SIPs, Shabat identified the enzymatic triggering event as rate-determining in the overall process of SIP depolymerization involving bovine serum albumin (BSA) as the triggering enzyme. For these studies, concentrations of 1.0 mg/mL were used in solutions buffered at pH = 7.4.[14] For comparison, typical serum albumin concentrations in human physiology range from 0.3 to 0.5 mg/mL.[42] Although studies involving more complex biological systems may require additional SIP design optimization, foreign and unnatural biological triggering agents have each been demonstrated in successful *in vitro* studies.[2,29−32,34] The wealth of kinetic information on enzyme-mediated cleavage makes enzyme-triggered SIPs attractive targets for applications in which fine-tuning of initiation kinetics or highly specific triggering events are required.

3.2. Redox-Mediated Cleavage. The ease of installation and activation of redox-mediated triggers facilitated their early introduction into self-immolative scaffolds. Spanning small to macromolecular systems, examples of redox triggers include transition metal-mediated reductions (Table 1, entries 7 and 8),[3,4,6,16−18,25,43] reduction of disulfide linkages (entry 9),[21] and oxidation of boronates with peroxides (entries 10 and
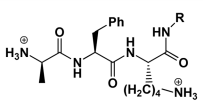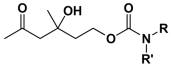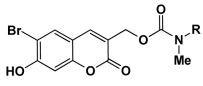
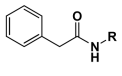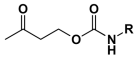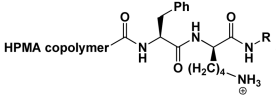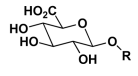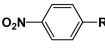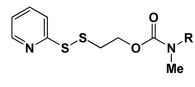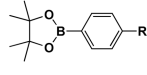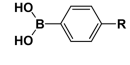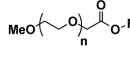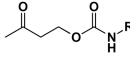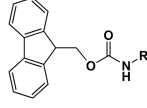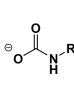11).[19,41,44−49] For example, Phillips adapted the aryl allyl ether utilized in dendritic and oligomeric systems (entry 8) for use in linear polymers by installing an allyl carbonate triggering group at the head of a phthalaldehyde-based SIP (see section 2.2).[25] Upon exposure to a Pd[0] source, the allyl fragment was removed and subsequent decarboxylation revealed a hemiacetal, thereby commencing the depolymerization process. Disulfides have also been developed as reductive triggers for SIPs having DPs of ∼35 (M_w ∼3.0 kDa) and offer the potential for biologically relevant redox triggering (entry 9). As depicted in Scheme 2B, Gillies incorporated disulfide end groups which were found to be activated in response to dithiothreitol. The disulfide linkage is especially attractive for biological applications as it holds promise for activation under reducing intracellular environments.[50] The use of phenylboronates as triggers for SIPs introduced a platform for activation under oxidative conditions (entry 10). Shabat has demonstrated this class of trigger in dendritic systems (entry 11) to be responsive to hydrogen peroxide generated from either triacetone triperoxide[44] or enzymatic action[45,49] (see section 5.1). In each of these systems, conversion of the boronate moiety into an electron-releasing phenol leads to initiation of the self-immolative cascade.

3.3. Nucleophile-Mediated Cleavage. Although explored to a lesser extent in comparison with other triggering manifolds, nucleophilic attack can also serve to liberate electron-releasing functionalities (entries 12 and 13).[20,25,28,51] This is also an attractive option in cases in which the components of the SIP are not stable to aqueous conditions, as the use of tetrabutylammonium fluoride for silyl ether cleavage requires no adventitious water.[25,28] Water itself can also serve as a nucleophile to hydrolyze labile esters,[20] but this method has seen limited use as more specific trigger/stimulus pairs are often desired.

3.4. Acid/Base-Mediated Cleavage. Traditional acid- and base-sensitive protecting groups also provide a facile means of triggering SIPs (entries 14−16).[5,15,19,20,32,36,38,52,53] In particular, the fidelity and familiarity of Boc and Fmoc protecting groups have essentially established these functionalities as standards for comparison when developing new triggering moieties. Their reactivities are ideally suited to SIP applications, as each strongly diminishes the electron-donating ability of the amine. The reagents required to install and activate these triggers are inexpensive and readily available, and pH modulation is a simple process for on-demand triggering of SIPs. In a recent example, these triggers were featured in SIPs that were incorporated into advanced nanoscale materials capable of on-demand depolymerization of microcapsule shells (see section 5.3).[53]

3.5. Photomediated Cleavage. A particularly exciting advance in the field of SIPs is the development of triggers capable of remote activation. Photomediated cleavage of nitrobenzyl carbamates and bromocoumarins (entries 17 and 18)[5,18,54] requires only the appropriate wavelength and intensity of light to initiate the depolymerization process; in other words, no additional chemical reagents are required to activate the SIP. This type of remote activation is especially attractive for drug delivery applications, as i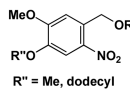t introduces the potential for spatiotemporal control of release profiles in a noninvasive manner.[55] Toward this end, Almutairi and co-workers developed linear polymers incorporating a light-sensitive *o*-nitrobenzyl carbamate (entry 17) or bromocoumarin trigger (entry 18). Upon exposure to the appropriate

Table 1. Triggers for SIPs, Grouped According to Triggering Class[a]

entry	trigger class	structure and response to stimulus	stimulus	SI platform (ref.)
1	E	(peptide structure with Ph, HN–R, H₃N⁺, (H₂C)₄–NH₃⁺) → H₂N–R	plasmin	oligomer (2)
2	E	(structure) → ⁻O–C(=O)–N(R')R	antibody 38C2	dendrimer (31, 32, 34)
3	E	(phenylacetamide structure) → H₂N–R	penicillin G amidase	dendrimer (33-38, 41) polymer (15, 19) oligomer (39, 40)
4	E	(carbamate structure) → ⁻O–C(=O)–N(H)R	bovine serum albumin, antibody 38C2	polymer (14, 19)
5	E	HPMA copolymer–(peptide, Ph, (H₂C)₄–NH₃⁺) → H₂N–R	cathepsin B	dendrimer (29)
6	E	(glucuronide structure, HO₂C, HO, OH, O–R) → HO–R	β-glucuronidase	dendrimer (30)
7	R	O₂N–⟨aryl⟩–R → H₂N–⟨aryl⟩–R	Zn/AcOH	dendrimer (3) oligomer (16)
8	R	(allyl)–O–R → ⁻O–R	Pd, Pd/NaBH₄	dendrimer (4, 6, 17, 43) polymer (25) oligomer (18)
9	R	(pyridyl disulfide–O–C(=O)–N(Me)R) → HS–CH₂CH₂–O–C(=O)–N(Me)R	dithiothreitol	polymer (21)
10	R	(pinacol boronate–aryl–R) → ⁻O–⟨aryl⟩–R	H₂O₂	dendrimer (41, 44) polymer (19) oligomer (48)
11	R	(HO)₂B–⟨aryl⟩–R → ⁻O–⟨aryl⟩–R	H₂O₂	dendrimer (45-47, 49)
12	N	tBu–Si(Me)₂–O–R → ⁻O–R	fluoride	dendrimer (51) polymer (25, 28)
13	N	MeO–(O)ₙ–C(=O)–O–R → HO–R	H₂O	polymer (20)
14	A	(tBu–O–C(=O)–N(R')R) → ⁻O–C(=O)–N(R')R	H⁺	dendrimer (5, 32,36, 38, 52) polymer (20, 53)
15	A	(ketone–O–C(=O)–N(H)R) → ⁻O–C(=O)–N(H)R	piperidine, morpholine	polymer (15, 19)
16	A	(fluorenylmethyl–O–C(=O)–N(H)R) → ⁻O–C(=O)–N(H)R	piperidine	polymer (53)
17	P	(MeO, R''O, NO₂ nitrobenzyl–OR; R'' = Me, dodecyl) → ⁻O–R	UV radiation	dendrimer (5) polymer (54) oligomer (18)
18	P	(Br, HO bromocoumarin–O–C(=O)–N(Me)R) → ⁻O–C(=O)–N(Me)R	NIR radiation	polymer (54)

[a]E = enzyme, R = redox, N = nucleophile, A = acid/base, and P = photo. R = self-immolative segment, R′ = H or Me.

wavelength of light, the photosensitive moiety was removed, triggering depolymerization and complete degradation of high M_w (>35 kDa) polymer in 25 days. Nanoparticles based on these SIPs were also formulated (see section 5.3), with these capsules capable of releasing hydrophobic dye upon triggering with UV light (*o*-nitrobenzyl carbamate and bromocoumarin) or NIR irradiation (*o*-nitrobenzyl carbamate). Although bromocoumarin-based triggers were successfully activated via

NIR irradiation in model SIP systems, the hydrophobic environment imposed by nanoparticle formation presumably inhibited efficient NIR triggering.

4. DEPOLYMERIZATION OF SELF-IMMOLATIVE POLYMERS

Upon removal of the triggering group from the SIP chain end, three distinct depolymerization mechanisms have been demonstrated: (1) 1,6- and 1,4-eliminations to form quinone methides, (2) cyclizations to form imidazolidinones, oxazolidinones, or 1,3-oxathiolan-2-ones, and (3) breakdown of hemiacetals to dialdehyde monomers (Figure 2). Each
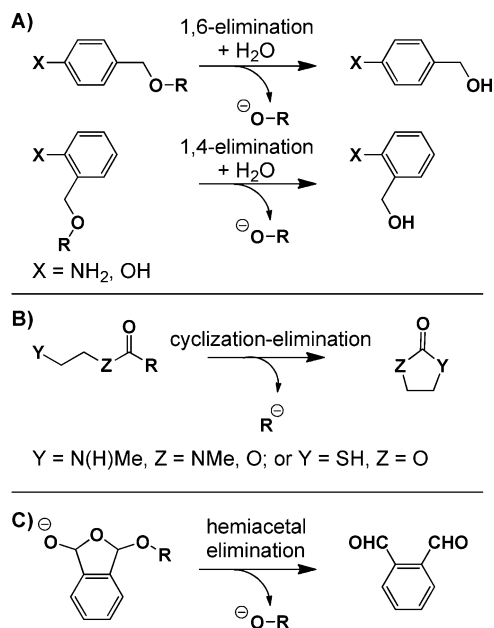
Figure 2. Self-immolative responses of different types of monomer units: (A) 1,6- and 1,4- elimination to form quinone methides, (B) cyclization−elimination, and (C) hemiacetal elimination.

mechanism exhibits distinct breakdown kinetics, and the times for each to reach complete depolymerization are qualitatively ordered as hemiacetal eliminations < 1,6-eliminations < 1,4-eliminations < cyclization−eliminations. As will be described below, some depolymerization pathways produce highly reactive monomeric intermediates whereas others result in more stable small molecule products.

4.1. 1,6- and 1,4-Eliminations. Repeat units containing *p*-benzylic or *o*-vinylogous linkages eliminate in a 1,6-fashion, whereas 1,4-eliminations are observed from repeat units bearing *o*-benzylic connectivities (Figure 2A). In each case, a reactive quinone methide intermediate is formed. The released species can either be a small molecule output or an activated chain end poised to continue the depolymerization. Routing the

elimination events through both the *o*- and *p*-positions gives rise to multifunctional SIPs designed for main-chain disassembly and release of side-chain output molecules. In most cases, complete depolymerization is achieved in 5−10 h in systems utilizing exclusively elimination via quinone methide formation. This is usually monitored by observing the concentration of a specific reporter molecule released from the output position or monitoring the production of a fluorogenic monomer unit.[14] Under physiological conditions, Shabat has determined 1,4-elimination to be slower than 1,6-elimination, and thus in linear systems backbone depolymerization is expected to occur before side-chain release.[39]

Preliminary studies of the rates of 1,4-elimination have shown that the electronic nature of the arene core significantly affects elimination kinetics.[52] Replacement of a methyl group with an ethyl ester in the position para to the electron-donating phenoxide increased the rate of elimination 30-fold in both first- and second-generation self-immolative dendrimers. Solvent has also been shown to influence elimination rates. Both 1,6- and 1,4-eliminations were found to occur more rapidly in aqueous media than in organic solvents. For example, depolymerization of SIPs (Figure 1D) in phosphate buffered saline was found to occur 8 times faster than in MeOH/DMSO solution.[15] In aqueous conditions, the solution is generally maintained at a slightly basic pH to facilitate elimination to the quinone methide, and accordingly depolymerization in organic solvents is aided by exogenous bases.[5] When utilizing aprotic solvents, it has been found that AcOH also accelerates depolymerization.[15]

When the immediate product of self-immolation is a highly reactive quinone methide, these intermediates are rapidly trapped by adventitious nucleophiles. In most cases the nucleophile is a solvent molecule such as water; however, in the presence of more potent nucleophiles other depolymerization products can arise. Such trapping reactions were investigated by Shabat and co-workers on a single-elimination model system (Scheme 4).[19] In a solution of 90:1 MeOH/morpholine, they observed trapping by only the more potent nucleophile, contrasting the usual product and leading the way toward interesting enzyme-labeling applications (see section 5.4).

4.2. Cyclization−Eliminations. An alternative method of self-immolative depolymerization is based upon an intramolecular 5-exo-trig cyclization with concurrent release of an electron-rich leaving group (Figure 2B).[20,21,54] This has been demonstrated to occur in systems forming ureas, carbamates, and thiocarbonates. The polyurethanes developed by Gillies (Scheme 2B) are based upon this type of elimination event. Compared with elimination through an arene monomer, cyclization−elimination is much slower and appears to be the rate-limiting step in all reported self-immolative systems in which it is incorporated. For example, Almutairi and co-workers synthesized polymers of this type of ~35 kDa. Upon exposure

Scheme 4. Trapping of Single-Elimination Model System by Low Concentrations of Morpholine in MeOH
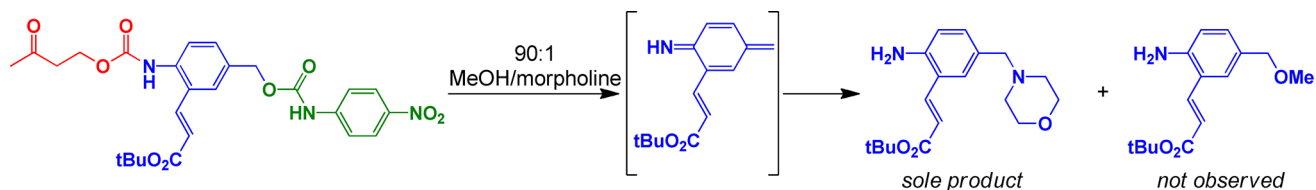
to triggering conditions, complete depolymerization was observed over a span of 25 days.[54] Shabat synthesized dendrimers capable of either direct quinone methide elimination or cyclization−elimination followed by quinone methide elimination (Figure 3).[33] Incorporation of the cyclizing
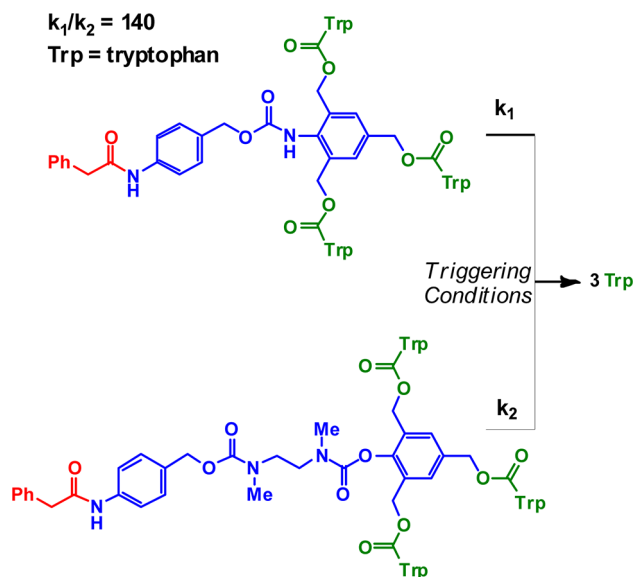
Figure 3. Use of moieties capable of cyclization−eliminations for tuning of output release kinetics. Reproduced with permission from ref 33. Copyright 2007 Elsevier.

moiety slowed the degradation process by a factor of 140, with complete release of reporter molecules occurring after days instead of hours. Thus, cyclizing units can be used to tune the degradation kinetics.

4.3. Hemiacetal Eliminations. The head-to-tail self-immolative breakdown of PPA recently reported by Phillips (Figure 2C)[25,28] occurs much more rapidly than depolymerization observed from other types of SIPs. Upon trigger cleavage at the head of the polymer, a hemiacetal is revealed. Subsequent reversion to the free aldehyde eliminates the next hemiacetal, thus propogating the self-immolative sequence. In solution, this process has been observed to take place in a matter of seconds, and depolymerization in solid materials required only 15 min for complete reversion to phthalaldehyde monomer units.[25] The remarkably fast depolymerization of PPA-based SIPs stands in stark contrast to what is observed from other classes

of SIPs and expanded applications taking advantage of this characteristic are anticipated.

5. APPLICATIONS OF SELF-IMMOLATIVE POLYMERS

The majority of potential applications for self-immolative systems take advantage of the amplified release of covalently bound molecules, as activation of a single triggering moiety results in release of multiple small molecules. In principle, the extent of amplification observed with SIPs increases linearly with the degree of polymerization, and amplification with self-immolative dendrimers scales exponentially with increasing generations. Largely due to the steric congestion associated with the synthesis of higher generation self-immolative dendrimers, third-generation variants are the largest that have been reported (8 outputs released per macromolecule).[5] Thus, the amplifying ability of self-immolative dendrimers has remained synthetically limited and is generally lower when compared with SIPs achieving high DPs of repeat units equipped for side-chain release. These amplified responses have largely been applied to the release of reporter molecules or therapeutic agents for furthering sensor or drug release applications, respectively. Additionally, SIP depolymerization has been targeted for applications that degrade components of nanoscale materials. It is important to note that in the following application sections several examples have thus far only been applied to dendritic systems.

5.1. Sensors. SIPs are well suited for applications as sensory materials due to their signal amplification ability, which decreases the detection limit for a particular analyte capable of trigger activation. Shabat has further increased the amplified response by modifying dendrimers to release agents that are converted into the triggering agent under the reaction conditions (Figure 4).[45−47,49] In these systems, the first deconstruction event initiates a chain reaction that leads to exponential amplification from activation of a single trigger.

In general, monitoring signal output has involved observation of diagnostic UV−vis or photoluminescence signals from released reporter molecules. For example, release of *p*-nitrophenol is easily detected and quantified via UV−vis spectrometry, and release of fluorogenic monomer units or reporter molecules (e.g., 6-aminoquinoline) can be monitored via photoluminescence spectrometry.[14,38] Shabat has also recently developed the release of FRET pairs for fluorescent signal generation.[41] Although dose-responsive detection has only been reported for hydrogen peroxide and triacetone triperoxide,[44,45] most of the SIP models that have been
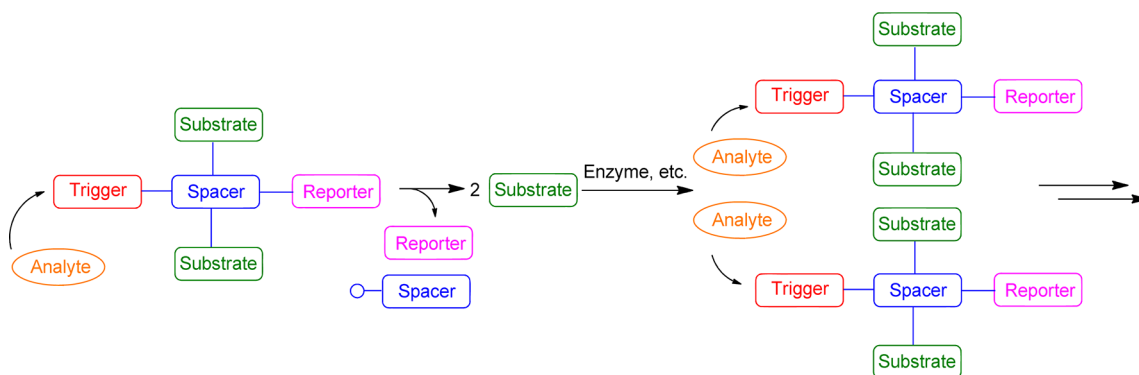
Figure 4. Representative depiction of a single round of an enzyme-mediated dendritic chain reaction.

developed could conceivably be adapted to act as sensors for their corresponding triggering agents.

5.2. Drug Release. The principle of signal amplification can also apply to drug delivery platforms in which the reporter molecules have been replaced by a desired pharmaceutical agent. Drug release was recognized early in the development of self-immolative systems but is yet to be realized in a linear SIP. Scheeren and co-workers demonstrated that the rate of drug release from self-immolative oligomers (DP = 2 or 3) was 2−3 times greater for doxorubicin prodrugs and 6−10 times greater for paclitaxel prodrugs than that observed when a single spacer prodrug was used.[2] The increased release rate from the oligomer was attributed to reduced steric interactions between the bulky drug molecules and the triggering enzyme. Although an increased drug release rate is a potential advantage of using self-immolative systems, the ability to increase drug loading with SIP platforms is arguably their most attractive feature. This evolutionary step in SIP design will likely be borne out via systems capable of side-chain release (e.g., SIPs from monomer **2** in Scheme 2), as opposed to release of drug molecules from the chain end of a self-immolative sequence. By increasing the drug loading per trigger, burst release profiles can be achieved which have been shown to have higher drug efficacy against cancer cells than the release of a single drug per triggering event.[7] Dimeric and trimeric prodrugs have also been developed that release 2 and 3 different types of drugs, respectively, from the same dendrimer.[32] Different drug combinations could have synergistic effects and incorporation of different ratios of pharmaceuticals could be tuned to specific types of disease.

Further developments with SIPs may lead to targeted drug delivery by incorporating triggers that facilitate the release of therapeutics near diseased tissue. Toward this end, triggers have been developed that are cleaved by enzymes often overexpressed in many types of tumor tissue (Table 1, entries 5 and 6).[30,56] Multisite targeting is also envisioned from recently developed OR logic gate triggering systems. This concept was demonstrated in a self-immolative dendrimer in which either of two orthogonal triggers was activated in the presence of its corresponding stimuli.[34]

5.3. Degradable Nanoscale Materials. While many targeted applications of SIPs have utilized the small molecules released upon depolymerization, other approaches focus on the depolymerization event itself as the desired function of the SIP. Specifically, stimuli-responsive depolymerization has been used to irreversibly degrade hydrophobic components of micelles, nanoparticle frameworks, microcapsule shells, and solid patterned plastics. These degradable platforms may find application in areas including drug delivery, self-healing materials (by release of small molecules that promote cross-linking, monomer polymerization, etc.), and lithography. Gillies demonstrated the hydrolytic degradation of micelles formed from self-assembly of block copolymers comprising hydrophobic SIP blocks, hydrophilic PEG blocks, and a water-sensitive trigger.[20] Nile red, a hydrophobic fluorescent dye, was encapsulated within the hydrophobic core of the micelle and was released as the micelle was degraded. Such systems are attractive for applications requiring slow release of a particular compound.

Small molecule release has also been demonstrated from degradable capsules. Moore used SIPs as building blocks in microcapsule shells that were responsive toward acidic or basic media using either Boc or Fmoc groups, respectively.[53] Upon exposure to either 4 M HCl or 5% piperidine solution, respectively, depolymerization of the microcapsule shell resulted in on-demand release of the core contents. Building upon previously demonstrated work,[57,58] Almutairi prepared nanoparticles comprising light-activated SIP components via emulsion formulation.[54] Upon exposure to appropriate wavelengths of light, the SIPs were degraded, leading to deconstruction of the architectures and release of encapsulated Nile red dye. A notable characteristic about payload release from these nanoparticles is the observation that quantitative SIP deconstruction was not necessary for nearly complete release of the nanoparticle contents. Thus, content release can be achieved in shorter time spans than those required for complete SIP depolymerization.

Taking advantage of highly labile PPA-based SIPs, Phillips was able to achieve triggered depolymerization in the solid state.[25] A patterned plastic film was prepared from two PPAs with differing end groups. At the center of the film was a circular region comprised of PPA with fluoride-sensitive silyl ethers as triggers. After exposure to fluoride and subsequent depolymerization, the released monomer was rinsed away yielding plastic films with a cylindrical hole. It is expected that this method could be evolved to offer new approaches in lithographic techniques. It is important to note that while other PPA-based systems have been used for lithographic purposes,[59,60] this is the first PPA with end-group functionalization that triggers controlled head-to-tail depolymerization of the polymer.

5.4. Other Applications. An interesting utility of SIPs involves releasing small molecules capable of performing secondary functions other than reporting or providing therapeutic effects. Shabat demonstrated the release of diphenylalanine from self-immolative dendrimers.[37] Diphenylalanine forms dipeptide nanotubes in solution but does not do so when bound to the dendrimer. The triggered release of this self-assembling molecule enabled the spatiotemporal control of the formation of the nanostructures. Shabat also demonstrated the use of SIPs for activity-linked labeling of enzymes.[19] The SIP was capped with an enzymatic trigger which, upon cleavage in the active site, released reactive azaquinone methide intermediates which were trapped by nucleophilic amino acid residues in the protein. This method was also shown to be highly selective for labeling the triggering enzyme in a competitive environment, likely due to the production of high local concentration of reactive azaquinone methide units. Phillips demonstrated use of the concentration gradient of monomers released from depolymerizing PPA thin films as the driving force for single-use microscale pumps.[28] The pumping action was triggered by the presence of fluoride, thus allowing the pump to be activated by a specific stimulus. Pump action was able to be sustained for >15 min and was able to push particles through a 5 mm channel containing a 90° turn.

6. OUTLOOK AND CHALLENGES

Advancements in the field of self-immolative polymers have collectively resulted in systems capable of side-chain release, fast deconstruction, and conversion into either functional or unreactive small molecules. While no single type of SIP possesses all of these desirable characteristics, the diversity of trigger structures in combination with differing SIP main chains combine to make this class of functional polymeric materials highly versatile. The basic platform has been applied toward demonstrating the potential use of SIPs in several applications,

often with relatively little augmentation of the SIP architecture. Although the general modularity of the designs described herein shows great promise for innovative future technologies, there remain unanswered challenges and unrealized capabilities in the area of SIPs.

The ideal SIP would be comprised of monomers that could be easily obtained and possess the ability for facile side chain functionalization, both of which have yet to be achieved in combination. For instance, phthalaldehyde is commercially available, but side-chain release has not been realized. Similarly, while *p*-aminobenzyl alcohol-based monomers with vinylogous side chains can be readily functionalized with different output molecules, their preparation requires lengthy syntheses and purification protocols. More generally, increasing the solubility of the known polyurethane-based SIPs would also constitute a significant contribution.

From a synthetic perspective, more powerful approaches toward accessing SIPs via controlled chain growth polymerization mechanisms are highly desirable. The molecular weights of SIPs prepared via polycondensation reactions are difficult to control as their polymerizations proceed through step growth mechanisms. Thus, SIPs often exhibit characteristics typical of step growth polymers, such as relatively low molecular weight ranges and broad PDIs. Higher molecular weights, such as those achieved with PPA, and low PDIs would not be the only advantages of a chain growth polymerization, as new SIP architectures such as block copolymers utilizing different self-immolative monomers might be obtained. It would be important that these polymerizations do not detract from the modular nature of SIPs, as the ability to tune the polymers for different applications is one of their most attractive features.

Particular attention should also be paid to the mechanism and kinetics of depolymerization when designing advanced SIP systems. Collectively, the time to completely depolymerize from trigger to output varies from seconds to days for known SIPs. The ability to modulate the depolymerization profile for a single type of monomer such that variation between rapid and prolonged depolymerization can be controlled is thus far unrealized. While Shabat has already reported preliminary studies of the rates of 1,4-elimination based upon electronic modification of the arene core (see section 4.1), additional systematic investigation of the relationship between monomer structure and depolymerization kinetics would be valuable for future SIP designs.

Undesired side reactions will continue to be an area of concern as specialized SIPs are developed for precise applications. For instance, a particular challenge facing PPAs is the lack of compatibility of the polymer backbone with protic conditions, which severely limits the utility of this class of SIPs in its current iteration. Issues of high reactivity also face SIPs which operate via quinone methide intermediates, as these are highly unstable and rapidly react with nucleophiles. As discussed above, Shabat has demonstrated that reaction of these quinone methides with biomolecules is possible. Although the activity of the enzymes studied was not greatly affected, the formation of highly reactive intermediates in a more complex biological environment could lead to unwanted side effects in the application of SIP-based drug release platforms. Therefore, a logical parameter for the design or optimization of SIPs is avoidance of reactive species, either in the pretriggered state or generated as a consequence of polymer deconstruction.

While there is considerable opportunity for improvement of the SIP repeat unit, focus must also be given to expanding trigger designs. The SIP trigger is the first relay between the functional macromolecule and the surrounding environment. The area of sensors is likely to experience the greatest benefit from trigger developments, as this area requires high fidelity of analyte/trigger combinations. Development of new triggers that help target drug release to the sites of disease will also be useful. For these applications, more in-depth studies also need to be conducted such as greater exploration into the sensitivity and selectivity of sensors and *in vivo* studies of SIPs for drug delivery. Further expansion of SIPs into solid-state materials would be accelerated by development of new polymer structures, as PPA is currently the only demonstrated option for such roles. The release of monomer units that become functionally active upon depolymerization is another avenue of future SIP development. A particularly intriguing application of this concept would be the development of SIP monomer units capable of repolymerization under orthogonal triggering conditions, thus providing a system capable of switching between covalent polymeric materials and small molecules in response to different stimuli. Overall, these challenges present considerable opportunities for the convergence of synthetic chemistry and materials science with multiple other disciplines, and we believe the future of stimuli-responsive materials is likely to see increased focus on self-immolative macro-molecules.

■ AUTHOR INFORMATION

Corresponding Author
*E-mail boydston@chem.washington.edu, Ph (206) 616-8195, Fax (206) 685-8665.

Author Contributions
[†]These authors contributed equally to this work.

Notes
The authors declare no competing financial interest.

Biographies

Gregory I. Peterson received his B.S. in Chemistry from Pacific Lutheran University in 2010. There he did undergraduate research with Prof. Dean A. Waldow preparing multiblock copolymers via anionic polymerizations. He is currently working toward his Ph.D. in chemistry at the University of Washington, Seattle, under the supervision of Asst. Prof. Andrew J. Boydston. His research interest includes the synthesis and application of stimuli-responsive, functional macromolecules.

Michael B. Larsen was born in 1988 in Denver, CO. In 2009 he obtained his BA in chemistry from the Colorado College, where he served as department paraprofessional and conducted research under Asst. Prof. Rongson Pongdee (now at Sewanee). He is currently working toward his doctorate in chemistry under the supervision of Asst. Prof. Andrew J. Boydston. His research interests include the development of novel mechanophores and methods of triggering self-immolative polymers.

Andrew J. Boydston received his B.S. and M.S. degrees in Chemistry in 2001 and 2002, respectively, both from the University of Oregon under the mentorship of Professor Michael M. Haley. After completing his Ph.D. in Chemistry in 2007 at the University of Texas at Austin under the guidance of Professor Christopher W. Bielawski, he began postdoctoral studies at the California Institute of Technology with Professor Robert H. Grubbs. In 2010, he began his independent career at the University of Washington where he is currently appointed as an Assistant Professor of Chemistry. His research focuses on stimuli-responsive macromolecules, polymer design and synthesis, and electro-organic synthesis.

■ REFERENCES

(1) Carl, P. L.; Chakravarty, P. K.; Katzenellenbogen, J. A. *J. Med. Chem.* **1981**, *24*, 479−480.

(2) de Groot, F. M. H.; Loos, W. J.; Kockkock, R.; van Berkom, L. W. A.; Busscher, G. F.; Seelen, A. E.; Albrecht, C.; de Bruijn, P.; Scheeren, H. W. *J. Org. Chem.* **2001**, *66*, 8815−8830.

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

(4) Li, S.; Szalai, M. L.; Kevwitch, R. M.; McGrath, D. V. *J. Am. Chem. Soc.* **2003**, *125*, 10516−10517.

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

(6) Szalai, M. L.; Kevwitch, R. M.; McGrath, D. V. *J. Am. Chem. Soc.* **2003**, *125*, 15688−15689.

(7) Shabat, D. *J. Polym. Sci., Part A: Polym. Chem.* **2006**, *44*, 1569−1578.

(8) Wang, R. E.; Costanza, F.; Niu, Y.; Wu, H.; Hu, Y.; Hang, W.; Sun, Y.; Cai, J. *J. Controlled Release* **2012**, *159*, 154−163.

(9) Wang, W.; Alexander, C. *Angew. Chem., Int. Ed.* **2008**, *47*, 7804−7806.

(10) Esser-Kahn, A. P.; Odom, S. A.; Sottos, N. R.; White, S. R.; Moore, J. S. *Macromolecules* **2011**, *44*, 5539−5553.

(11) Avital-Shmilovici, M.; Shabat, D. *Soft Matter* **2010**, *6*, 1073−1080.

(12) Wong, A. D.; DeWit, M. A.; Gillies, E. R. *Adv. Drug Delivery Rev.* **2011**, DOI: 10.1016/j.addr.2011.09.012.

(13) Blencowe, C. A.; Russell, A. T.; Greco, F.; Hayes, W.; Thornthwaite, D. W. *Polym. Chem.* **2011**, *2*, 773−790.

(14) Sagi, A.; Weinstein, R.; Karton, N.; Shabat, D. *J. Am. Chem. Soc.* **2008**, *130*, 5434−5435.

(15) Weinstein, R.; Sagi, A.; Karton, N.; Shabat, D. *Chem.—Eur. J.* **2008**, *14*, 6857−6861.

(16) Warnecke, A.; Kratz, F. *J. Org. Chem.* **2008**, *73*, 1546−1552.

(17) Ortiz, A.; Shanahan, C. S.; Sisk, D. T.; Perera, S. C.; Rao, P.; McGrath, D. V. *J. Org. Chem.* **2010**, *75*, 6154−6162.

(18) Kevwitch, R. M.; Shanahan, C. S.; McGrath, D. V. *New J. Chem.* **2012**, *36*, 492−505.

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

(20) DeWit, M. A.; Gillies, E. R. *J. Am. Chem. Soc.* **2009**, *131*, 18327−18334.

(21) DeWit, M. A.; Beaton, A.; Gillies, E. R. *J. Polym. Sci., Part A: Polym. Chem.* **2010**, *48*, 3977−3985.

(22) Ito, H.; Willson, C. G. *Polym. Eng. Sci.* **1983**, *23*, 1012−1018.

(23) Aso, C.; Tagami, S.; Kunitake, T. *J. Polym. Sci., Part A: Polym. Chem.* **1969**, *7*, 497−511.

(24) Kostler, S.; Zechner, B.; Trathnigg, B.; Fasl, H.; Kern, W.; Ribitsch, V. *J. Polym. Sci., Part A: Polym. Chem.* **2009**, *47*, 1499−1509.

(25) Seo, W.; Phillips, S. T. *J. Am. Chem. Soc.* **2010**, *132*, 9234−9235.

(26) Phillips, S. T.; Seo, W.; Robbins, J.; Olah, M.; Schmid, K.; Dilauro, A. M. Signal-responsive plastics. W.O. Patent 2012/005806, Jan 12, 2012.

(27) Tsuda, M.; Hata, M.; Nishida, R.; Oikawa, S. *J. Polym. Sci., Part A: Polym. Chem.* **1997**, *35*, 77−89.

(28) Zheng, H.; Yeung, K.; Robbins, J. S.; Pavlick, R. A.; Wu, M.; Liu, R.; Sen, A.; Phillips, S. T. *Angew. Chem., Int. Ed.* **2012**, *51*, 2400−2404.

(29) Erez, R.; Segal, E.; Miller, K.; Satchi-Fainaro, R.; Shabat, D. *Bioorg. Med. Chem.* **2009**, *17*, 4327−4335.

(30) Grinda, M.; Clarhaut, J.; Renoux, B.; Tranoy-Opalinski, I.; Papot, S. *Med. Chem. Commun.* **2012**, *3*, 68−70.

(31) Shamis, M.; Lode, H. N.; Shabat, D. *J. Am. Chem. Soc.* **2004**, *126*, 1726−1731.

(32) Haba, K.; Popkov, M.; Shamis, M.; Lerner, R. A.; Barbas, C. F., III; Shabat, D. *Angew. Chem., Int. Ed.* **2005**, *44*, 716−720.

(33) Sagi, A.; Segal, E.; Satchi-Fainaro, R.; Shabat, D. *Bioorg. Med. Chem.* **2007**, *15*, 3720−3727.

(34) Amir, R. J.; Popkov, M.; Lerner, R. A.; Barbas, C. F., III; Shabat, D. *Angew. Chem., Int. Ed.* **2005**, *44*, 4378−4381.

(35) Danieli, E.; Shabat, D. *Bioorg. Med. Chem.* **2007**, *15*, 7318−7324.

(36) Shamis, M.; Shabat, D. *Chem.—Eur. J.* **2007**, *13*, 4523−4528.

(37) Adler-Abramovich, L.; Perry, R.; Sagi, A.; Gazit, E.; Shabat, D. *ChemBioChem* **2007**, *8*, 859−862.

(38) Amir, R. J.; Danieli, E.; Shabat, D. *Chem.—Eur. J.* **2007**, *13*, 812−821.

(39) Erez, R.; Shabat, D. *Org. Biomol. Chem.* **2008**, *6*, 2669−2672.

(40) Meyer, Y.; Richard, J.-A.; Delest, B.; Noack, P.; Renard, P.-Y.; Romieu, A. *Org. Biomol. Chem.* **2010**, *8*, 1777−1780.

(41) Redy, O.; Kisin-Finfer, E.; Sella, E.; Shabat, D. *Org. Biomol. Chem.* **2012**, *10*, 710−715.

(42) National Library of Medicine: Medline Plus. Albumin - serum. http://www.nlm.nih.gov/medlineplus/ency/article/003480.htm (accessed 4/2/12).

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

(44) Sella, E.; Shabat, D. *Chem. Commun.* **2008**, *44*, 5701−5703.

(45) Sella, E.; Shabat, D. *J. Am. Chem. Soc.* **2009**, *131*, 9934−9936.

(46) Avital-Shmilovici, M.; Shabat, D. *Bioorg. Med. Chem.* **2010**, *18*, 3643−3647.

(47) Sella, E.; Lubelski, A.; Klafter, J.; Shabat, D. *J. Am. Chem. Soc.* **2010**, *132*, 3945−3952.

(48) Major Jourden, J. L.; Daniel, K. B.; Cohen, S. M. *Chem. Commun.* **2011**, *47*, 7968−7970.

(49) Karton-Lifshin, N.; Shabat, D. *New J. Chem.* **2012**, *36*, 386−393.

(50) Zhang, L.; Liu, W.; Lin, L.; Chen, D.; Stenzel, M. H. *Biomacromolecules* **2008**, *9*, 3321−3331.

(51) Perry-Feigenbaum, R.; Sella, E.; Shabat, D. *Chem.—Eur. J.* **2011**, *17*, 12123−12128.

(52) Perry, R.; Amir, R. J.; Shabat, D. *New J. Chem.* **2007**, *31*, 1307−1312.

(53) Esser-Kahn, A. P.; Sottos, N. R.; White, S. R.; Moore, J. S. *J. Am. Chem. Soc.* **2010**, *132*, 10266−10268.

(54) de Gracia Lux, C.; McFearin, C.; Sankaranarayanan, J.; Fomina, N.; Almutairi, A. *ACS Macro Lett.* **2012**, *1*, 922−926.

(55) Timko, B. P.; Whitehead, K.; Gao, W.; Kohane, D. S.; Farokzhad, O.; Anderson, D.; Langer, R. *Annu. Rev. Mater. Res.* **2011**, *41*, 1−20.

(56) Withana, N. P.; Blum, G.; Sameni, M.; Slaney, C.; Anbalagan, A.; Olive, M. B.; Bidwell, B. N.; Edgington, L.; Wang, L.; Moin, K.; Sloane, B. F.; Anderson, R. L.; Bogyo, M. S.; Parker, B. S. *Cancer Res.* **2012**, *72*, 1199−1209.

(57) Fomina, N.; McFearin, C.; Sermsakdi, M.; Edigin, O.; Almutairi, A. *J. Am. Chem. Soc.* **2010**, *132*, 9540−9542.

(58) Fomina, N.; McFearin, C.; Sermsakdi, M.; Morachis, J. M.; Almutairi, A. *Macromolecules* **2011**, *44*, 8590−8597.

(59) Knoll, A. W.; Pires, D.; Coulembier, O.; Dubois, P.; Hedrick, J. L.; Frommer, J.; Duerig, U. *Adv. Mater.* **2010**, *22*, 3361−3365.

(60) Coulembier, O.; Knoll, A.; Pires, D.; Gotsmann, B.; Duerig, U.; Frommer, J.; Miller, R. D.; Dubois, P.; Hedrick, J. L. *Macromolecules* **2010**, *43*, 572−574.