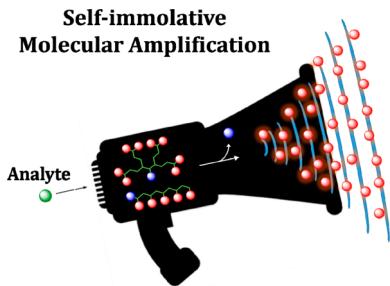


Dendritic, Oligomeric, and Polymeric Self-Immulative Molecular Amplification

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1. INTRODUCTION

The development of new chemical tools for the purpose of molecular amplification is arguably one of the most central challenges in science. Such tools have traditionally been based on enzymatic or other catalytic reactions. More than a decade ago, we developed a unique dendritic system that acts as a molecular amplifier. A single cleavage event at a dendron's focal point

initiates the disassembly of the dendritic molecule in a domino-like fashion from head to tail, resulting in release of multiple end groups from the dendron's periphery. We termed these compounds self-immulsive dendrimers since the molecular system structurally sacrifices itself to accomplish the amplification function. Interestingly, two other groups simultaneously reported analogous dendritic systems that disassemble to achieve the amplification function. We have since demonstrated self-immulsive amplification in applications such as drug delivery, supramolecular assembly, and diagnostic probe design. Further, on the basis of the self-immulsive fragmentation pathway, we have designed linear polymeric molecules that disassemble from head to tail in response to a stimulus event at the polymer's head. These self-immulsive polymers have the ability to provide amplified domino-like complete disassembly in response to a single bond cleavage.

Since our initial report, self-immulsive molecular amplification has been widely applied by numerous groups worldwide, and elegant amplification concepts based on self-immulsive disassembly have been developed.¹ In the past few years, several reviews have covered the field of self-immulsive linkers^{2–5} and their molecular systems.^{6–19} In this article, we review examples of dendritic and polymeric self-immulsive molecular platforms that provide an amplified response.

The terminology AB_n is commonly used to describe the structure of dendritic molecules, where A is the focal head and B is the branched tail group (n in number). In order to compose self-immulsive dendrimers, suitable AB_2 dendritic molecules have been designed. Such molecules are usually based on phenol or aniline derivatives with two hydroxymethyl substituents at the *ortho* and/or *para* positions. Tail units attached to benzylic substituents result in first-generation self-immulsive dendrons. The disassembly mechanism occurs through the quinone methide elimination, such that a single bond cleavage at the AB_2 dendritic molecule's head leads to release of the two tail units from the benzylic substituents through double quinone methide eliminations. Assembly of two AB_2 dendritic molecules at the benzylic positions of another AB_2 unit results in a second-generation self-immulsive dendron. Higher-order dendrons can be obtained as well.

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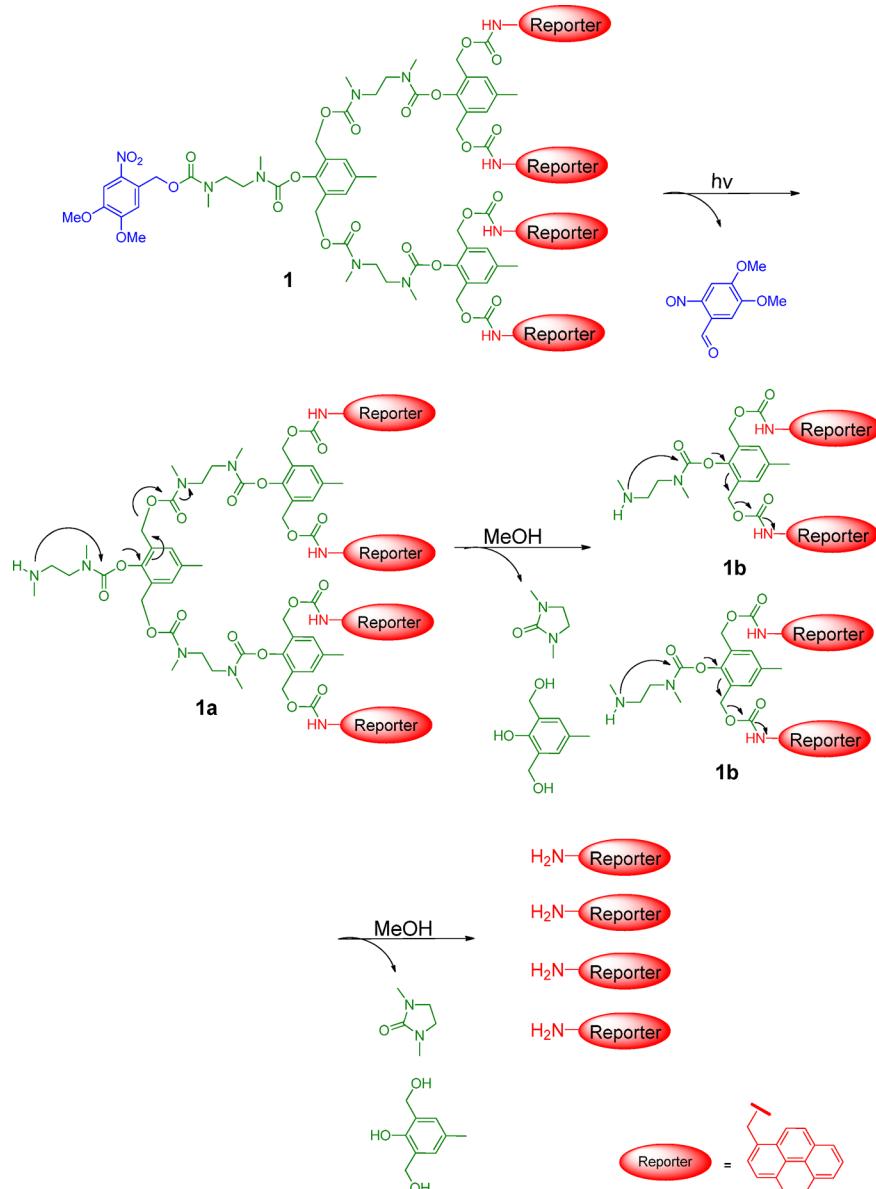


Figure 1. Second-generation self-immolative dendron releases aminomethylpyrene after irradiation with UV light.

2. SELF-IMMOLATIVE DENDRITIC SYSTEMS

2.1. Self-Immulative Dendrimers

Self-immolative dendrimers are a unique class of molecules that can amplify a single cleavage event received at the focal point into release of multiple tail groups at the periphery. Our group has developed carbamate-based self-immolative dendrimers consisting of an AB₂ branching unit and N,N'-dimethylethylenediamine as a cyclization spacer.²⁰ Cleavage of the photolabile 4,5-dimethoxy-2-nitrobenzyl trigger at the focal point of **1** results in cyclization of the diamine spacer on **1a**, giving the N,N'-dimethylurea derivative (Figure 1). The cyclization of the diamine spacer is the rate-limiting step. The intermediate **1b** is subsequently generated via double 1,4-eliminations followed by decarboxylation reactions. Four molecules of aminomethylpyrene are released from the second-generation dendrimer through a process of self-immolative sequential reactions.

The synthesis and disassembly of a third-generation self-immolative dendrimer was demonstrated with the 4-nitroaniline molecule as a reporter and the *tert*-butoxycarbonyl (Boc) group

as a trigger. This dendrimer releases eight end-group units upon a single activation event (Figure 2). Dendrimer **2** is the first and only third-generation self-immolative dendrimer that has been reported.

Simultaneously with us,²⁰ de Groot and co-workers reported a dendritic molecular system based on vinylbenzylic moieties that can release end units via double 1,8-eliminations.²¹ A nitro group was used to mask the focal-point aniline in an oxidized form. Two molecules of the paclitaxel anticancer drug were conjugated to the periphery of the first-generation dendrimer **3** (Figure 3). Reduction of the nitro group to an amino group (Zn, acetic acid) initiates a fragmentation cascade via double 1,8-eliminations followed by decarboxylation reactions, releasing the dendrimer's end-unit drug molecules. These authors also reported a synthesis of a second-generation self-immolative dendrimer obtained by grafting two additional molecules of 2-(4-aminobenzylidene)-propane-1,3-diol to the first-generation moiety. This dendrimer, **4**, releases four molecules of paclitaxel (Figure 3).

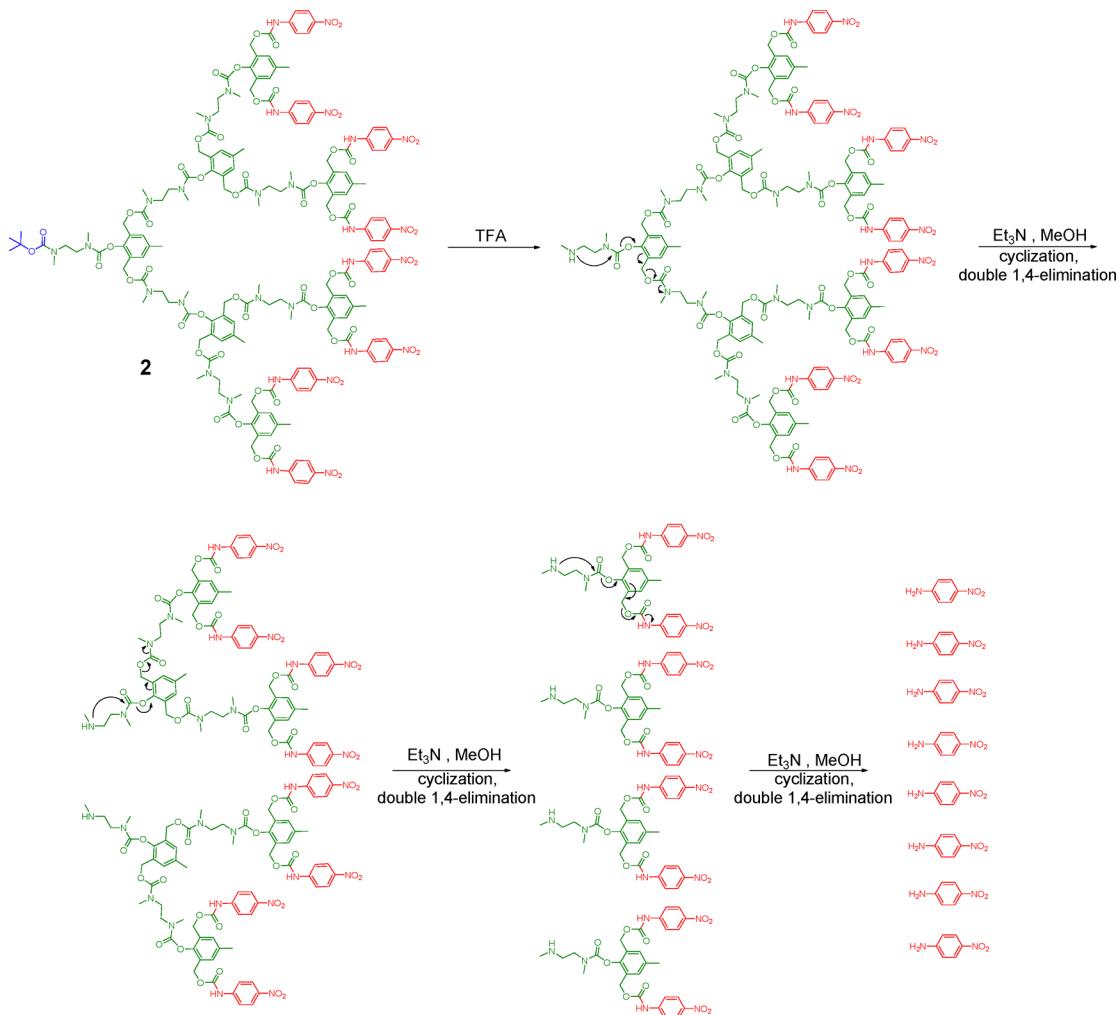


Figure 2. Third-generation self-immolative dendron triggered by trifluoroacetic acid to release the 4-nitroaniline tail units.

A bit later, McGrath and co-workers reported the synthesis of self-immolative dendrimer **5**, which is based on an AB₂ unit with benzyl ether linkages (Figure 4).²² Removal of the allyl ether protecting group (or alternatively the photolabile substituent) initiates a sequence of both 1,4- and 1,6-elimination reactions leading to fragmentation of the dendrimer backbone and release of the 4-nitrophenol end unit. Zeroth-, first-, and second-generation dendrimers can release one, two, and four reporters, respectively. These syntheses demonstrated the utility of the dendrimer backbone for signal amplification.

Until recently, the maximum number of reporter units that could be linked to one monosubstituted benzene ring was limited to three, corresponding to the one *para* and two *ortho* benzylic positions of the ring. We prepared AB₆ self-immolative dendritic adaptor **6** equipped with six molecules of aminomethylpyrene as reporter units (Figure 5).²³ The cleavage of the Boc trigger of dendron **6** initiated the cyclization of dimethylurea, affording the phenolate intermediate. The latter gradually underwent two 1,8- and four 1,6-quinone methide eliminations to release all six aminomethylpyrene reporter units.

Although chemical activation of self-immolative dendrimers readily takes place, enzymatic activation has not been achieved for dendrimers of higher size than first generation. Higher-generation dendrimers are large and highly hydrophobic dendrimers and tend to aggregate in aqueous media; therefore, enzymes are not able to efficiently trigger their disassembly. Our

group prepared hydrophilic second-generation self-immolative dendrimer **7** equipped with four end units (Figure 6).²⁴ The reporter units on the dendritic platform were equipped with ionizable functional groups. Polar interactions with water significantly decreased the hydrophobicity of the dendrimers and prevented aggregate formation. These second-generation dendrimers were efficiently activated by the enzyme penicillin-G amidase (PGA). When fragmentation takes place in aqueous media, the highly reactive azaquinone methide reacts rapidly with a water molecule to generate the 4-aminobenzyl alcohol.

We have also demonstrated a simple approach to control the disassembly rate of self-immolative dendrimers.²⁵ Two types of dendrons were synthesized: one with a methyl substituent on the benzene building block (**8**) and the other with an ethylcarboxy ester (**9**) (Figure 7). Dendron **9** with the electron-withdrawing substituents had a higher disassembly rate than dendron **8** with methyl substituents. Control of the rate of self-immolative dendrimer disassembly could be especially applicable in diagnostic or therapeutic uses of these dendrimers when a specific release rate is needed.

The disassembly of self-immolative dendrimers through domino-like chain fragmentation is initiated by a single cleavage at the dendrimer's focal point. The treelike structure of a dendrimer enables the design of dendritic systems with signal-transduction pathways from the dendrimer periphery to the focal site. These systems can also act as receiver/reporter devices. Our

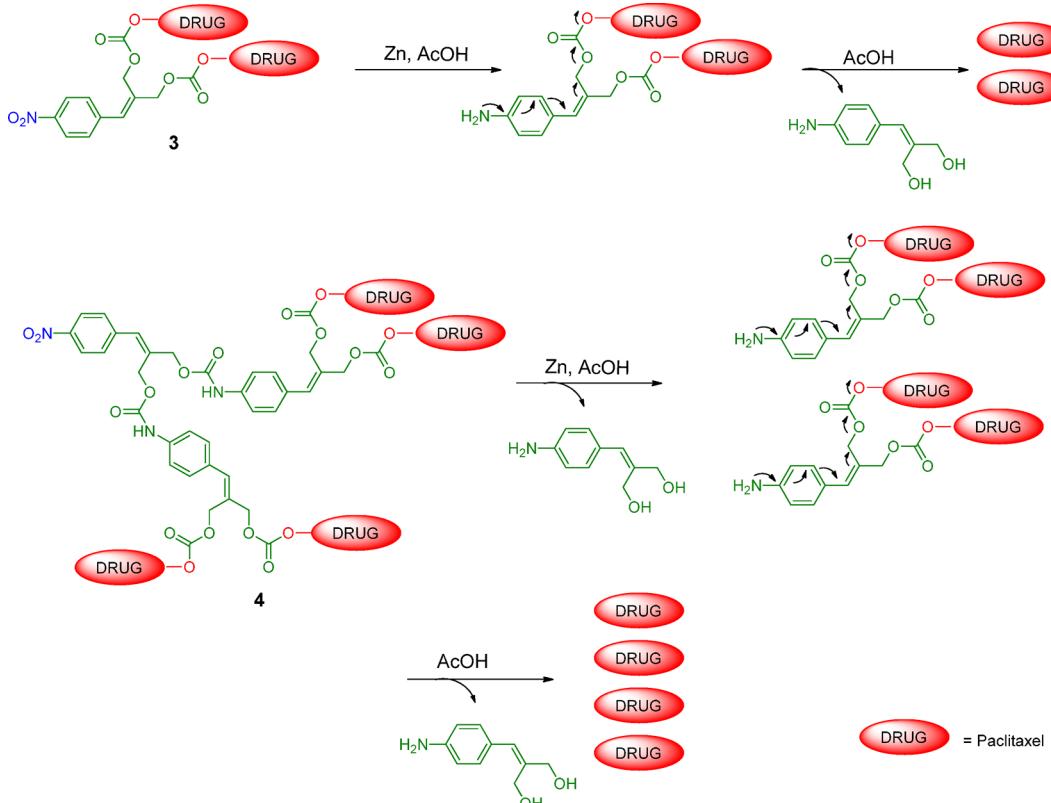


Figure 3. Activation of first- and second-generation self-immolative dendrimers releases two and four paclitaxel molecules, respectively, via 1,8-elimination.

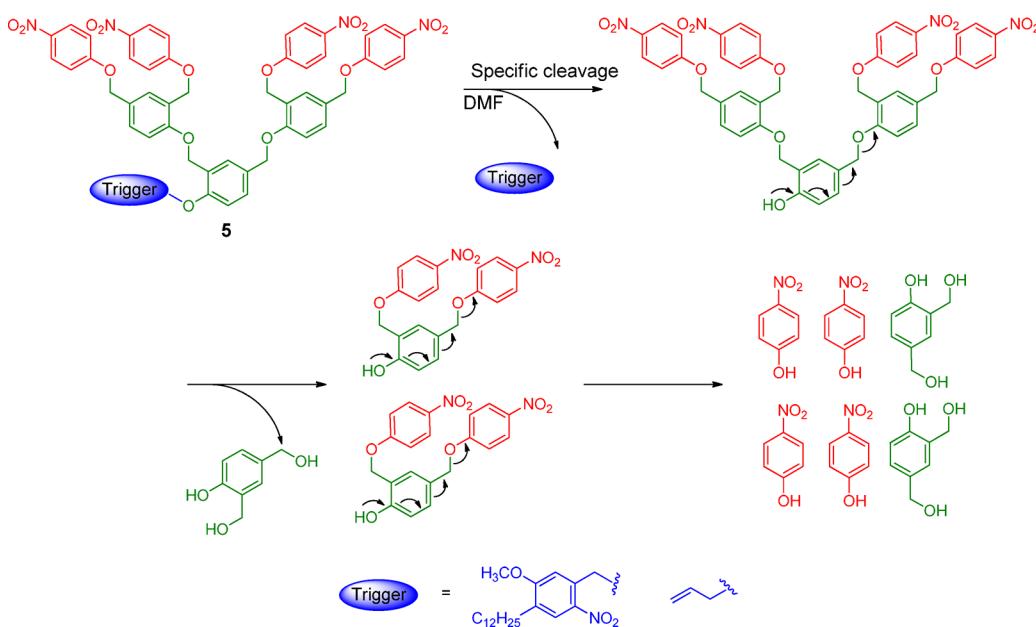


Figure 4. Activation of a second-generation dendrimer releases four molecules of 4-nitrophenol.

group has reported the self-immolative dendritic system **10** that disassembles through multienzymatic triggering followed by self-immolative chain fragmentation to release a reporter group from the focal point (Figure 8).²⁶ Cleaving any one of the multiple triggering units commences the fragmentation and the release of the reporter from the focal point. The trigger chosen was phenylacetamide, a substrate for PGA, and 4-nitrophenol was used as the reporter unit.

Following the same concept, our group reported a receiver–amplifier self-immolative dendritic system that is capable of transferring a cleavage signal in a convergent manner to the core and then amplifying it divergently to the periphery.²⁷ As shown in Figure 9, dendritic molecule **11** is programmed to initiate signal transduction through enzymatic cleavage of the phenylacetamide trigger by PGA; 6-aminoquinoline is used as the reporter unit. This unique chemical architecture allows a cleavage

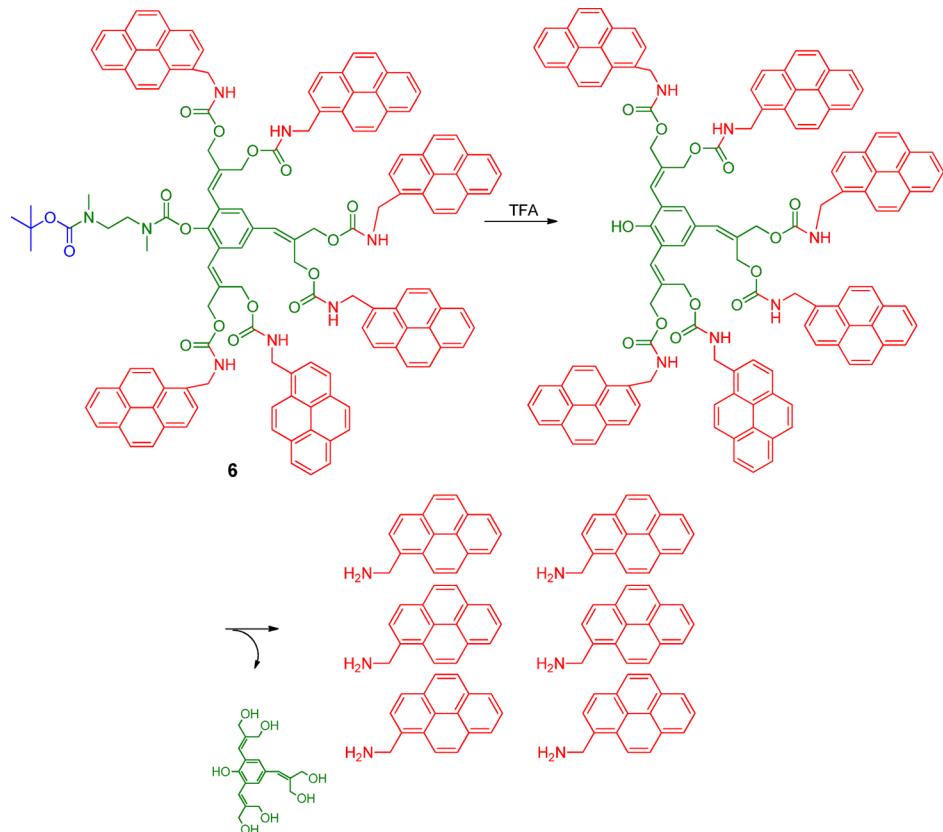


Figure 5. Molecular structure of a self-immolative AB_6 dendron with aminomethylpyrene reporter units and a Boc protecting group as a trigger.

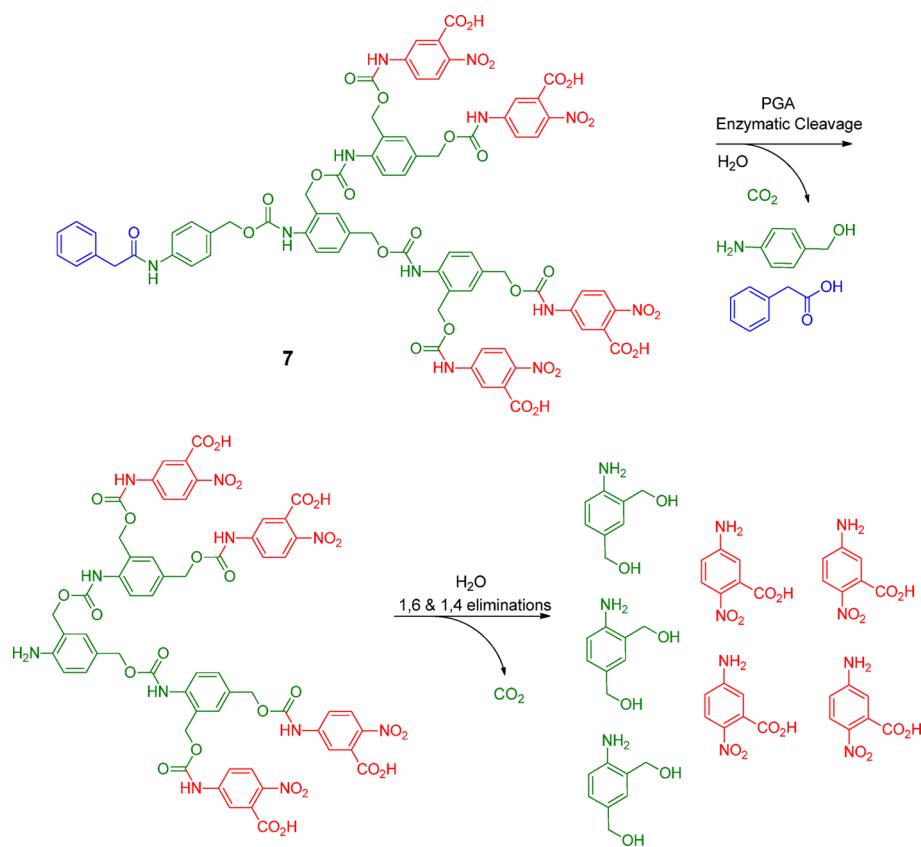


Figure 6. Disassembly of a second-generation self-immolative dendrimer upon enzymatic activation by PGA.

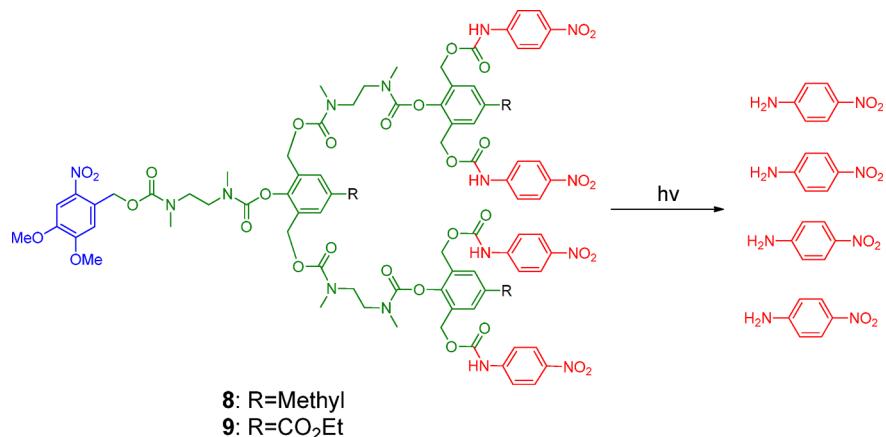


Figure 7. Chemical structure and disassembly reaction of second-generation self-immolative dendrons with different substituents on the benzene building block.

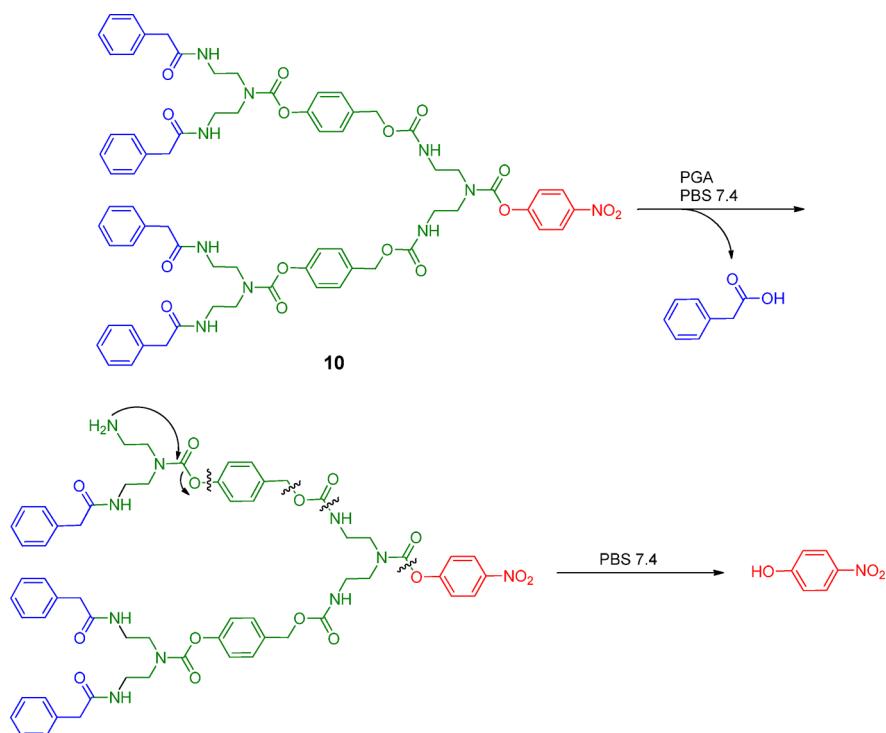


Figure 8. Disassembly of a self-immolative dendritic system through multienzymatic triggering by PGA to release the reporter 4-nitrophenol from the focal point. Cleavage of any of the triggers initiates the release of the reporter group.

signal received by any one of the four triggers to be transferred convergently to the core and then divergently to the periphery, resulting in signal amplification.

This device was also translated into a novel prodrug system with activation gated through a molecular OR logic trigger.²⁸ As shown in Figure 10, dendrimer **12** contains two different enzymatic substrates and the drug doxorubicin (DOX). The enzymatic substrates chosen were phenylacetamide, a substrate for PGA, and a retro-alcohol retro-Michael substrate that is cleaved by catalytic antibody 38C2. Cleavage of either trigger leads to degradation of the dendrimer and release of DOX.

Pyridine-based molecules have higher solubility in aqueous media than those with benzene rings. Thus, the use of self-immolative linkers based on a pyridinone methide species should increase the water solubility of dendrons and enable their application under physiological conditions. We have shown that

the pyridinone methide elimination can take place in a manner analogous to that of the benzene-based system.²⁹ Dendron **13** is composed of two 4-nitroaniline reporter units attached to a pyridine core; a phenylacetamide group serves as a trigger substrate for PGA (Figure 11). Enzymatic cleavage of dendron **13** initiates cascade reactions and releases the two reporters. Increased aqueous solubility was observed with compounds based on pyridine relative to those based on benzene. The pyridinone methide elimination is an alternative suitable for the design of self-immolative linkers that must function in an aqueous environment.

In 2011, the Phillips research group reported a new benzyl ether self-immolative AB₂ dendron, **14**, that is able to release two end units via double 1,6-eliminations (Figure 12). This class of dendrons was used for the design of various stimuli-responsive small molecules.³⁰ Cleavage of the trigger generates the related

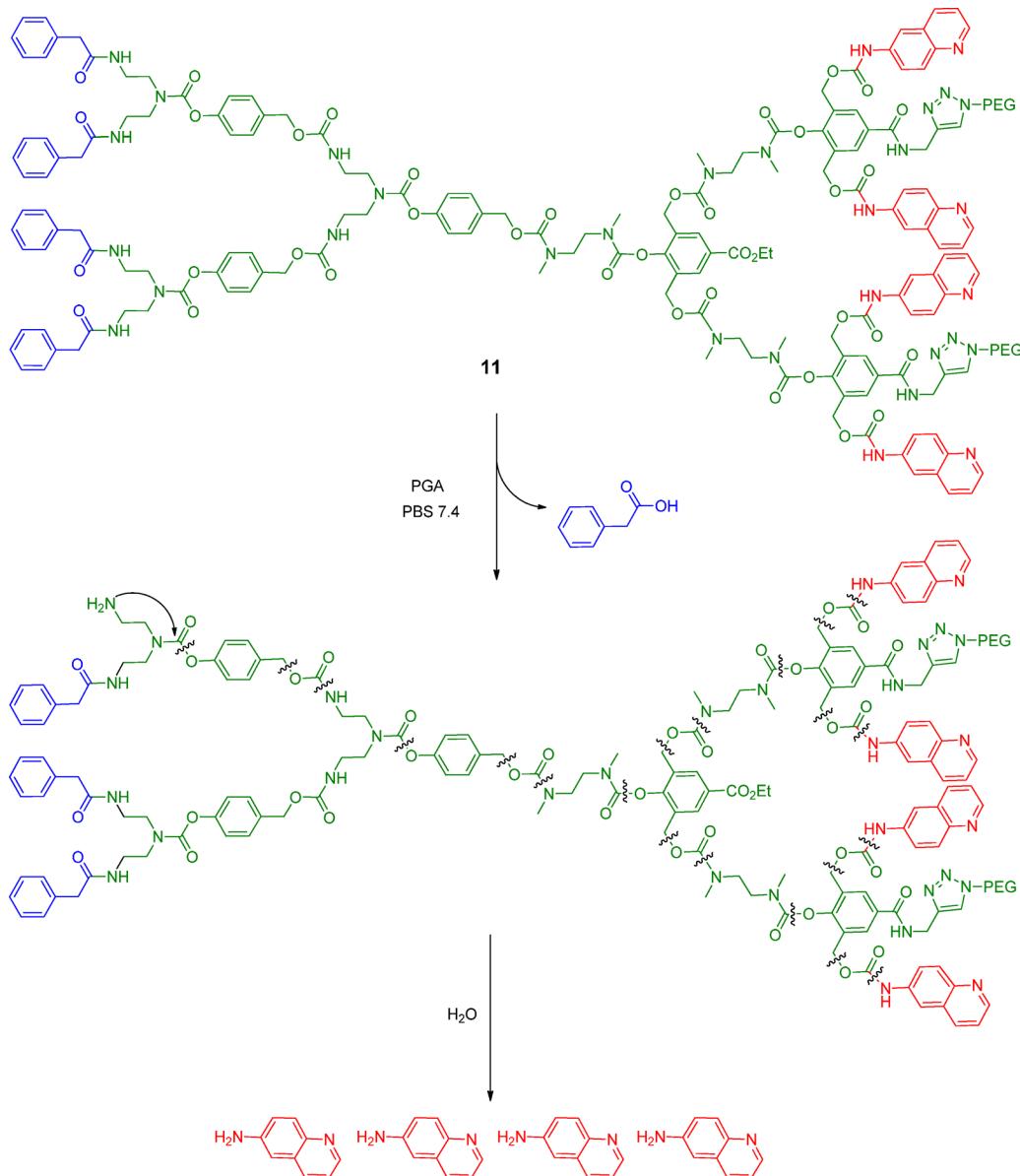


Figure 9. Self-immolative receiver–amplifier dendritic molecules with an enzymatic trigger (blue) that serves as a substrate for PGA and 6-aminoquinoline reporter groups (red).

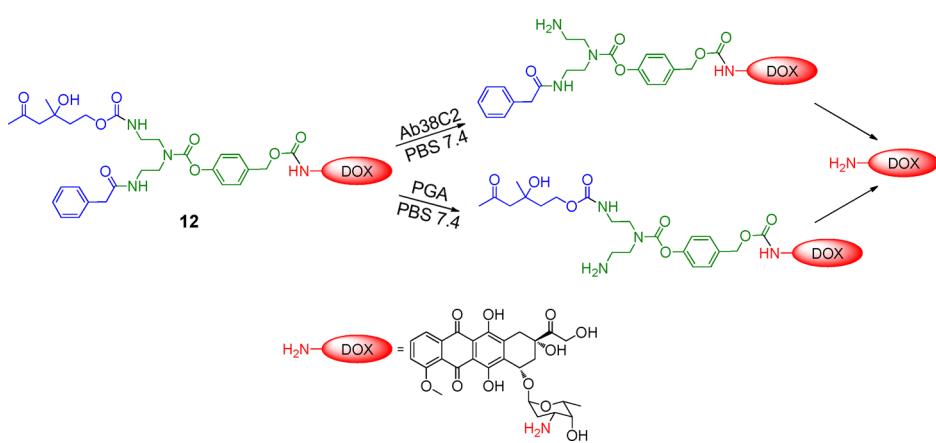


Figure 10. Dendritic prodrug activated through a molecular “OR” logic dual-triggering mechanism by PGA or catalytic antibody 38C2.

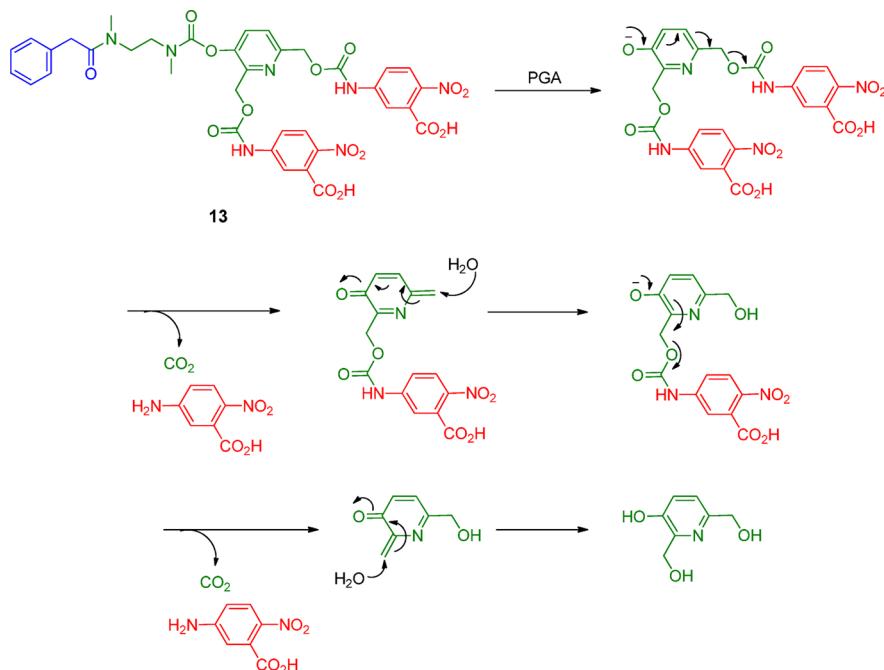


Figure 11. PGA-triggered double pyridinone methide eliminations release two reporter units from a pyridine ring system.

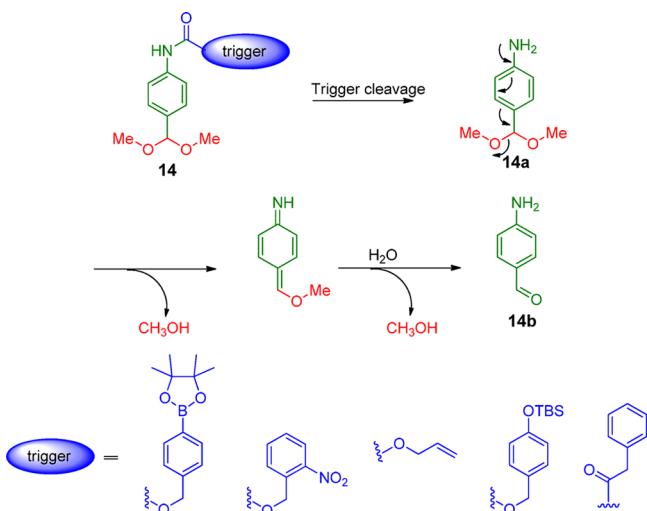


Figure 12. Design of a small-molecule controlled-release reagent capable of responding to a specific chemical signal with release of two different types of alcohols and **14b**, which has visible absorption (yellow color).

aniline intermediate **14a**, which undergoes a self-immolative reaction sequence that ends with spontaneous release of two copies of a pendant alcohol via double 1,6-elimination reactions along with the colorimetric indicator **14b**. This dendron has higher stability under physiological conditions than that based on a carbonate linkage. Furthermore, the group designed a β -D-glucuronidase-responsive probe that simultaneously releases two different types of alcohols and a colorimetric indicator.

2.1.1. Self-Immulative Dendritic Prodrugs. Conjugation of self-immulative dendrimers with bioactive molecules as end units produces a system capable of releasing multiple drugs upon a single activation event. We initially demonstrated this concept using an AB_2 self-immulative dendritic unit with therapeutic agents attached to a specific triggering substrate. Cleavage of the trigger generates the related phenol intermediate, which

undergoes a self-immolative reaction sequence that results in spontaneous release of the drugs via a double 1,4-elimination. The first two examples of a self-immolative homodimeric prodrug containing the chemotherapeutic drugs camptothecin (CPT) and DOX (prodrugs **15** and **16**, respectively) are shown in Figure 13. These anticancer drugs were grafted with the retro-aldo retro-Michael substrate of antibody 38C2 as a trigger. A heterodimeric prodrug consisting of the AB_2 self-immolative dendritic system and two different drugs as end units was also prepared (Figure 13, prodrug **17**). A synergistic cytotoxic effect was observed with this heterodimeric prodrug upon bioactivation by the catalytic antibody 38C2.³¹

Our group has also reported an AB_3 dendritic molecular system with three CPT drug molecules (prodrug **18**; Figure 14).³² Activation of the trigger by antibody 38C2 results in the release of the three drug molecules through a cyclization step and triple quinone methide eliminations. The single-triggered self-immolative homotrimeric prodrug was more potent than the related self-immolative monomeric prodrug in the presence of catalytic antibody 38C2. Furthermore, we have also prepared a self-immolative heterotrimeric prodrug system using CPT, DOX, and etoposide end units and a specific trigger activated by antibody 38C2 (prodrug **19**; Figure 15). A single cleavage event at the trigger releases the three different anticancer drugs almost simultaneously.

The first generation of self-immolative dendritic prodrugs are a potential platform for drug release amplification. Second-generation self-immolative dendrimers have not been as promising because of aggregation resulting from the hydrophobic structure as well as low cleavage efficiencies and steric hindrance at the dendron's focal site. In order to overcome these obstacles, we grafted dendrimer **20** with poly(ethylene glycol) (PEG).³³ The PEG tails decrease the hydrophobic properties of the dendritic molecule and increase its aqueous solubility, thereby preventing aggregate formation. A dendritic prodrug with two PEG-5000 tails equipped with four CPT molecules and a single-triggering substrate activated by PGA was assembled, as

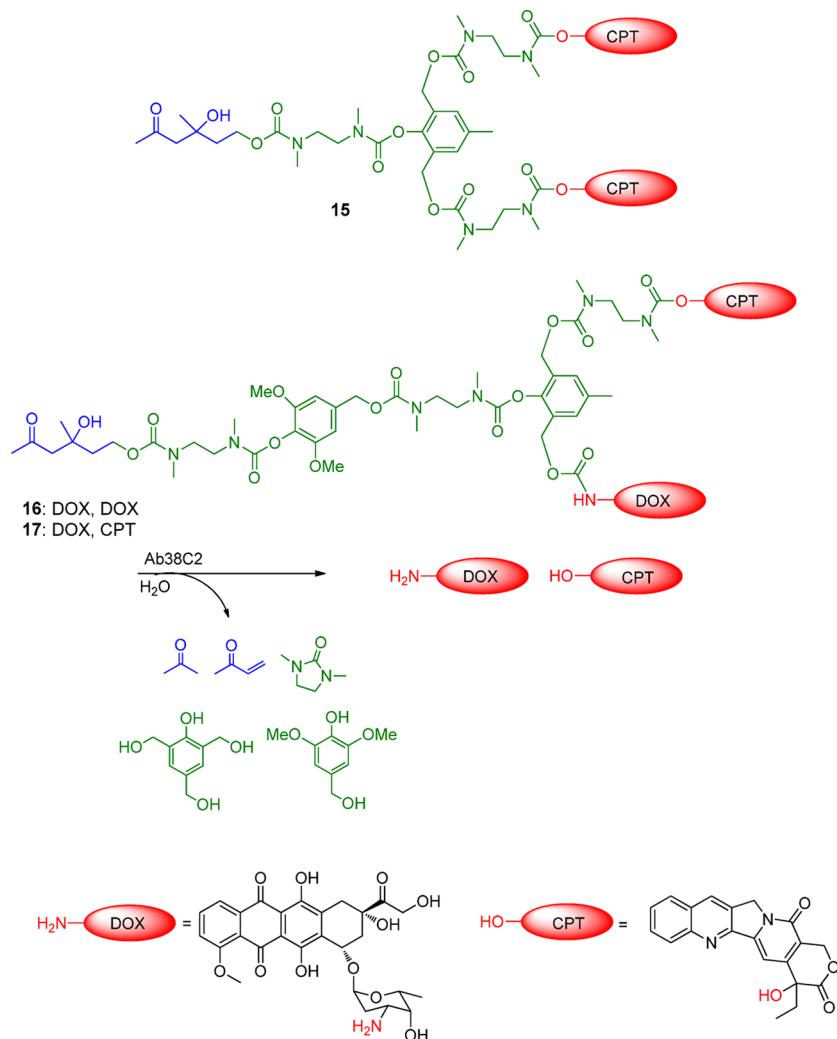


Figure 13. Disassembly pathway of homodimeric and heterodimeric prodrugs of doxorubicin and camptothecin triggered by catalytic antibody 38C2.

shown in Figure 16. The self-immolative homotetrameric prodrug was effectively activated by PGA under physiological conditions, and four CPT molecules were released to the medium.

Next, we carried out a comparison of the disassembly of an AB_3 self-immolative dendritic platform based on 1,6- and 1,4-eliminations with a platform containing the N,N' -dimethylethylenediamine moiety. Both systems can release three active drugs upon a single cleavage by the model enzyme PGA (Figure 17). The elimination-based AB_3 dendritic prodrug 21 showed a significant enhancement of drug release in comparison with cyclization-based AB_3 dendritic prodrug 22. This difference was clearly reflected in a cytotoxicity assay.³⁴

In another example, Papot and co-workers functionalized our AB_2 self-immolative dendron with therapeutic drugs (Figure 18).³⁵ The single-triggered molecular system 23 is composed of the β -glucuronidase enzymatic substrate and DOX and MS-275 drug units. Interestingly, they showed that the AB_2 self-immolative amplifier is also cytotoxic as a result of its transformation into the azaquinone methide, which acts as a potential alkylating species.

Papot and co-workers also reported the synthesis and characterization of an AB_2 self-immolative prodrug that includes a triggering substrate activated by β -glucuronidase and two DOX molecules (prodrug 24; Figure 19).³⁶ Upon β -glucuronidase

activation, the dendritic prodrug was 2-fold more toxic toward H661 lung cancer cells than its monomeric counterpart.

The same group replaced the trigger with a substrate activated by lysosomal β -galactosidase and incorporated folic acid as a targeting moiety (Figure 20).³⁷ Because of the presence of the folate, the self-immolative molecular system 25 recognized a population of cells that express the folate receptor in an autonomous manner.

We have reported an AB_3 dendritic prodrug conjugated to N -(2-hydroxypropyl)methacrylamide (HPMA) copolymer.³⁸ HPMA copolymers are water-soluble, nonimmunogenic, and nontoxic ligands that enable targeted drug delivery to tumor cells due to the enhanced permeability and retention (EPR) effect. The copolymer–dendritic conjugate prodrug 26 was designed to release a triple cargo of the hydrophobic drug paclitaxel (PTX) upon cleavage of the substrate Gly-Phe-Leu-Gly by the endogenous enzyme cathepsin B (Figure 21). This strategy resulted in higher loading capacity of PTX molecules per HPMA polymer molecule and enhanced the PTX cytotoxicity relative to a monomeric HPMA–PTX conjugate. The HPMA–dendritic PTX bioconjugate was more cytotoxic to murine prostate adenocarcinoma cells than was the monomeric HPMA–PTX conjugate.

Another elegant example of dendritic prodrug design was reported by the Zhang research group.³⁹ They synthesized a UV-

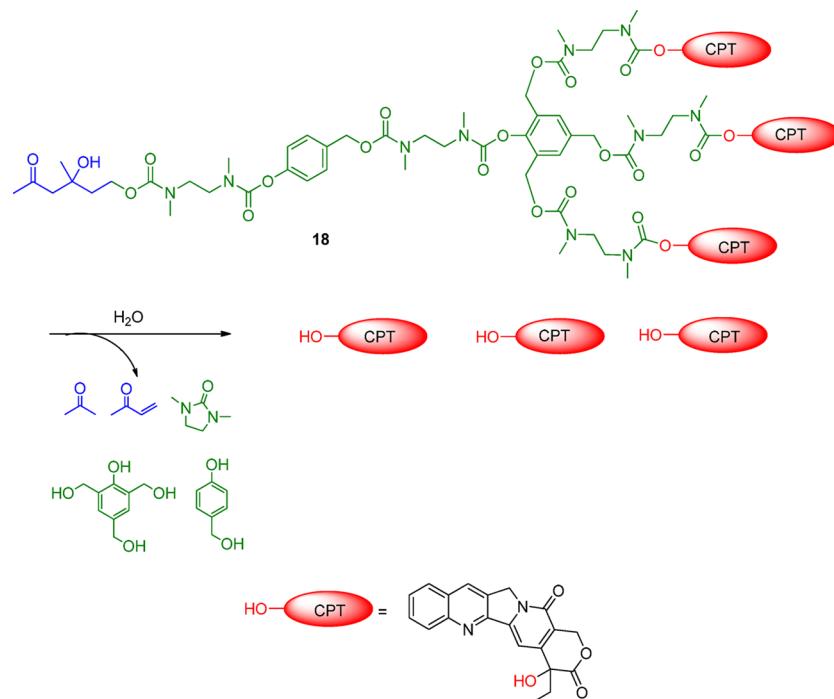


Figure 14. Molecular structure and disassembly pathway of the CPT trimeric prodrug **18** triggered by a single cleavage event catalyzed by antibody 38C2.

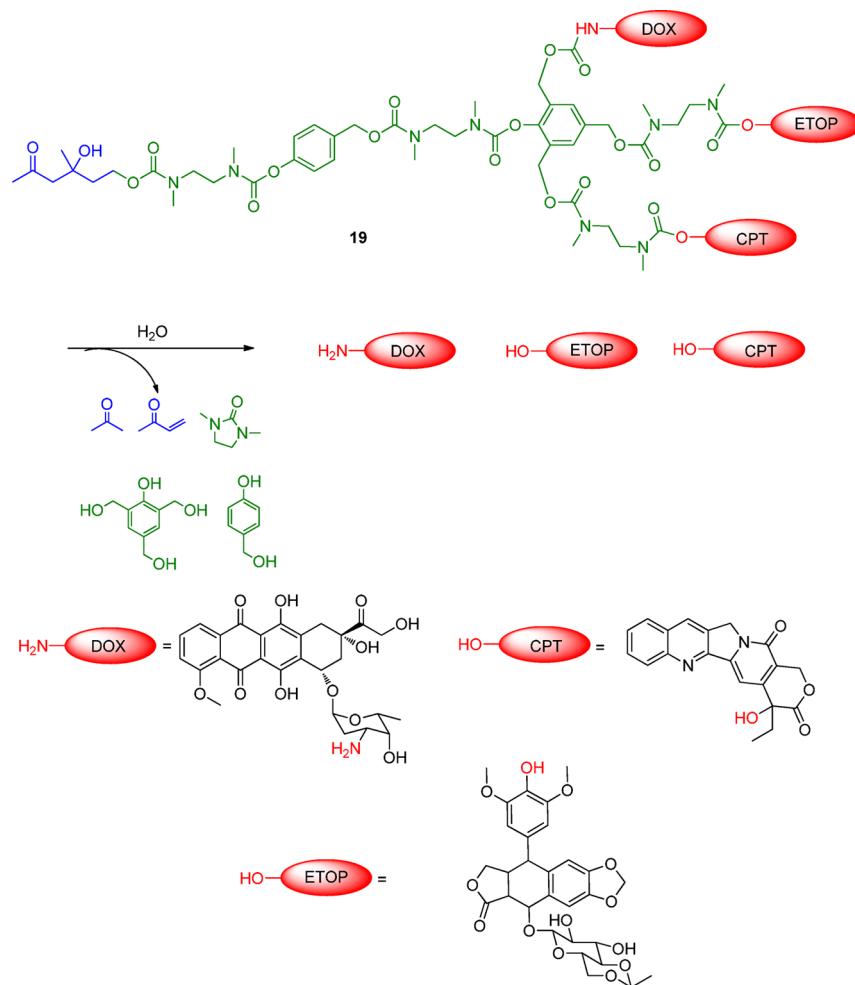


Figure 15. Single-triggered heterotrimeric prodrug system with the anticancer drugs CPT, DOX, and etoposide (ETOP).

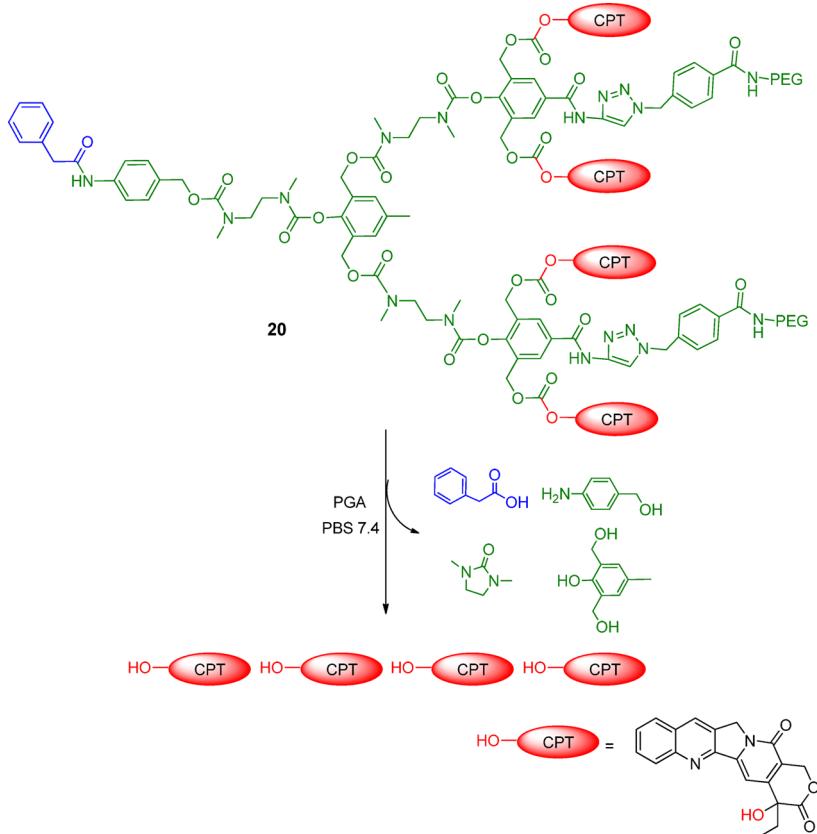


Figure 16. Disassembly pathway of second-generation dendritic prodrug **20** functionalized with PEG tails to enhance the solubility triggered by enzymatic activation by PGA.

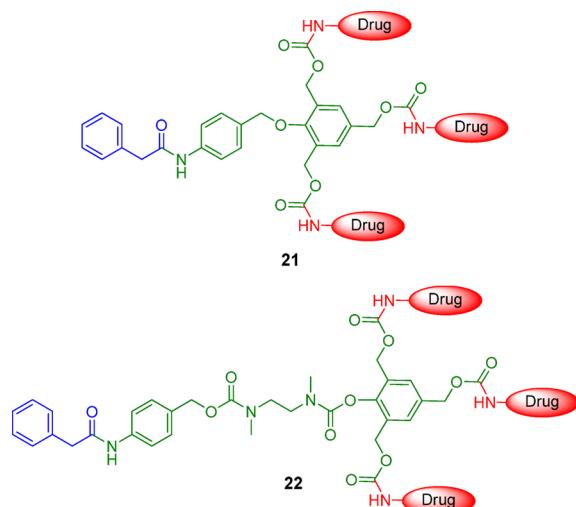


Figure 17. Chemical structures of AB₃ self-immolative dendritic prodrugs with melphalan tail units and a trigger that is activated by PGA. Elimination-based prodrug **21** released drugs more efficiently than cyclization-based prodrug **22**.

responsive self-immolative dendrimer based on a phenol AB₃ system that is linked through carbonate bonds to three CPT molecules at the periphery. The self-immolative dendron was conjugated to a DNA strand, creating an amphiphilic prodrug (Figure 22). In an aqueous environment, prodrug 27 undergoes self-assembly into nanostructures (Figure 23); the nanostructures are rapidly taken into cells, and the attached DNA is resistant to nuclease cleavage. UV irradiation at 365 nm results in

detachment of the nucleic acid shell, exposing the phenolate of the self-immolative dendron. Triple elimination releases the active CPT drug. This strategy has potential clinical applications.

2.1.2. Self-Immulative Dendritic Probes. Self-immolative dendrimers can act as molecular signal amplifiers because of their ability to release multiple end units. A single triggering event via an analyte-responsive group induces a cascade of reactions based on 1,4- and 1,6-eliminations, leading to disassembly and end-group release. This signal amplification principle was implemented in a molecular AB₃ probe system designed to detect the explosive triacetone triperoxide (TATP).⁴⁰ Treatment of TATP with acid results in the generation of H₂O₂, and therefore, a probe for H₂O₂ can be used to detect TATP. Probe **28** containing an arylborate ester that reacts with H₂O₂ was exposed to TATP. The aniline intermediate generated subsequently underwent triple azquinone methide eliminations to release three fluorogenic reporters (Figure 24). A fluorescence response study indicated that the fluorescence intensity produced by probe **28** in the presence of micrograms of triacetone triperoxide in aqueous buffer was about 3 times higher than that observed in the presence of 3 equiv of nondendritic probe **29** (Figure 25).

Chemiluminescent probes based on 3-hydroxyphenyl-1,2-dioxetane are used in various diagnostic applications and can be activated by various enzymatic or chemical reactions. A number of limitations have restricted their chemical and biological applications, including the short lifetime of the light emission and low chemiluminescence intensities at low concentrations of analyte in aqueous solutions. In order to address some of these problems, Akkaya and co-workers engineered an amplification system, dendron **30**, composed of one AB₂ self-immolative dendritic unit equipped with two chemiluminescent 3-

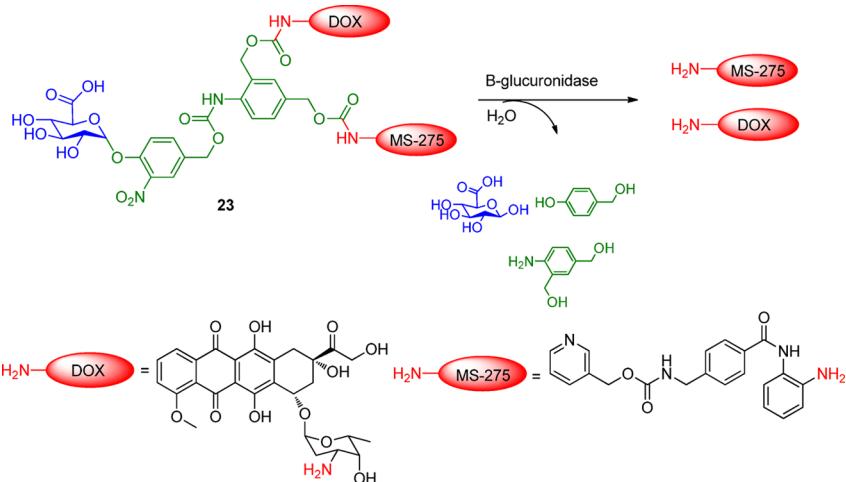


Figure 18. β -Glucuronidase catalyzes the release of two anticancer drugs from AB_2 self-immolative molecular dendritic system 23.

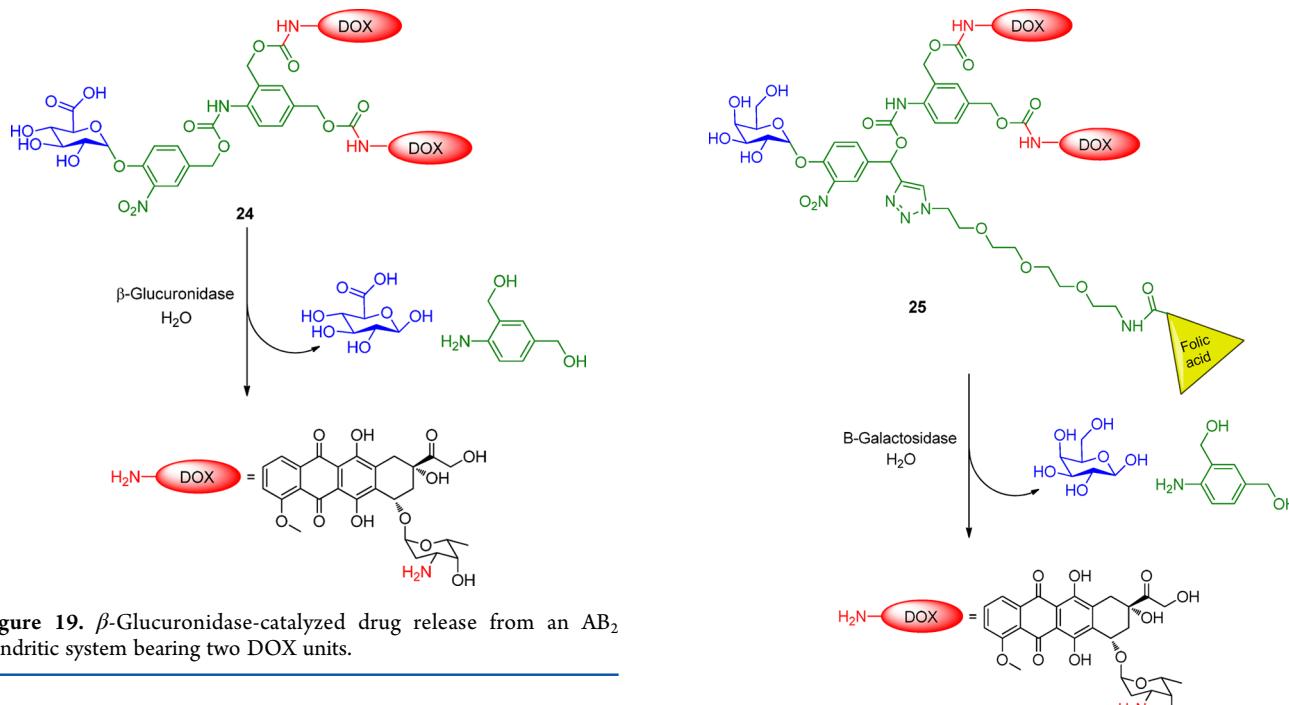


Figure 19. β -Glucuronidase-catalyzed drug release from an AB_2 dendritic system bearing two DOX units.

hydroxyphenyl-1,2-dioxetane structures (Figure 26).⁴¹ The triggering cleavage event in the presence of fluoride results in double 1,4-eliminations and leads to significant amplification of the signal produced in response to the presence of fluoride compared with that of the native molecule 31. The reported quantum yield of the chemiluminescence process ($\phi_{\text{cl}} = 0.46$) was almost twice that of 31.

Most molecular probes currently used for the detection of enzymatic activity are based on the generation of chromogenic species through the catalytic activity of a specific enzyme. The chromogenic behavior is usually monitored by fluorescence or UV-vis spectroscopic techniques. Fluorescence can be detected at very low chromophore concentrations; however, quenching of the fluorescence signal is observed in certain environments. Our research group reported the first example of a molecular probe with dual output signals offering two detection modes, UV-vis and fluorescence, allowing the use of the same molecular probe in different environments (Figure 27).⁴² Dendron 32 consists of a phenylacetamide moiety, which acts as a trigger substrate for the bacterial enzyme PGA, and 4-nitrophenol and 6-aminoquinoline

Figure 20. β -Galactosidase-catalyzed release of two drug units from an AB_2 self-immolative molecular dendritic system with a moiety that binds to the folate receptor.

as the reporter units. The reporter molecules are attached through stable carbamate linkages that maintain the signals in an OFF position. Cleavage of the phenylacetamide trigger initiates the release of the two reporter units, and the signal for each turns ON. The 4-nitrophenol is detected by its visible yellow color, and 6-aminoquinoline is detected by its fluorescence emission.

Jullien and co-workers reported 33, a dendritic self-immolative system that allows the controlled release of two reporter units by photoactivation.⁴³ Equipped with a UV-sensitive trigger, the self-immolative adaptor is conjugated to two different fluorophores through carbonate bonds (Figure 28). The carbonate bonds mask the phenol moieties of the dyes, thus quenching their fluorescence. The kinetic disassembly of dendron 33 has been thoroughly analyzed in cell-based assays.

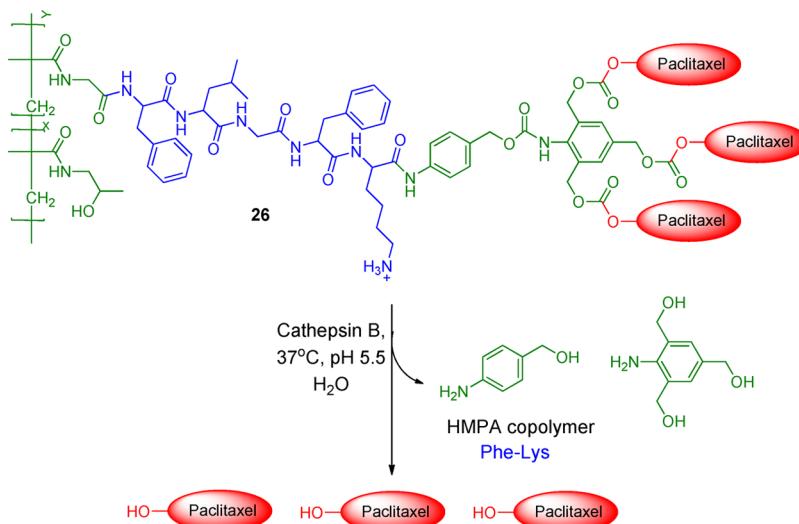


Figure 21. Chemical structure of an HPMA copolymer-AB₃ dendritic prodrug conjugate and its disassembly mechanism.

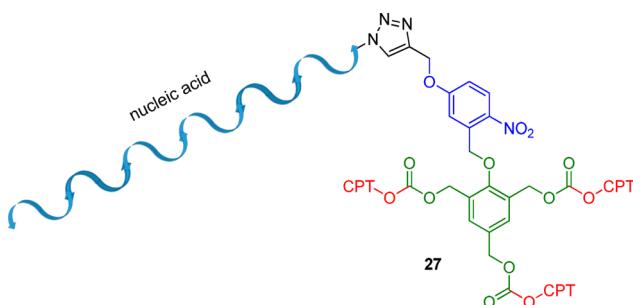


Figure 22. Design of amphiphilic self-immolative dendritic prodrug 27.

Molecular probes based on diverse classes of turn-ON optical fluorescence signals are used in various diagnostic applications. We have reported an AB₂ self-immolative dendritic adaptor for homo-Förster resonance energy transfer (homo-FRET) prepared using a dye with a small Stokes shift, as shown in Figure 29.⁴⁴ Probe 34 is an AB₂ self-immolative molecule with Cy5 dye substituents, which have a small Stokes shift, at the *ortho* and *para* benzylic positions. The triggering event is followed by 1,6-azaquinone methide elimination to generate aniline derivative 34a. Consecutive 1,6- and 1,4-eliminations then release the two Cy5 molecules. The fluorescence spectrum of probe 34, compared with that of free Cy5, indicated a homo-FRET quenching effect. The use of probe 34 for the detection of protease PGA has been demonstrated. Similarly, we have

designed other FRET molecular probes consisting of fluorophores and quenchers.⁴⁴

Using this homo-FRET-based modular design, we have developed a new dendritic platform for the preparation of theranostic prodrugs. An example is prodrug 35 (Figure 30), which is based on self-immolative dendritic units that hold two FRET dyes in close spatial proximity, thereby quenching their fluorescence.⁴⁵ Prodrug 35 is equipped with phenylacetamide as a PGA substrate and CPT conjugated through a self-immolative bridge. The linker is constructed from two aniline adaptor units attached to a pair of fluorescein dyes. Activation of the trigger moiety by PGA exposes the aniline unit, which undergoes sequential 1,6-eliminations that increase the distance between the fluorescent dyes and released the active CPT. We demonstrated a linear correlation between drug release and the fluorescence signal.

Hennig and co-workers synthesized several turn-ON optical probes based on the self-immolative dendritic platform 36 (Figure 31).⁴⁶ The probes were synthesized starting from 2,4- and 2,6-bis(hydroxymethyl)aniline. The probes are equipped with phenylacetamide, a PGA substrate. Two benzylic positions are conjugated to dye molecules through a carbamate bond, thus holding the two dyes in close spatial proximity. This closeness ensures quenching of the fluorescence due to the formation of the nonfluorescent H-dimer of identical dyes. Incubation of the probes with PGA leads to hydrolysis of the phenylacetamide followed by double elimination reactions that lead to release of

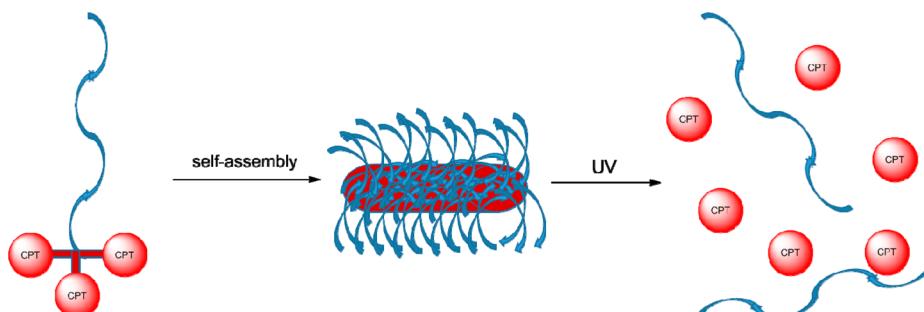


Figure 23. Illustration of the self-assembly and disassembly self-immolative dendritic prodrug 27 upon UV irradiation. DNA is shown in blue and the dendrimer scaffold in red.

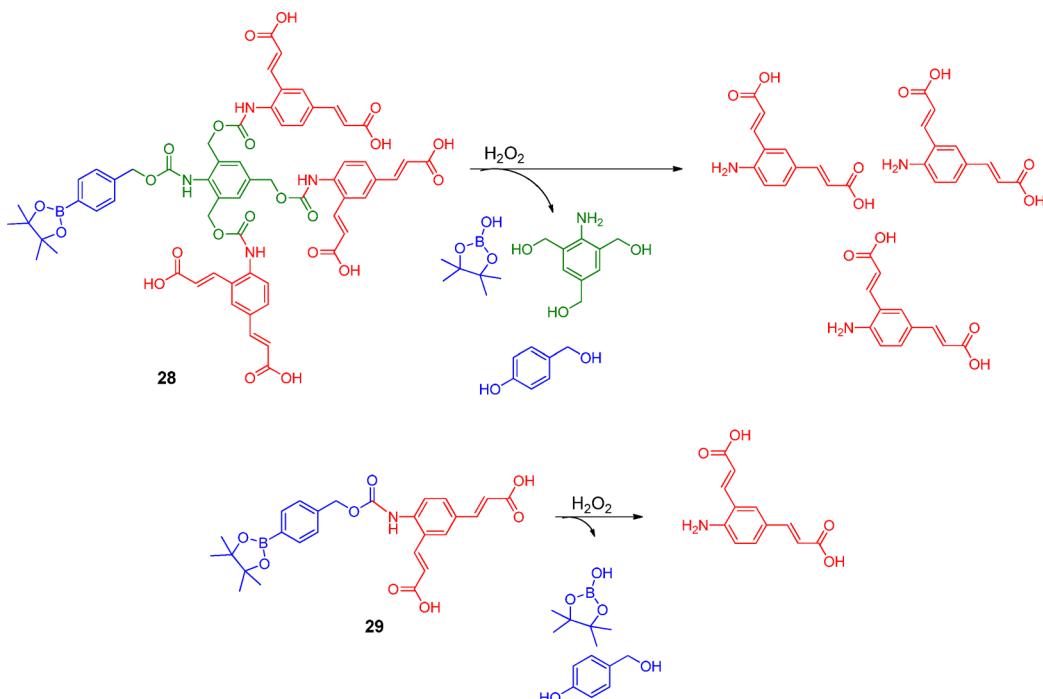


Figure 24. Probe 28 reacts with a single molecule of hydrogen peroxide to release three reporter units. The probe is a sensitive detector of the explosive TATP.

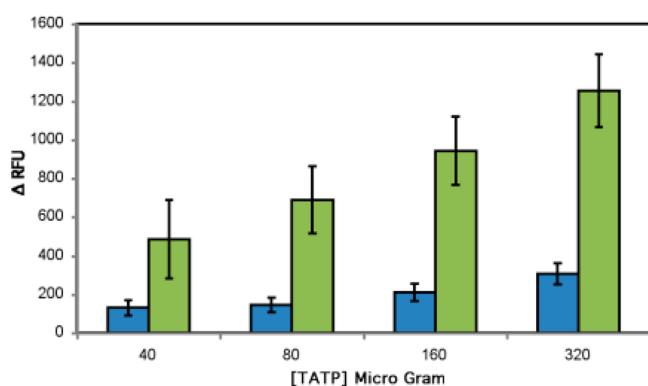


Figure 25. Fluorescence response of probes 29 (blue) and 28 (green) in the presence of TAPP. Reproduced with permission from ref 40. Copyright 2008 Royal Society of Chemistry.

the dye molecules. The authors also reported a detailed photophysical and kinetic analysis of these dendritic optical probes.

Warnecke and Kratz⁴⁷ reported a dendritic platform based on a 2,4-bis(hydroxymethyl)aniline linker. This linker allows branching. System 37 bears three tryptamines as leaving groups that are connected via carbamate bonds to the linker (Figure 32). Cleavage of the trigger initiates sequences of both 1,4- and 1,6-elimination, which are followed by a decarboxylation reaction and the release of the tryptamines. Chain degradation through 1,6-elimination occurs much more rapidly than the effector release through 1,4-elimination.

2.1.3. Other Self-Immulative Dendritic Applications.

Two-photon near-infrared (NIR)-responsive triggers with an enhanced action cross section are of great interest. Triggers of this type synthesized to date suffer from relatively low action cross sections. One way to overcome this problem is to amplify the signal generated upon one triggering event in a dendritic cascade pathway. Almutairi's research group has reported zeroth-, first-, and second-generation self-immulsive dendrimers that undergo disassembly upon exposure to two-photon NIR irradiation.⁴⁸ Scaffold 38 is constructed from two self-immulsive linkers, an AB₂ *p*-cresol system and an *N,N'*-dimethylethylenedi-

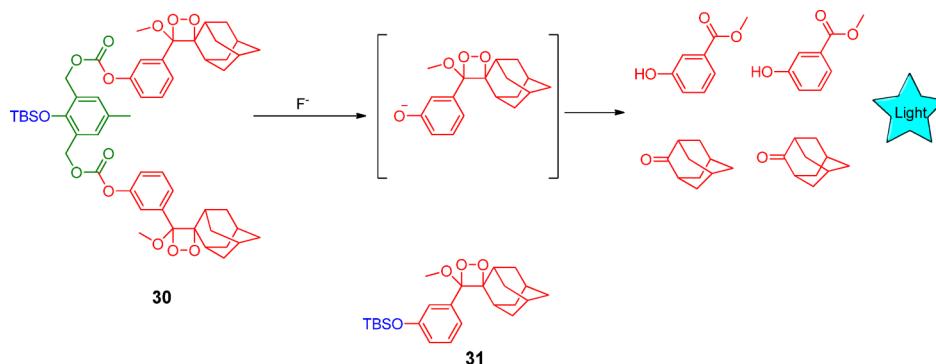


Figure 26. AB₂ self-immulsive chemiluminescent fluoride sensor.

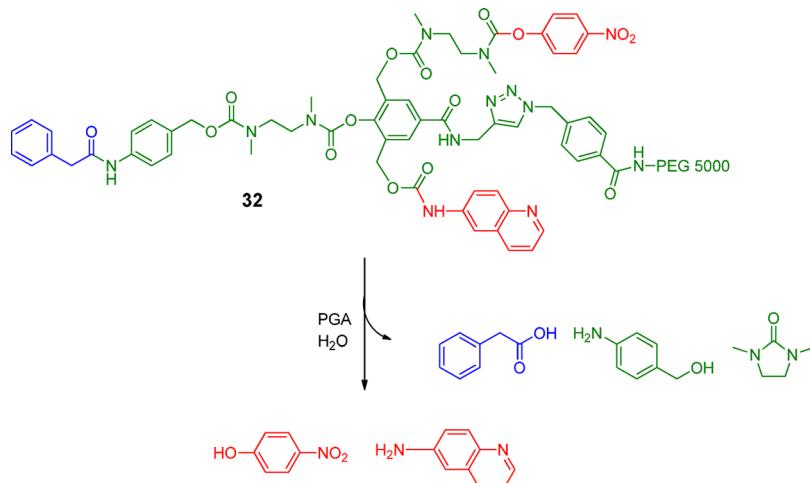


Figure 27. Chemical structure and activation of a molecular probe with UV–vis and fluorescence outputs for PGA activity.

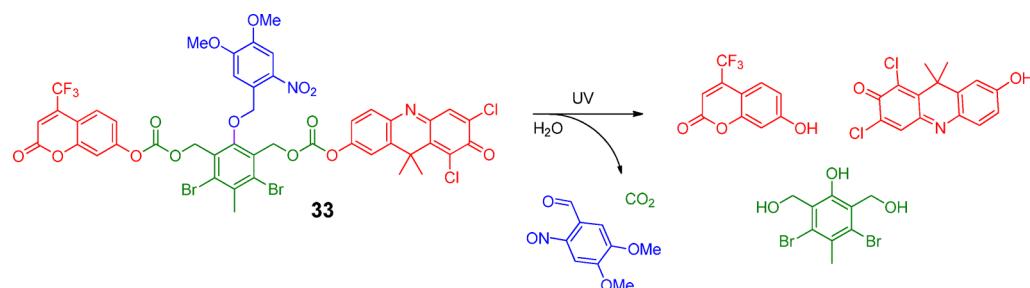


Figure 28. Structure and degradation of a self-immolative dendron that releases two different fluorophores upon UV irradiation.

amine. 4-Bromo-7-hydroxycoumarin (BHC) was chosen as a two-photon NIR trigger. At the periphery the researchers placed four glutamic acid molecules as the reporter groups (Figure 33). Cleavage of the BHC trigger by irradiation at a wavelength of 740 nm results in complete disassembly of the dendron through multiple 1,4-eliminations and cyclization reactions, resulting in release of the four glutamic acid molecules (Figure 34). This self-immolative dendritic platform was used to enhance the cleavage signal generated by each two-photon NIR triggering event.

Aromatic dipeptide nanotubes (ADNTs) exemplify a unique class of organic nanostructures that can self-assemble to form ordered bioinspired nanostructures. Biocompatible and water-soluble ADNTs are readily formed under mild conditions and have remarkable chemical and thermal stability and extraordinary mechanical strength. A limiting factor in the utilization of ADNT systems was that the formation of the nanoassembly process could not be precisely controlled by an external signal. Our group reported AB₃ self-immolative dendritic carrier 39, which can release three diphenylalanine molecules upon activation by PGA (Figure 35), resulting in the formation of well-ordered nanostructures. The dendritic system prevents the formation of any organized structures until the diphenylalanine groups are released.⁴⁹

Quinone methides are highly electrophilic and are responsible for DNA alkylation observed with drugs such as tamoxifen.⁵⁰ Fakhari and Rokita⁵¹ reported the synthesis of an AB₂ dendron that was utilized to produce a DNA-based scaffold for molecular transport. Upon trigger cleavage, the quinone methide is generated and can covalently bond to DNA (Figure 36). If the quinone methide is electron-rich, the covalent linkage is reversible. The tandem exchange of the bis(quinone methide)

intermediate yields an autonomous and bipedal-like migration of cross-linking within helical DNA (Figure 37). The cross-linking of the quinone methide and DNA can be controlled by altering the substituents on the phenol. The cross-linking efficiency is highly correlated with the electron-richness of the quinone methide, with 43 being more efficient than 42 and 41 more efficient than 40.

2.2. Dendritic Chain Reaction

Signal amplification techniques are used to enhance the detection sensitivity of analytes for diagnostic and imaging purposes. Our group has developed a novel modular technique for exponential amplification of chemical signals based on a dendritic chain reaction (DCR).⁵² DCR is a distinct amplification approach that takes advantage of disassembly and end-cap release features of self-immolative dendrons (Figure 38). The activation of an AB₃ dendron by an appropriate analyte leads to the release of one chromogenic reporter by 1,6-elimination and two reagent molecules by 1,4-eliminations. The released reagent molecules can then activate two additional AB₃ dendrons by cleavage of their triggers. This disassembly pathway simultaneously generates a chemical signal and an appropriate analyte that cleaves the trigger of another dendritic molecule to amplify the signal.

2.2.1. One-Component Dendritic Chain Reaction. The first example of such a DCR amplification cycle was demonstrated by our group in 2009.⁵³ We showed that hydrogen peroxide molecules cleave the trigger of dendron 44, which then releases one 4-nitroaniline reporter by 1,6-elimination and two choline molecules by double 1,4-elimination (Figure 39). Choline oxidase (COX) oxidizes two free choline molecules and consequently generates four molecules of hydrogren

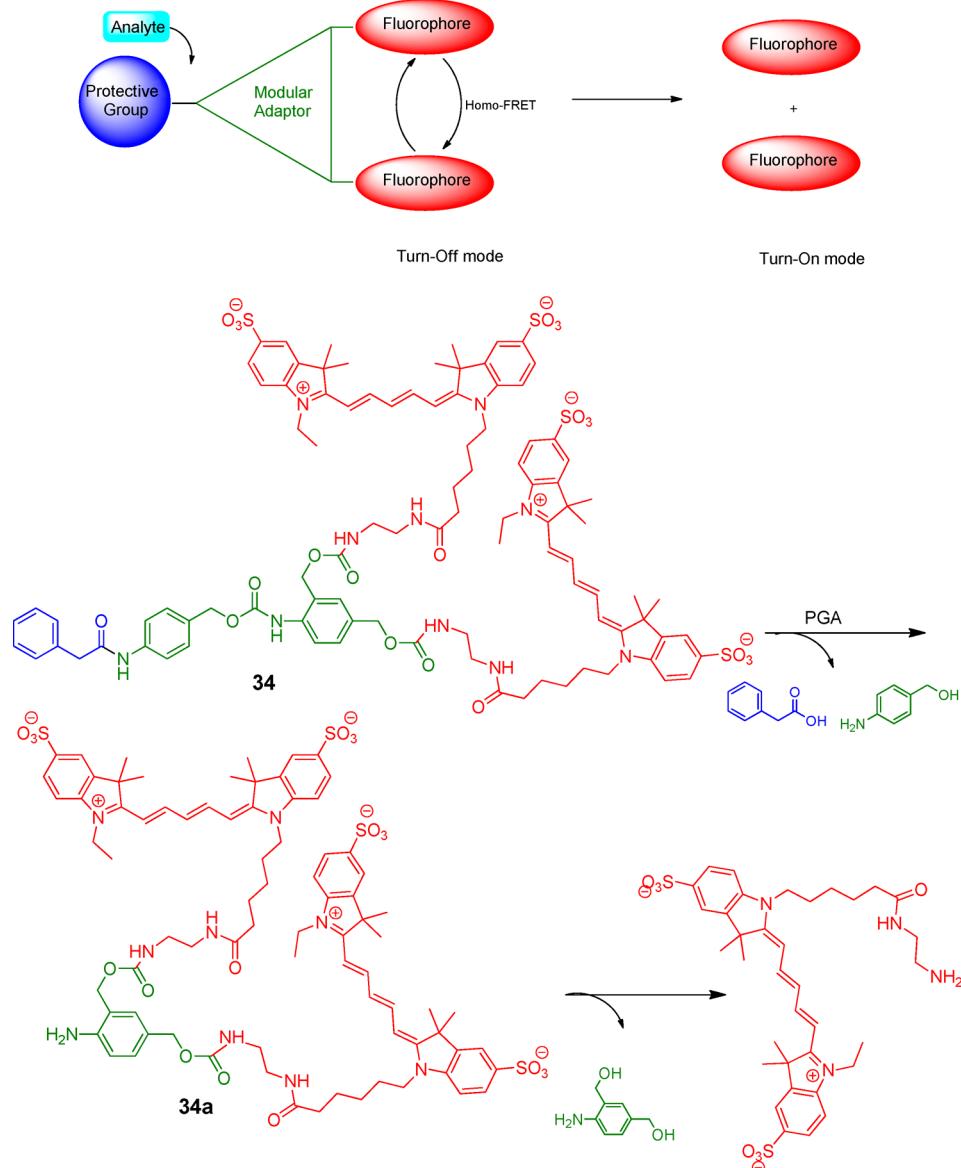


Figure 29. Modular design of a homo-FRET optical probe with a fluorophore–fluorophore pair.

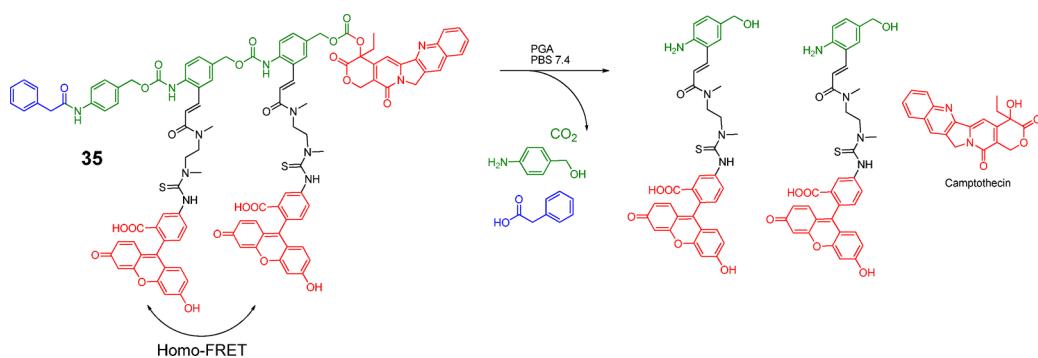


Figure 30. Design and disassembly of enzyme-responsive theranostic prodrug 35.

peroxide, which in turn activate four additional dendrons. The release rate of 4-nitroaniline increases exponentially until complete disassembly of all dendrons in the sample has been achieved.

A spectroscopic evaluation study of the DCR technique using dendron 44 was carried out by incubation of 44 with various

amounts of hydrogen peroxide in the presence of COX. The release of 4-nitroaniline was monitored at a wavelength of 405 nm (Figure 40). The sensitivity of the DCR technique is apparent when presented next to a signal obtained without the addition of COX. In this example, the obtained signal-to-noise ratio was more than 50-fold.

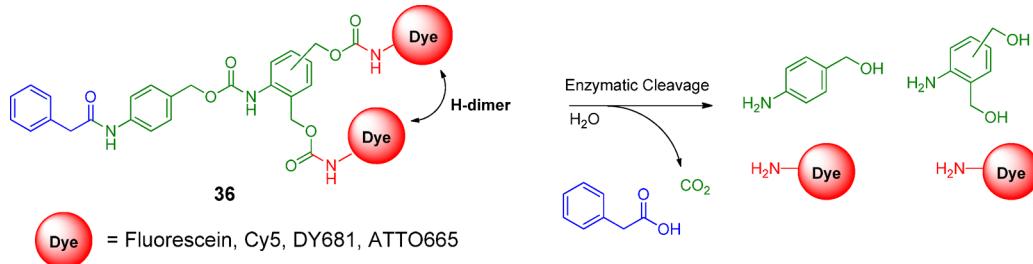


Figure 31. General design of optical probes based on H-dimerized fluorophores.

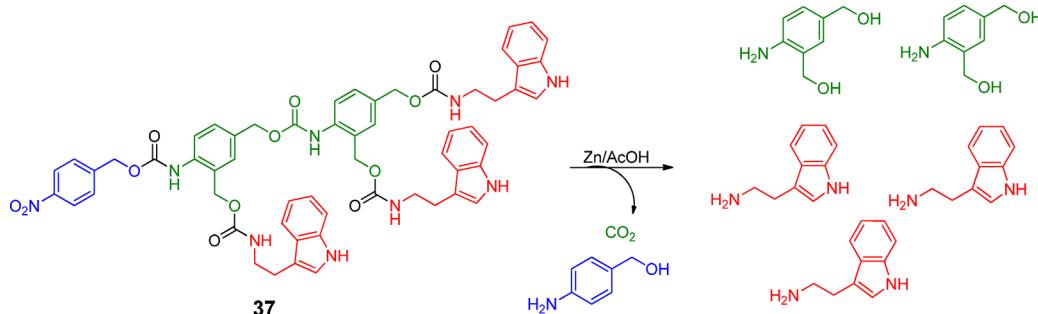


Figure 32. Structure and disassembly of a 2,4-bis(hydroxymethyl)aniline-based dendritic system bearing three tryptamines.

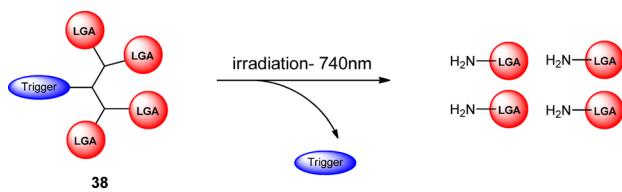


Figure 33. Illustration of the disassembly of a second-generation self-immolative dendron upon two-photon NIR excitation; the reporters are glutamic acid (LGA).

Using the modular design of the DCR technique, our group developed DCR probe **45** in which the choline substituents in dendron **44** were replaced by methanol (Figure 41).⁵⁴ Dendron **45** had higher stability in aqueous media, underwent less spontaneous hydrolysis, showed a lower background signal, and exhibited higher sensitivity in detection of hydrogen peroxide than probe **44**. Methanol released from dendron **45** via double 1,4-elimination is oxidized by alcohol oxidase (AOX) to produce

two molecules of hydrogen peroxide. The amplification cycle repeats until all of the reporter molecules are released (Figure 42).

In another example, DCR probe **46** was designed for the detection of fluoride anion. The probe is an AB₃ self-immolative dendron equipped with a silyl ether trigger (*tert*-butyldimethylsilyl (TBS)) and 4-nitroaniline as a chromogenic reporter (Figure 43). The probe activity is based on a DCR that generates fluoride anions through 1,4-eliminations during the disassembly pathway.⁵⁵ Fluoride detection using a self-immolative technique was also reported by Baker and Phillips,⁵⁶ who showed that probe **47** releases two fluoride anions via double 1,6-elimination, affording the chromogenic product 4-aminobenzaldehyde (Figure 44).

2.2.2. Two-Component Dendritic Chain Reaction. Our group has developed a simplified approach to achieve exponential amplification of a diagnostic signal through a two-component dendritic chain reaction (2CDCR).⁵⁷ The first component, dendron **44**, is an AB₂ self-immolative dendron

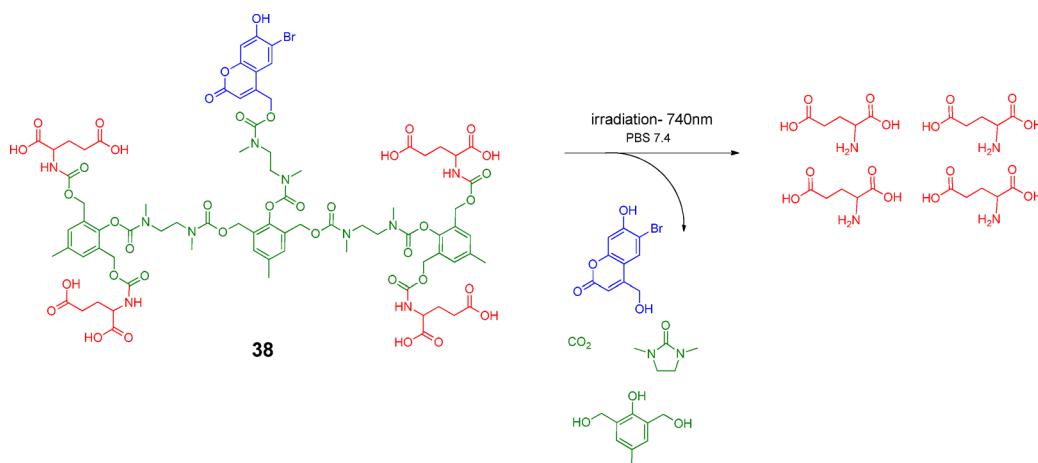


Figure 34. Structure of the second generation self-immolative dendrimer and its disassembly upon photoactivation by NIR radiation.

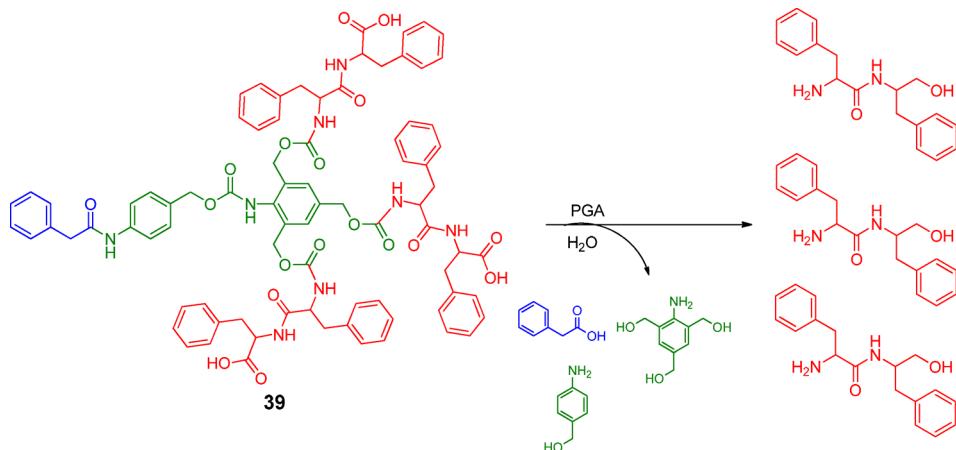


Figure 35. AB₃ self-immolative dendritic system with diphenylalanine end units and a PGA enzyme substrate as a trigger. After release from the dendritic carrier, the diphenylalanine dipeptides (red) form nanostructures.

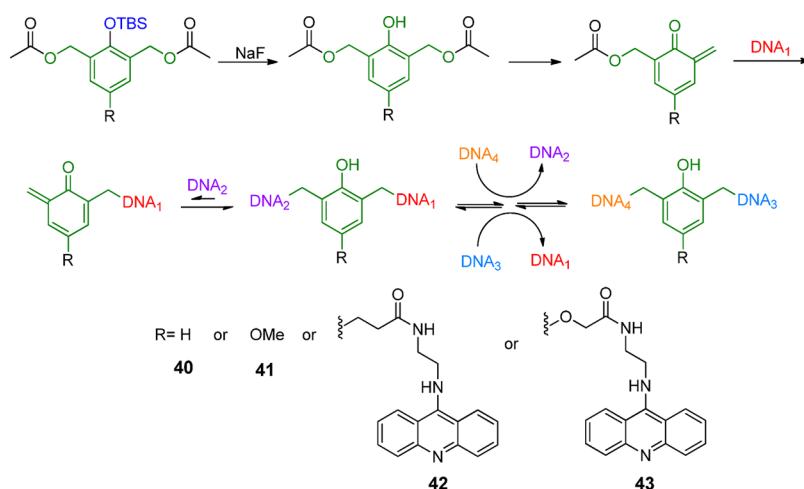


Figure 36. Disassembly of an AB₂ dendron generates quinone methides that covalently bond to DNA. The bond between the DNA and quinone methide is reversible, and DNA exchange occurs (see Figure 37).

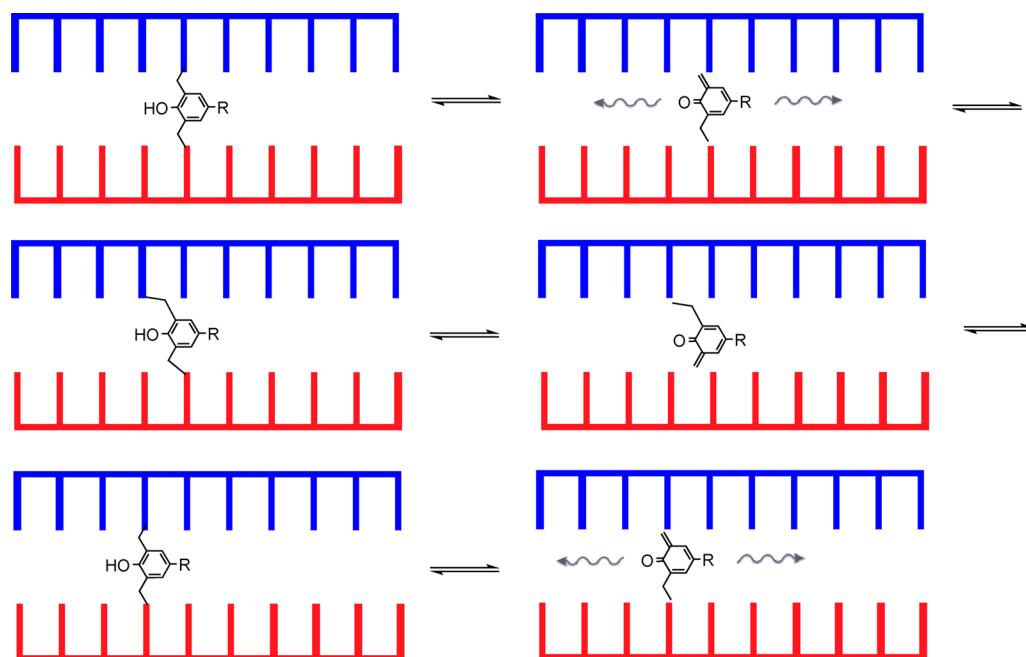


Figure 37. Capture and release of a bis(quinone methide) intermediate results in bipedal-like walking of the compound within duplex DNA.

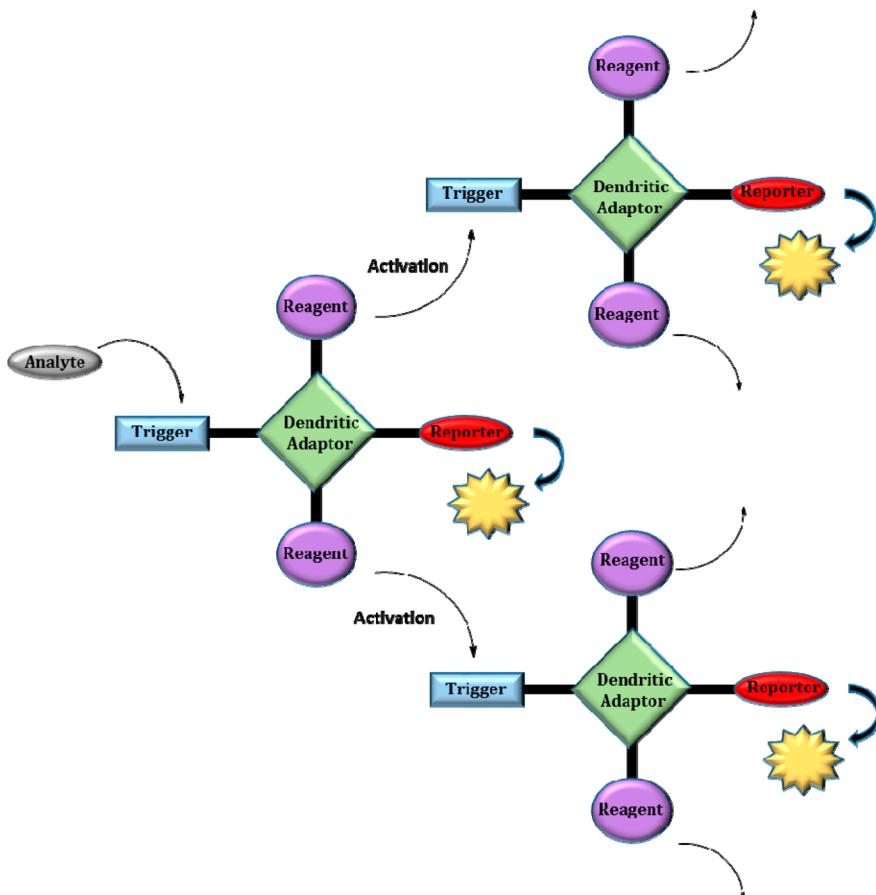


Figure 38. Graphical illustration of the DCR amplification pathway. Adapted from ref 53. Copyright 2009 American Chemical Society.

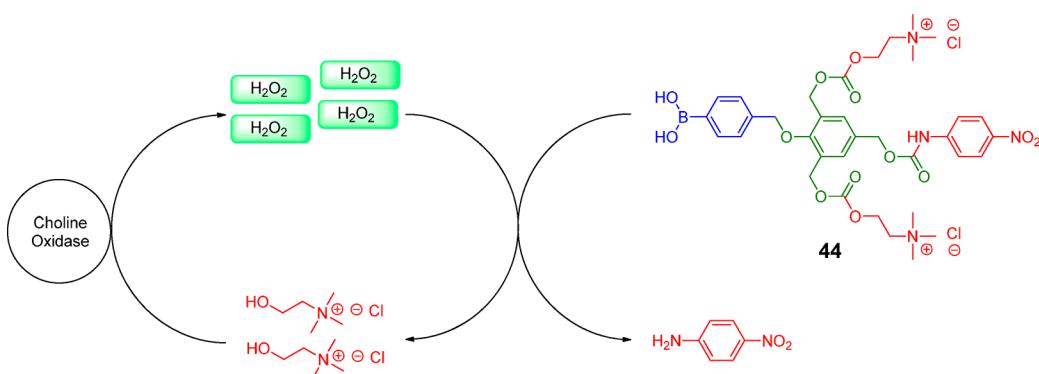


Figure 39. DCR system based on H_2O_2 triggering and choline molecules.

equipped with two choline units and phenylboronic acid as a trigger for hydrogen peroxide. The second component, **48**, is composed of the same trigger (i.e., phenylboronic acid) and 5-amino-2-nitrobenzoic acid as a reporter (Figure 45). The AB_2 self-immolative dendron **44** acts as an amplifier moiety, whereas component **48** acts as a probe that releases a chromogenic molecule to produce a diagnostic signal. The cleavage of dendron **44** induced by a hydrogen peroxide molecule results in the release of two choline molecules. The two free choline molecules are oxidized by COX to produce four molecules of hydrogen peroxide. This hydrogen peroxide activates two additional AB_2 dendrons (**44**) and two probe molecules (**48**). The rate of disassembly is exponentially increased until all of the reporter molecules are released.

An independent 2CDCR amplification cycle that does not require additional reagents or enzymes was reported by our group for the detection of ubiquitous sulfhydryls (Figure 46).⁵⁸ Probe **50** is composed of the 5-amino-2-nitrobenzoic acid reporter attached to the benzoquinone trigger for sulfhydryl; dendron **49** is equipped with two mercaptoacetic acid units and a benzoquinone trigger. The triggered cleavage of dendron **49** by a thiol molecule initially generates intermediate **49a**, which undergoes double elimination to release two mercaptoacetic acid molecules. Since the concentration of dendron **49** is at least twice of that of probe **50**, the rate of the system disassembly exponentially increases until all of the available 5-amino-2-nitrobenzoic acid reporter molecules have been released.

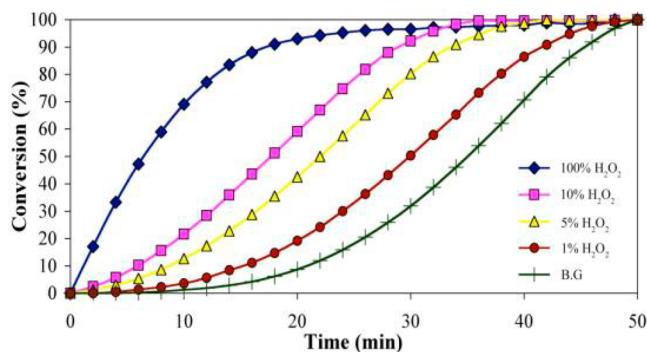


Figure 40. Release of 4-nitroaniline from dendron **44** in the presence of COX upon addition of different concentrations of H_2O_2 . Background noise (B.G.) was subtracted from the presented data. Reproduced from ref 53. Copyright 2009 American Chemical Society.

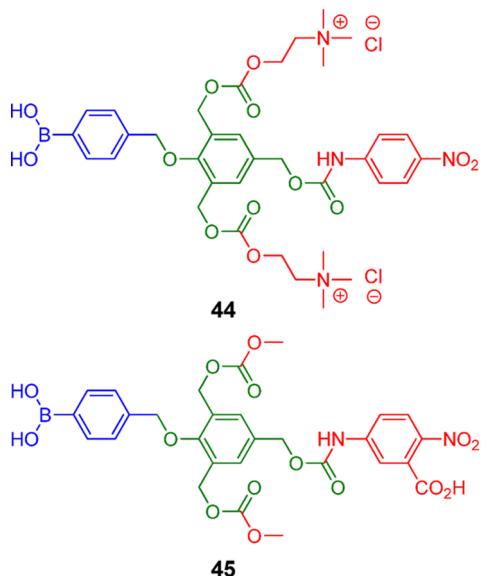


Figure 41. Chemical structures of DCR probes for detection of hydrogen peroxide.

To evaluate the effect of dendron generation on the signal amplification of 2CDCR systems, we prepared dendron **51** and probe **52**.⁵⁹ Dendron **51** is composed of two glucose units and a phenylboronic acid trigger for H_2O_2 , whereas probe **52** is composed of the 5-amino-2-nitrobenzoic acid reporter attached to a phenylboronic acid trigger. Cleavage of the trigger on dendron **51** by a molecule of H_2O_2 affords two free glucose

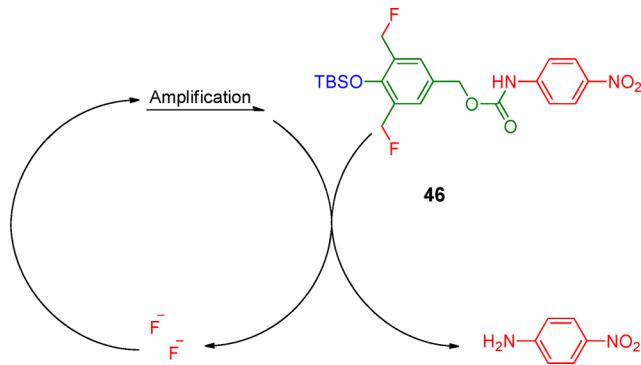


Figure 43. DCR-based probe for detection of fluoride anion.

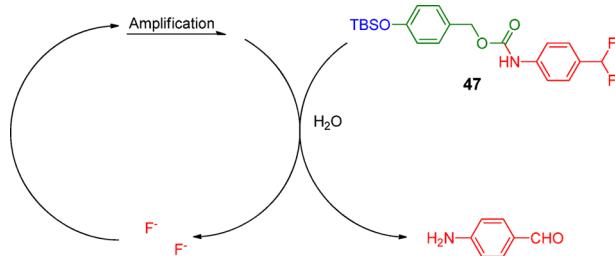


Figure 44. Pathway for autoinductive signal amplification for fluoride detection. Probe **47** degrades through double 1,6-elimination.

molecules, which then are oxidized by glucose oxidase to produce two molecules of H_2O_2 . The released H_2O_2 molecules simultaneously activate additional molecules of dendron **51** and probe **52** (Figure 47). Four different self-immolative dendrons (**53–56**) with various numbers of glucose end units were also synthesized. Each dendron was equipped with phenylboronic acid as a trigger. Dendrons **53** (AB_2 , two glucose units) and **54** (AB_3 , three glucose units) are based on a first-generation dendritic platform, whereas dendrons **55** (AB_4 , four glucose units) and **56** (AB_6 , six glucose units) are based on a second-generation dendritic platform (Figure 48). Of this series, the AB_3 self-immolative dendron **54** exhibited the best characteristics for use in a probe system, with rapid disassembly and good stability under aqueous conditions.

Hamachi's group utilized the DCR concept to fashion a multicomponent supramolecular hydrogel for naked-eye detection of small-molecule analytes. They constructed an H_2O_2 -responsive hydrogel, BPmoc- F_3 (**58**) (Figure 49) bearing a boronic acid moiety (BPmoc) and three diphenylalanines (F_3).⁶⁰ Upon exposure to H_2O_2 , the boronic acid moiety is removed, the

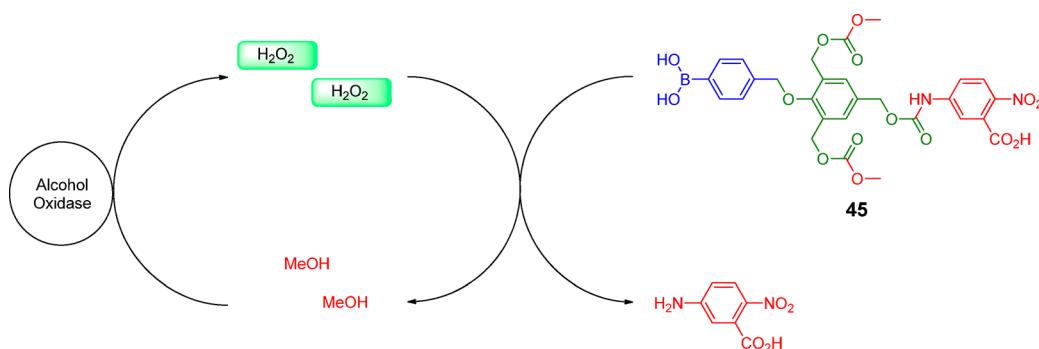


Figure 42. DCR probe for detection of H_2O_2 based on generation of H_2O_2 from methanol by alcohol oxidase.

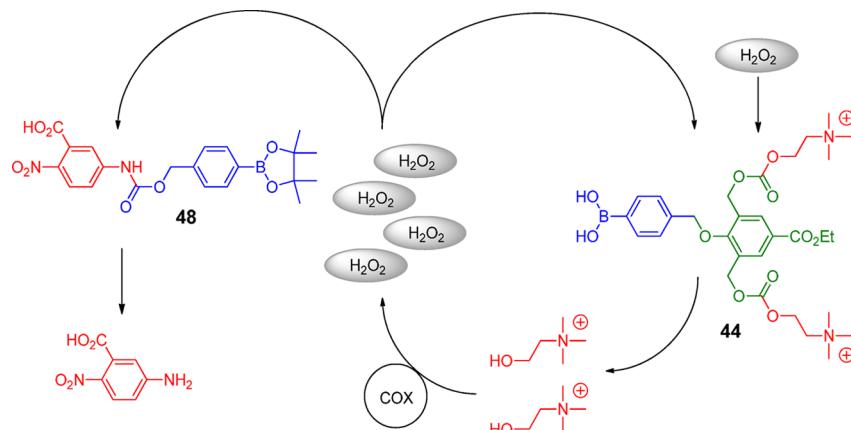
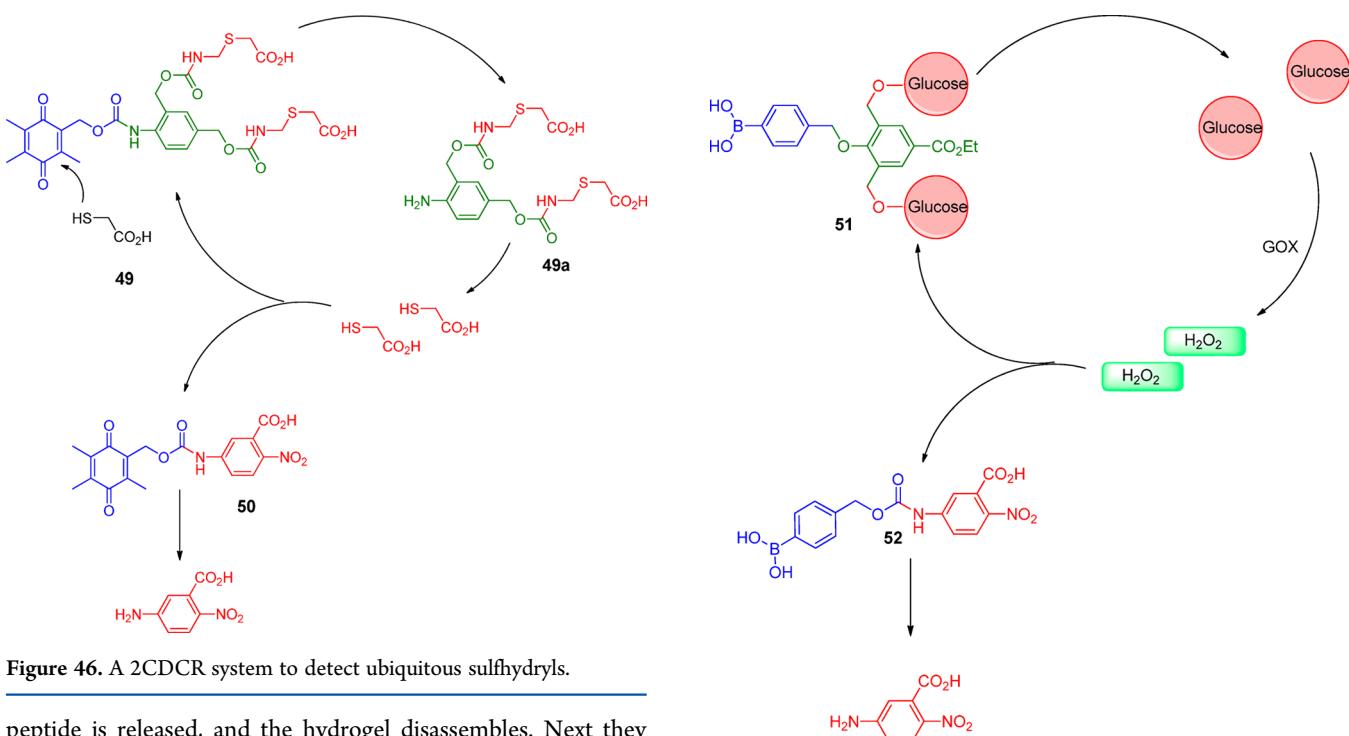
Figure 45. Two-component DCR system for detection of H_2O_2 .

Figure 46. A 2CDCR system to detect ubiquitous sulphhydryls.

peptide is released, and the hydrogel disassembles. Next they encapsulated an amplification system composed of dendron **57** and the enzyme sarcosine oxidase (SOx) inside the hydrogel.⁶⁰ The **57/SOx** pair did not disrupt the formation of a hydrogel from **58**, and the gel state was retained with 5 (or fewer) equiv of **57** relative to **58**. The boronic acid moiety of **57** reacts with H_2O_2 to generate sarcosine by spontaneous 1,6-elimination, 1,4-elimination, and decarboxylation reactions. The two released sarcosine molecules are oxidized by SOx, generating two H_2O_2 molecules as byproducts. This chain reaction acts as an amplification cycle for H_2O_2 , which leads to rapid disassembly of the hydrogel (Figure 49). The sensitivity to H_2O_2 , detected by the gel–sol transition, was significantly enhanced by the signal amplification system. An array chip consisting of these multicomponent hydrogels enabled the detection of H_2O_2 , which is characteristic of hyperuricemia disease in human plasma samples.

Recently, the Huang group reported the synthesis of DCR probe **59** for the detection of fluoride anion.⁶¹ The probe releases fluorogenic coumarin via 1,6-elimination in the presence of fluoride ion followed by ejection of two fluoride anions by double 1,4-elimination to yield coumarin **59a** (Figure 50). This chain

Figure 47. Amplification cycle of 2CDCR glucose-based probe systems for detection of H_2O_2 dependent on oxidation by glucose oxidase (GOx).

reaction acts as an amplification cycle that leads to the complete release of coumarin **59a**, which emits at a wavelength of 445 nm when excited at 360 nm. Probe **59** was used both on its own in a one-component DCR and with probe **60** in a two-component DCR (Figure 51). Probe **60** also possesses a self-immolative structure. The trigger can be cleaved by fluoride anion to release a coumarin derivative (**60a**). Coumarin **60a** can be sensed at longer wavelengths than **59a** ($\lambda_{\text{ex}} = 500 \text{ nm}$ and $\lambda_{\text{em}} = 595 \text{ nm}$ for **60a**); however, probe **60** does not release fluoride anions and thus does not contribute to the amplification cycle.

2.2.3. Two-Component Amplification Systems. The Phillips group has reported a two-component amplification system for the detection of Pd^{2+} analyte.⁶² Pd^{2+} reacts specifically with probe **61** and releases the signal amplification reagent (fluoride anion) by double 1,6-eliminations, followed by generation of the colorimetric indicator 4-aminobenzaldehyde.

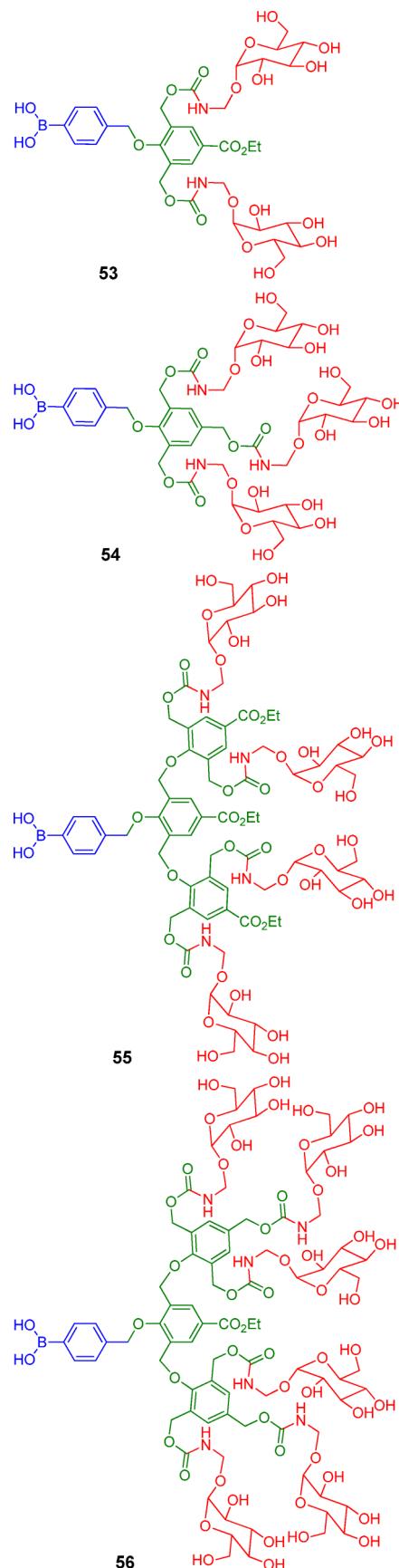


Figure 48. Chemical structures of self-immolative dendrons equipped with a phenylboronic acid trigger and various numbers of glucose end units that function in 2CDCR systems.

The fluoride anion reacts with probe **62** in an autocatalytic process to produce amplified quantities of the indicator and fluoride ions by a similar elimination pathway (Figure 52). The signal generated by the indicator increases exponentially until it comes to a standstill upon the complete disassembly of dendrons **61** and **62**.

In another example, a two-component amplification system for the detection of the enzyme β -galactosidase was reported.⁶³ Cleavage of the trigger of probe **63** by β -galactosidase generates the phenolate intermediate, which undergoes 1,6-elimination to release benzene-1,2,4-triol. Hydrogen peroxide is generated by auto-oxidation of the triol and leads to the generation of the chromogenic molecule 2-hydroxy-1,4-benzoquinone. The H_2O_2 analyte initiates the signal amplification cycle by reacting with probe **64** to release another two molecules of the triol. The released triols are auto-oxidized to generate two molecules of H_2O_2 and 2-hydroxy-1,4-benzoquinone (Figure 53). The rate of disassembly increases exponentially until all of the benzene-1,2,4-triol molecules are released.

Following the two-component amplification concept, the Phillips' group reported a novel strategy for creating polymeric materials that are capable of providing global, macroscopic changes in their properties in response to specific analytes.⁶⁴ They designed polymer **65**, which in response to a specific stimulus undergoes a hydrophilicity change in the material; the response is continuous in the absence of additional signal, making the magnitude of the change independent of the intensity of the applied stimulus (Figure 54). The system is composed of a polymer mounted with two types of components, which form a two-component amplification system. The first is a detection functionality based on *o*-nitrobenzyl carbamate, which reacts upon exposure to 300 nm light (the applied signal) to release a pendant carbamate and ultimately four fluoride ions by double 1,4- and 1,6-eliminations (Figure 55). The released fluoride ions are free to diffuse across the film and react with pendant TBS groups on the second amplification component. This ultimately leads to release of four additional fluoride ions by double 1,4- and 1,6-elimination reactions, and the amplification cycle continues until all of the TBS pendants have reacted. The change of the polymer's pendants from hydrophobic TBS groups to hydrophilic alcohols leads to a change in the hydrophilicity of the polymer itself. Consequently, the resulting polymer is significantly more hydrophilic than the starting polymer.

3. SELF-IMMOLATIVE POLYMERIC SYSTEMS

Self-immolative dendrimers are used as effective tools in a variety of scientific fields. However, it is difficult to synthesize large self-immolative dendritic systems because multistep syntheses are required. In addition, steric hindrance limits the number of reporter groups that can be incorporated on a dendrimer. In order to overcome such difficulties, our group developed new stimuli-responsive polymers that are capped at the head with an analyte-responsive trigger. Removal of the trigger by the analyte of interest results in a cascade of reactions that disassembles the polymer from head to tail in a domino-like manner (Figure 56). We have termed these macromolecules self-immolative polymers.⁶⁵

3.1. Self-Immolative Polycarbamates

The first design of a self-immolative polymer was based on polycarbamate **66**, as displayed in Figure 57. Removal of the end cap unmasks an aniline that initiates a series of consecutive 1,6-azaquinone methide elimination and decarboxylation reactions

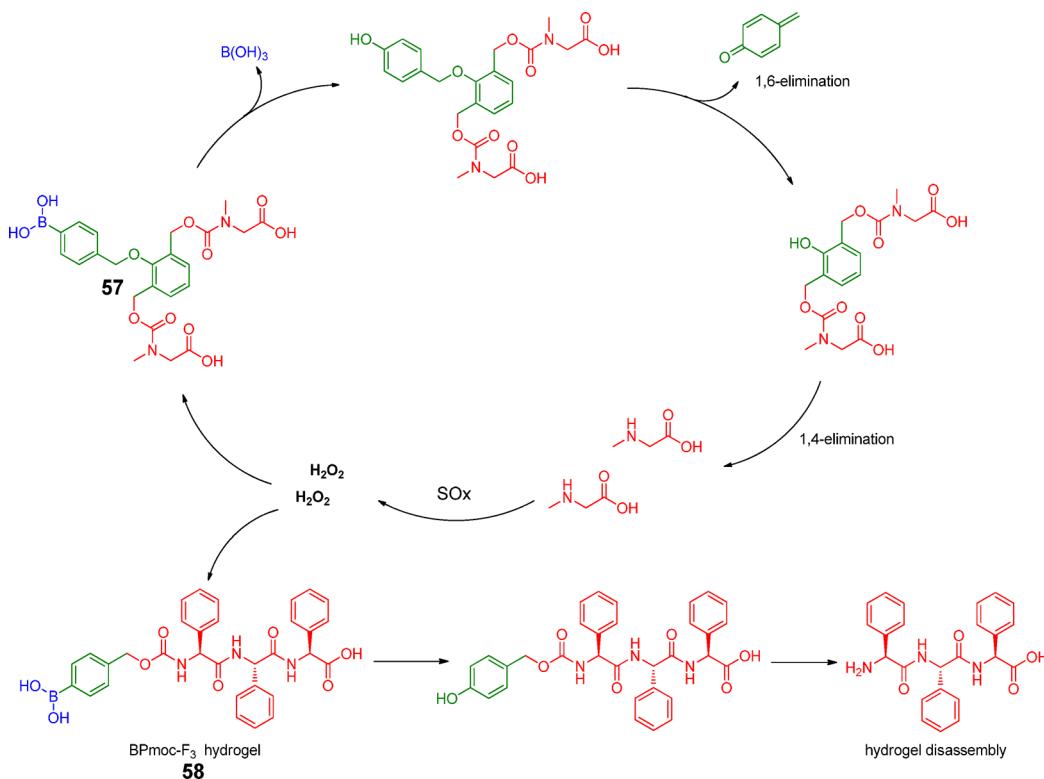


Figure 49. DCR system that enables small-molecule analyte detection through hydrogel disassembly.

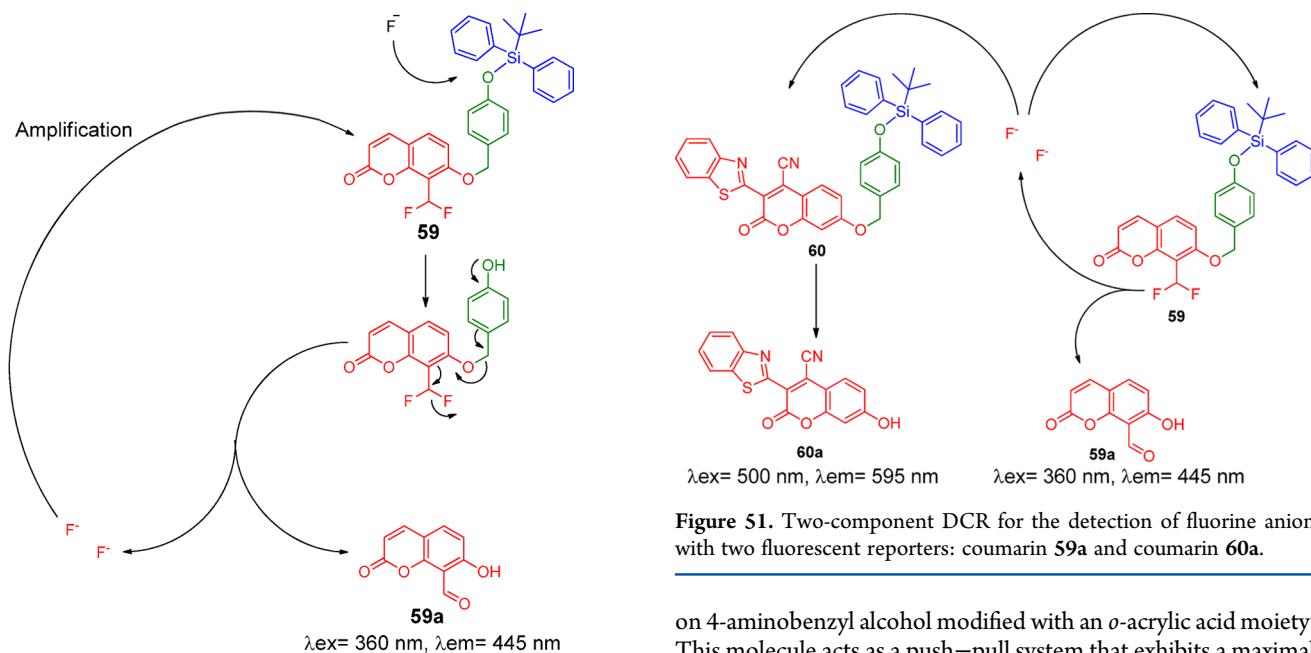


Figure 50. One-component DCR for the detection of fluorine anion via fluorescent reporter 59a.

leading to the total disassembly of polymer 66 to CO_2 and azaquinone methide units. When fragmentation of the polymer takes place in an aqueous medium, the highly reactive azaquinone methide reacts rapidly with a water molecule to generate the 4-aminobenzyl alcohol.

In order to create a detectable signal amplification that corresponds to the polymer's degradation, we designed and synthesized polymer 67 (Figure 58). The monomers are based

on 4-aminobenzyl alcohol modified with an *o*-acrylic acid moiety. This molecule acts as a push–pull system that exhibits a maximal emission at a wavelength of 510 nm. This fluorescence is quenched by masking of the aniline through a carbamate bond. Cleavage of the trigger generates strong signal amplification arising from release of the fluorogenic building blocks. Additionally, the ionized carboxyl groups result in water solubility under physiological conditions. Self-immolative polycarbamate 67 was synthesized with a 4-hydroxy-2-butanone end cap that can be activated through a β -elimination reaction catalyzed by bovine serum albumin (BSA). Incubation of the polymer with BSA results in the generation of a fluorescent signal produced from the disassembly of the polymeric backbone into its building blocks.

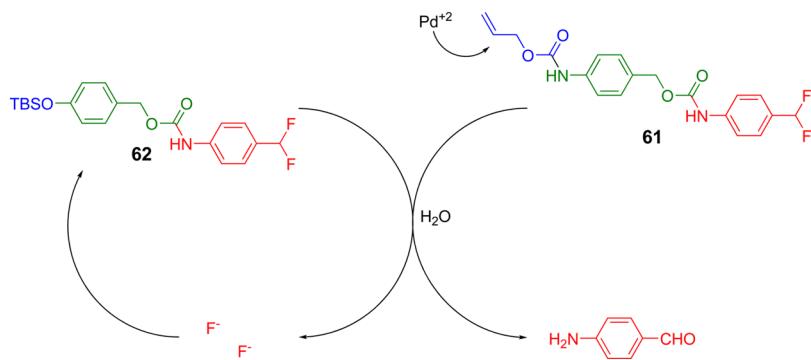


Figure 52. Self-immolative two-component amplification system for Pd^{2+} detection with 4-aminobenzaldehyde as a colorimetric indicator.

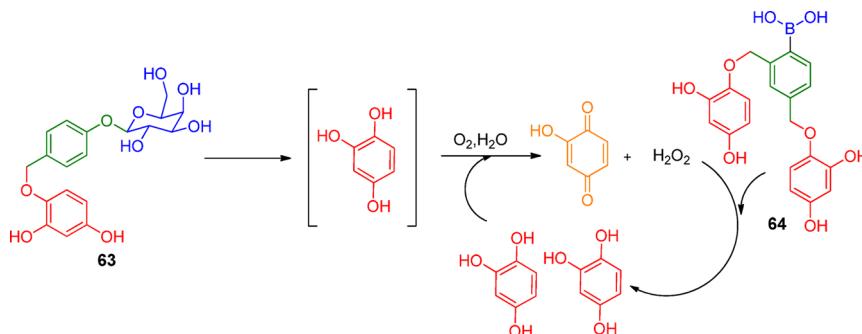


Figure 53. One-pot tandem assay strategy that uses a two-component amplification system to selectively detect the enzyme β -galactosidase.

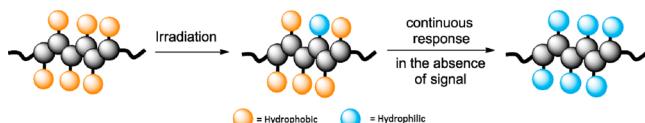


Figure 54. Schematic illustration of a synthetic polymeric material that is capable of changing its physical properties globally in response to specific applied signals that are fleeting and/or interact with only one portion of the material.

In order to verify the head-to-tail depolymerization, we synthesized polymer **68** with a conjugated 4-nitroaniline reporter as the terminal tail group. Monitoring of the release of 4-nitroaniline confirmed that the polymer disassembled from head to tail, as shown in Figure 59.

Self-immolative polymers act as unique platforms for signal amplification. By incorporation of suitable end caps, these systems can be used to detect a variety of chemical and biological activities with high sensitivity and low background. On the basis of this concept, we developed a different class of self-immolative polymers with a reporter group on each monomer. These self-immolative comb polymers disassemble in a reaction initiated by removal of the end cap to release numerous reporters, as illustrated in Figure 60.⁶⁶ The repeating unit of the comb polymer is composed of an AB_2 self-immolative dendritic aniline linker such as molecule **69** (Figure 61). Cleavage of the trigger initiates 1,6-elimination through the *para* position to release a reporter. Another 1,6-elimination spontaneously occurs through the vinylogous *o*-benzyl position to release a second reporter.

Polymer **70** was synthesized with a monomeric unit based on molecule **69** (Figure 62). Polycarbamate **70** contains a 4-nitroaniline unit as a side reporter and 4-hydroxy-2-butanone as an end-cap trigger. Activation of the 2-butanone trigger with piperidine through β -elimination initiates the degradation along

the polymer backbone, followed by the release of multiple side reporters.

In order to assess the polymer's potential as a biocompatible system, we synthesized polymer **71**, a water-soluble self-immolative comb polymer capped with an enzymatic trigger (Figure 63). The monomeric unit was constructed from two aniline segments, one holding an *o*-acrylic acid moiety and the other containing a releasable side reporter. Polymer **71** is equipped with an end cap designed for removal by PGA. Removal of the end cap initiates the disassembly of the polymer backbone, thereby releasing the 4-nitroaniline side reporters and the fluorogenic building blocks. Exchanging the side reporter with a drug molecule would generate a smart polymeric system that could be used not only as a signal amplification platform but also as a stimuli-responsive drug delivery system.

As mentioned above, the disassembly of self-immolative polymers (such as polymer **67**) is accompanied by the release of azaquinone methide intermediates. In an aqueous environment these highly reactive species react with water molecules to generate the fluorogenic building blocks. If the polymer's disassembly is initiated by the stimulus of a protein, the protein's nucleophilic residues might entrap the azaquinone methide units, resulting in a covalent linkage between the protein and the fluorescent building blocks. In order to demonstrate this polymer-based protein labeling strategy, we synthesized activity-linked fluorescent labeling probes **72** and **73** (Figure 64). Probe **72** was conjugated with a PGA enzyme substrate as a trigger. Removal of the trigger by PGA generates the azaquinone methide species, which labels the enzyme. Using this technique, we also labeled the catalytic antibody 38C2 using probe **73**, which has a trigger designed for activation through a retro-Michael reaction catalyzed by antibody 38C2. Incubation of probe **73** with the antibody produced the desired labeled protein.⁶⁷

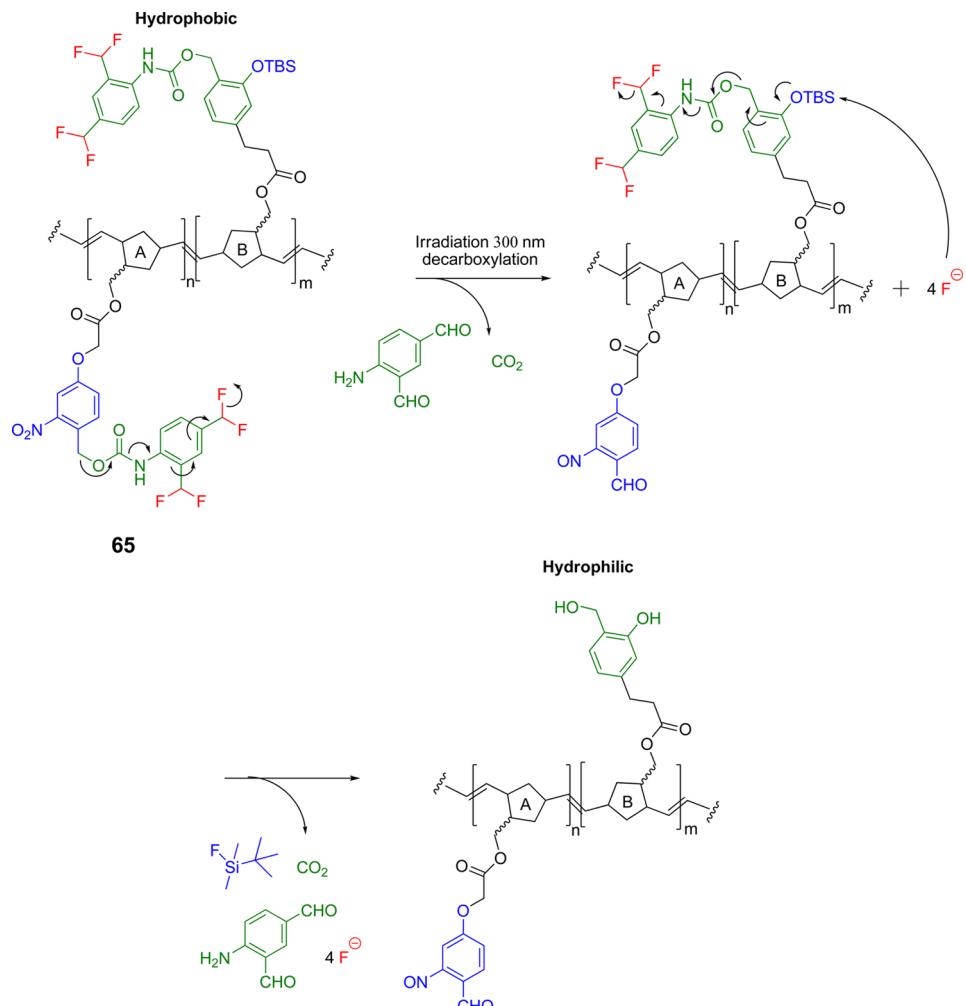


Figure 55. Structure and disassembly of poly(norbornene) AB copolymer **65** mounted with a two-component amplification system.

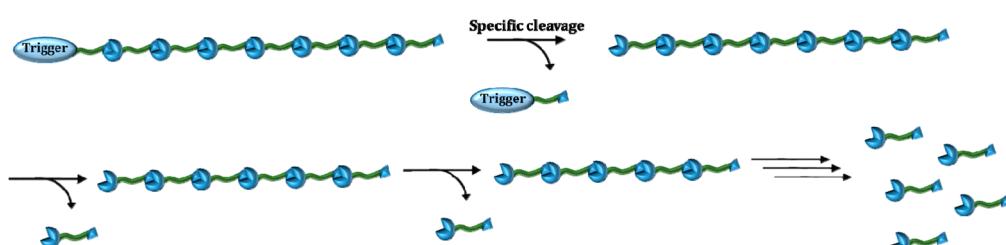


Figure 56. Schematic illustration of the disassembly of a self-immolative polymer from head to tail.

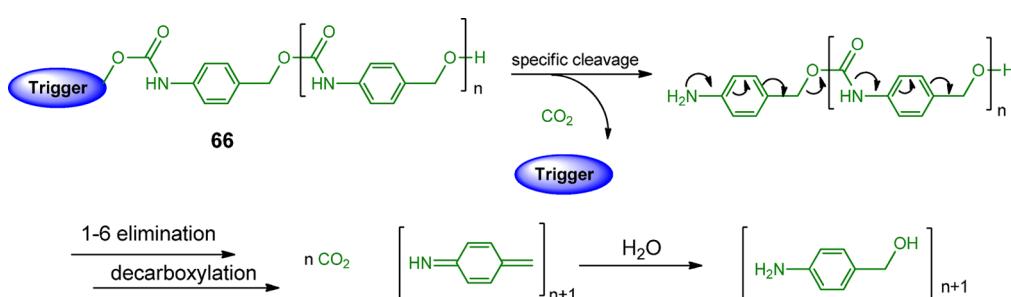


Figure 57. Structure and disassembly pathway of self-immolative polymer **66**.

To accelerate the depolymerization of self-immolative polycarbamate, a fundamental study of the azaquinone methide depolymerization rate was performed by the Phillips group.⁶⁸

The self-immolative polycarbamate disassembly proceeds through an azaquinone methide intermediate, which unlike its parent aniline repeating unit is not aromatic. This results in an

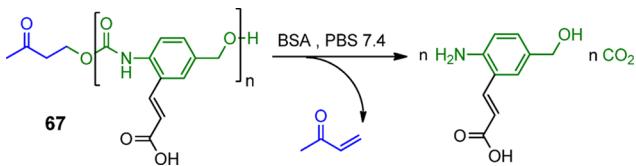


Figure 58. Structure and degradation of self-immolative polymer **67** under aqueous conditions.

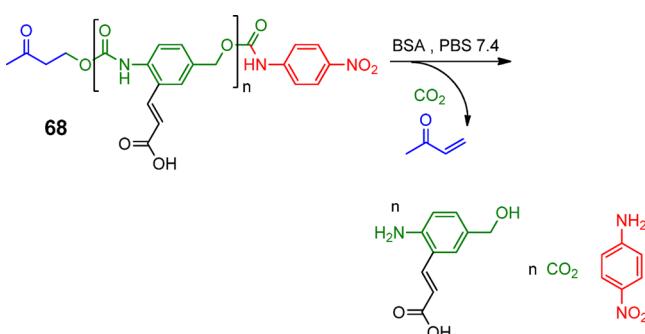


Figure 59. Structure and degradation of self-immolative polymer **68**, which was synthesized to verify the head-to-tail depolymerization.

energy penalty that decreases the depolymerization rate. Tuning the electronics and aromaticity properties of the polymer's repeating units can offset the energy penalty. The repeating unit of polymer **75** has an electron-donating group, the *m*-methoxy substituent (with respect to the aniline). Polymer **76** has less aromatic 1-naphthylamine building blocks. These self-immolative polycarbamates bear a boronic ester that serves as a trigger for cleavage initiated by hydrogen peroxide. Upon incubation with hydrogen peroxide, polymers **75** and **76** depolymerized more rapidly than polymer **74** composed of unsubstituted anilines (Figure 65).

The Phillips group reported the use of self-immolative polymers as phase-switching reagents designed to increase the sensitivity of quantitative point-of-care assays that are based on measurements over time. Removal of the trigger by a specific analyte initiates the depolymerization, thus converting the water-insoluble self-immolative polymer to water-soluble products. This switching reaction enables a sample to permeate through a three-dimensional paper-based microfluidic device, where the flow-through time corresponds to the quantity of the analyte in the sample.⁶⁹ These authors showed that this strategy made it

possible to quantify an active enzyme present at femtomolar concentrations.⁷⁰ The group has also reported a prototype self-immolative polymer for the detection of heavy metals (Hg^{2+} and Pb^{2+}) in a water sample; the limit of detection in this assay was in the nanomolar concentration range.⁷¹

Chujo and co-workers reported self-immolative polycarbamate-containing organic/inorganic hybrids.⁷² The repeating unit of polymer **77** was synthesized with TBS groups at the vinylogous *o*-benzyl positions (Figure 66), and a UV-light-sensitive trigger, 4,5-dimethoxy-2-nitrobenzyl alcohol, was introduced at the polymer terminus. The organic/inorganic hybrids were fabricated by the acid-catalyzed sol–gel reaction, thus generating UV-responsive self-immolative organic/inorganic hybrid films. These films can host molecular guests such as fluorescent dyes. Trigger activation by UV irradiation induces polymer disassembly through a cascade of 1,6-eliminations, resulting in the release of the guest molecules. Chujo and co-workers demonstrated the encapsulation and release of both hydrophobic and hydrophilic dyes from the organic/inorganic hybrid films.

The use of viruses as macromolecular vehicles for the controlled release of cargo is an appealing strategy that has not been fully explored. Viruses and viruslike particles have been designed to package, protect, and deliver their interior cargo to host cells. The virus capsid of the cowpea chlorotic mottle virus (CCMV) is an icosahedral plant virus that undergoes reversible self-assembly to form viruslike particles. CCMV is an attractive platform that has been used for the encapsulation of various functional materials. Cornelissen and co-workers reported the encapsulation of a self-immolative polymer inside CCMV assemblies (Figure 67).⁷³ They synthesized self-immolative polyurethane **78** equipped with a photolabile trigger at the polymer's head (Figure 68). Upon UV irradiation the end cap is removed, and **78** depolymerizes into monomeric units. The released small building blocks can diffuse out of pores in the CCMV capsid. Thus, this study provided a model for the controlled release of a molecular payload from the inner core of the CCMV. This strategy could be used to create drug delivery systems.

Another example of the use of self-immolative polymers was reported by the Moore group, who constructed a responsive microcapsule that discharges its interior contents when a triggering event occurs.⁷⁴ These microcapsules were created with a shell wall prepared from self-immolative polycarbamate, which was cross-linked to generate a polymeric network that

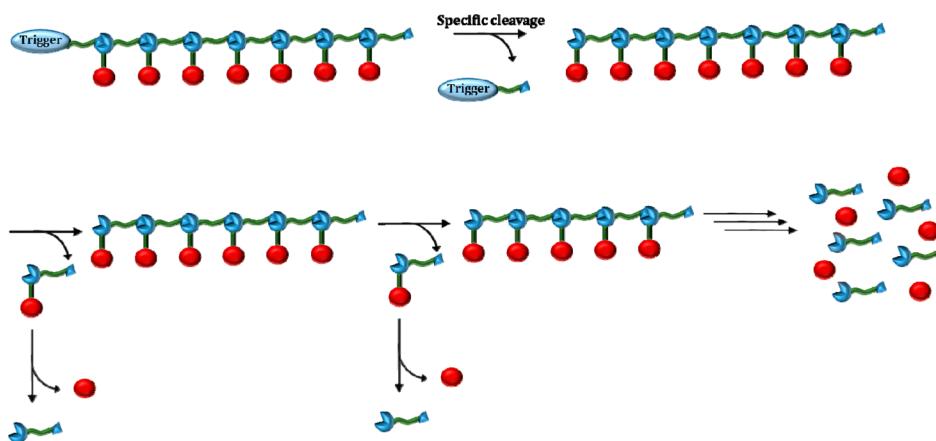


Figure 60. Illustration of the disassembly of a self-immolative comb polymer.

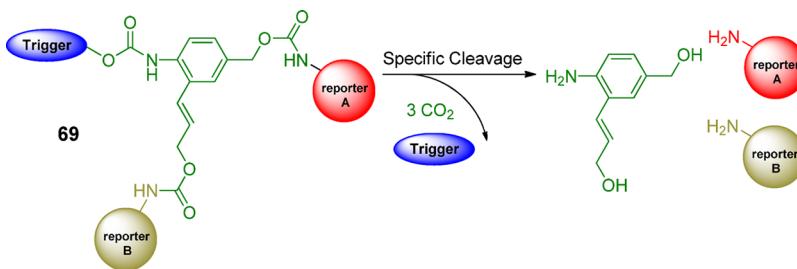


Figure 61. Disassembly of a unit fragment of a self-immolative comb polymer. Cleavage of the trigger initiates disassembly to release reporter A (red) and reporter B (yellow).

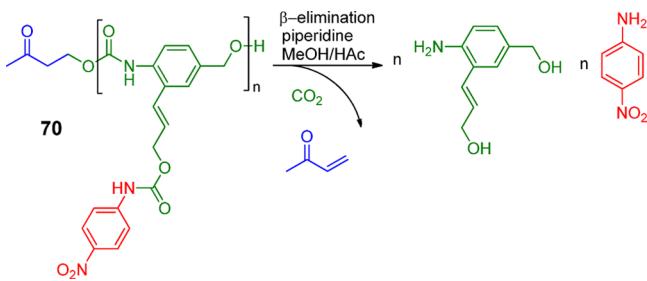


Figure 62. Structure and disassembly pathway of self-immolative comb polymer 70.

assembles into a microcapsule (Figure 69). The backbone of polymer 79 was synthesized from two species of aniline building blocks that were capped with either Boc or Fmoc protecting groups. Self-immolative polymer 79 was synthesized by mixing the two monomers 4-aminobenzyl alcohol and its analogous *o*-2-hydroxyethyl acrylate substituent in a 7:3 molar ratio. Exposing the microcapsule to specific deprotection conditions initiates a cascade of 1,6-elimination and decarboxylation reactions that creates a fracture in the microcapsule's shell wall, releasing the core contents.

The integration of self-immolative polymers as the responsive hydrophobic block within amphiphilic block copolymers is a desired feature in responsive materials design. Liu et al.⁷⁵ reported the self-assembly of such amphiphilic polymers (Figure 70) into self-immolative polymersomes (SIPsomes). The amphiphilic block copolymer 80 is composed of a hydrophilic poly(*N,N*-dimethylacrylamide) (PDMA) block and a hydrophobic self-immolative polycarbamate equipped with a trigger. UV, visible-light, and reductive milieu triggers were incorporated at the head of the self-immolative polymer. Cleavage of the trigger by a stimulus event initiates the depolymerization of the hydrophobic block through sequential 1,6-elimination reactions. This depolymerization degrades the SIPsome macrostructure

into water-soluble 4-aminobenzyl alcohol and PDMA. Using the SIPsomes, Liu and co-workers demonstrated triggered drug corelease and the construction of logic-gate-type programmed enzymatic reactions.

Boyston and co-workers reported a thermally responsive trigger for self-immolative polymers.⁷⁶ The trigger was integrated at the junction of block copolymer 81, composed of a self-immolative polymer and PDMA. Thermal activation of the bicyclic oxazine trigger initiates the disassembly of the block copolymer, releasing the self-immolative building blocks and the PDMA (Figure 71).

De Wit and Gillies⁷⁷ reported another class of self-immolative polymers composed of two well-known self-immolative linkers, *N,N'*-dimethylethylenediamine and 4-hydroxybenzyl alcohol. Conjugation of these building blocks through carbamate bonds generated the polycarbamate backbone of polymer 82. In order to prevent polymer degradation, a Boc protecting group was incorporated at the N-terminus. Removal of the protecting group unmasks the terminal amine, which undergoes cyclization, generating *N,N'*-dimethylimidazolidinone and exposing the phenolate, which initiates a 1,6-elimination reaction. Total polymer disassembly is achieved through alternating cyclization and elimination reactions (Figure 72).

The Boc protecting group was incorporated as one possible end cap for these self-immolative polymers. Capping the terminal phenol of polymer 82 by esterification with *O*-(2-carboxyethyl)-*O'*-methyl-PEG (mPEG acid) generated amphiphilic block copolymer 83 (Figure 73). In aqueous solution, copolymer 83 self-assembles into nanostructures. Hydrolysis of the ester bond initiates the depolymerization of the self-immolative block, which leads to the disassembly of the aggregates, as shown in Figure 74. These nanostructures can encapsulate hydrophobic guests such as fluorescent dyes.

The diversity of triggers that can be integrated as end caps into these self-immolative polymers were further demonstrated by the Gillies and Almutairi research groups. Gillies and co-workers

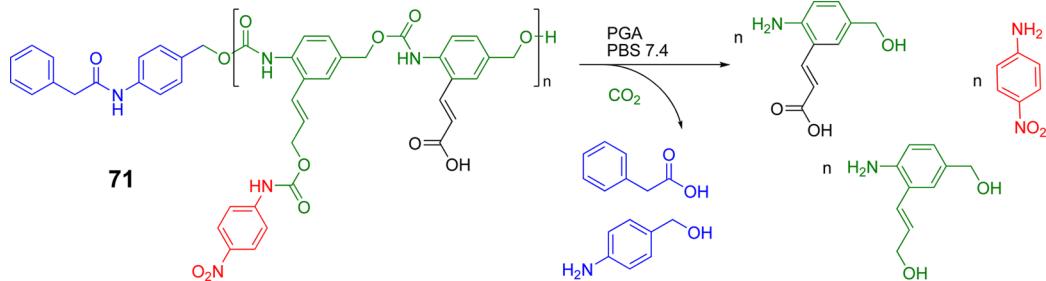


Figure 63. Design and disassembly of self-immolative comb polymer 71. The water-soluble polymeric system releases multiple reporters and fluorogenic molecules upon disassembly.

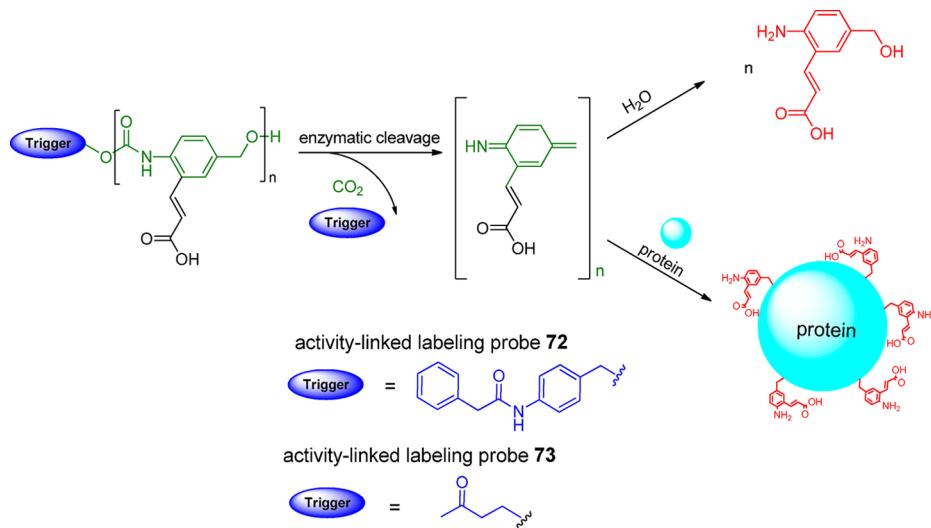


Figure 64. Schematic of labeling of proteins using self-immolative polymers.

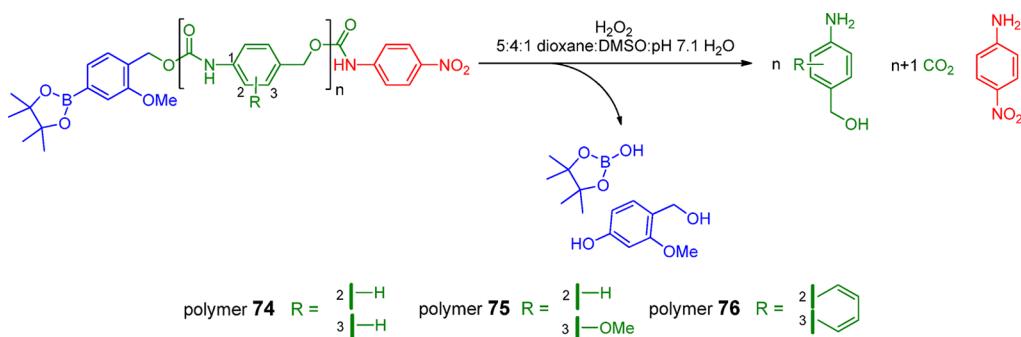


Figure 65. Disassembly pathway of self-immolative polymers **74**, **75**, and **76** used for the depolymerization rate study.

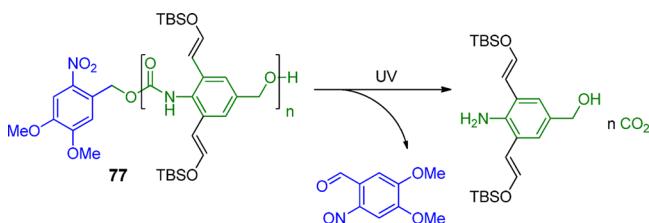


Figure 66. Design and disassembly of self-immolative polymer **77** used for controlled release through film disassembly.

introduced an azobenzene end cap (polymer **84**) to initiate degradation in the presence of reducing agents such as hydrazine (Figure 75). Cleavage of the azobenzene results in a change of

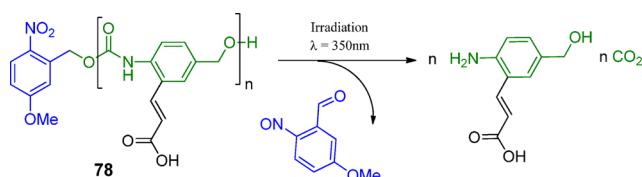


Figure 68. Structure and disassembly of self-immolative polymer **78**; disassembly occurs when the polymer is encapsulated inside the CCMV-like particle.

color: the intact trigger is observed in the visible range, whereas the reduction product exhibits only UV absorption.⁷⁸ Almutairi and co-workers incorporated UV- and two-photon NIR photolabile-responsive end caps into smart polymers **85** and

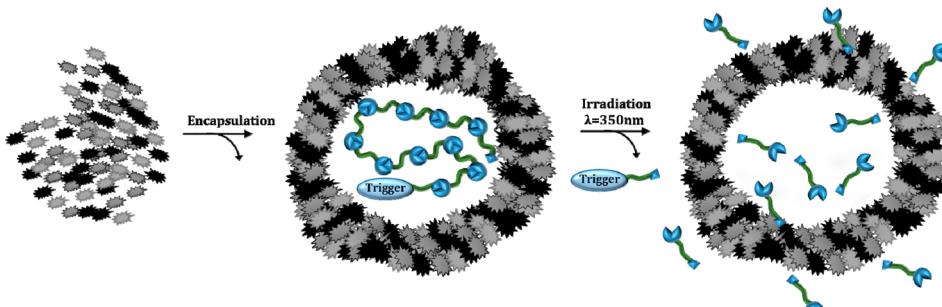


Figure 67. Schematic illustration of the encapsulation of self-immolative polymers within CCMV.

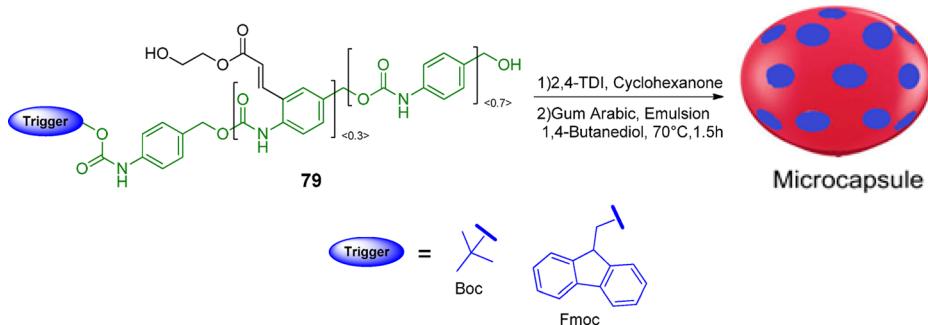


Figure 69. Structure of self-immolative polymer **79** and its assembly into a microcapsule.

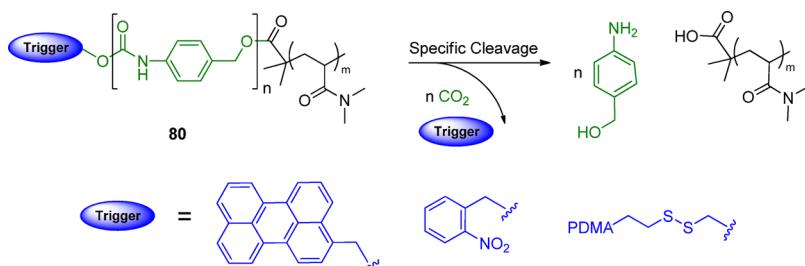


Figure 70. Degradation of amphiphilic block copolymer **80**; three triggers were evaluated.

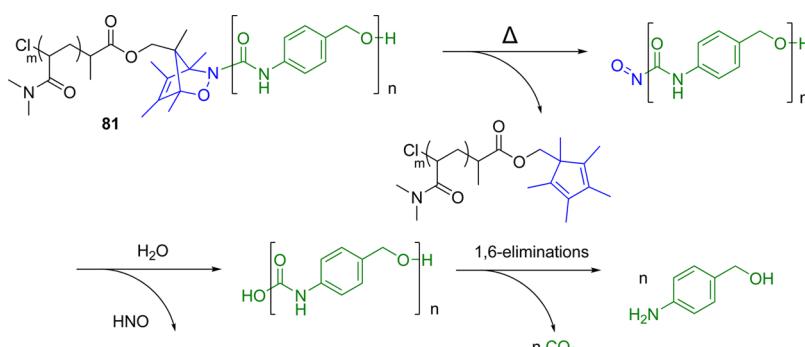


Figure 71. Disassembly pathway of thermal-responsive self-immolative block copolymer **81**.

86, respectively, to investigate the controlled response and disassembly upon UV or two-photon NIR irradiation (Figure 75).⁷⁹

Greater control over the depolymerization rate was achieved by exchanging the cyclization spacer with 2-(methylamino)-ethanol or 2-mercaptopropanol, thus creating polymers **87** and **88**, respectively (Figure 76).⁸⁰ These modifications change the electrophilicity and nucleophilicity of the sites involved in the cyclization reaction. The depolymerizations of polymers **87** and **88** are much faster than that of polymer **82** (the overall depolymerization period was reduced from days to hours). Polymer **87** rapidly disassembles because of the carbonate bonds between the monomers (the carbonate bond is more electrophilic than a carbamate bond). The rapid cyclization of polymer **88** is attributed to the low pK_a of the thiol. The Gillies group also synthesized several self-immolative polymers with different numbers of monomers in order and performed a kinetic study of the effect of the chain length on the degradation rate.⁸¹

3.2. Self-Immolative Polymers Bearing Multiple Triggering Units

Self-immolative polymers act as molecular amplifiers through domino-like disassembly in which a single triggering event leads

to complete disintegration of the polymer backbone. Another approach to obtain amplification can be achieved by introducing multiple triggering groups on a polymer backbone. Such a polymer was first reported by Almutairi and co-workers.⁸² Polymer **89** is composed of self-immolative linkers capped by a trigger and attached together using dicarboxylic acids. Upon triggering, in this case induced by light, cyclization of the diamine spacer leads to unmasking of the phenol monomer. Next, the monomer undergoes double 1,4-elimination, which leads to degradation of the polymeric chain (Figure 77).

Polymer **89** is efficiently degraded after trigger cleavage by either one-photon excitation (UV range) or two-photon excitation (NIR range). The cleavage using an irradiation wavelength of 365 nm is complete after 15 min, whereas about 5 h is needed when a wavelength of 750 nm is used. To overcome this time limitation, polymer **90** was synthesized (Figure 78). This polymer has a coumarin-based trigger, 6-bromocoumarin, which has a higher two-photon uncaging cross section (1 GM) compared with 4,5-dimethoxy-2-nitrobenzyl alcohol (0.01 GM).⁸³

Polymer **89** was also evaluated as a component for the assembly of nanoparticles that deliver a payload upon trigger cleavage. Nanoparticles were produced by the single emulsion

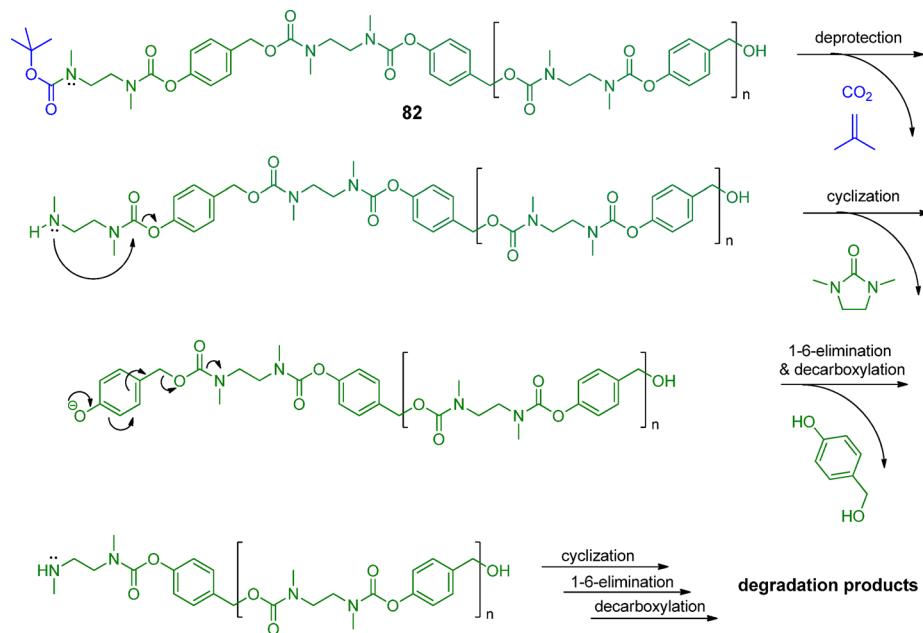


Figure 72. Disassembly pathway of self-immolative polymer **82** through cascade reactions of cyclization and elimination.

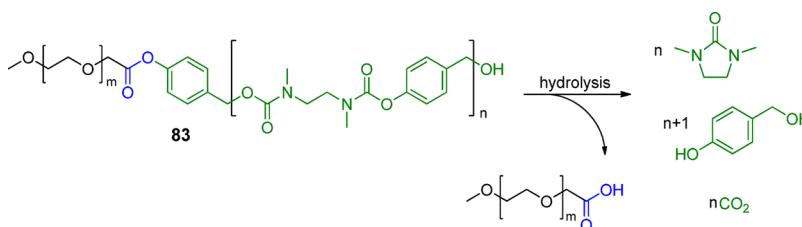


Figure 73. Design of copolymer **83** and degradation products of the self-immolative block resulting from hydrolysis.

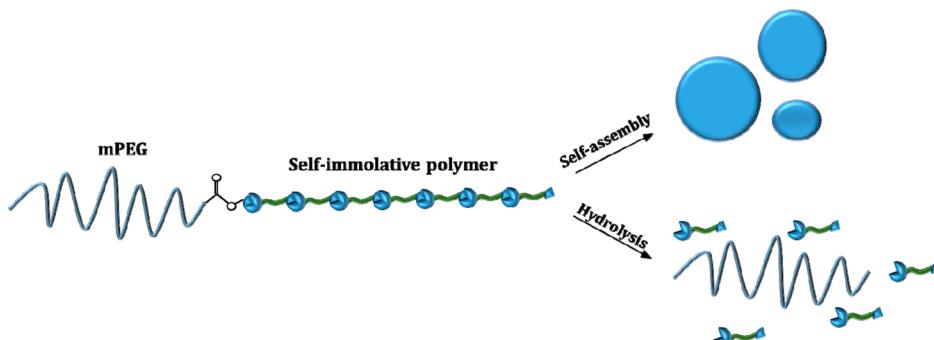


Figure 74. Illustration of the self-assembly and degradation of block copolymer **83**.

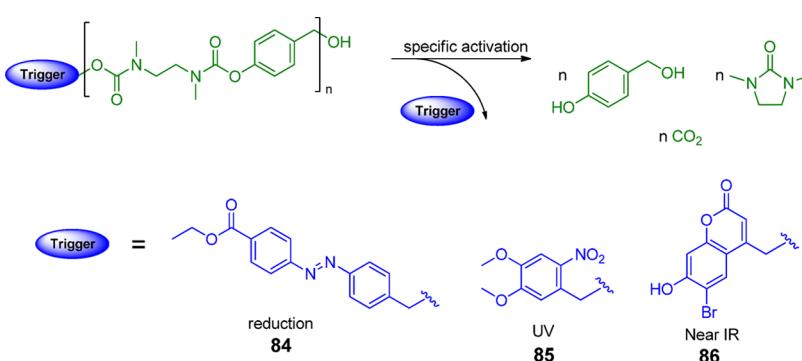


Figure 75. Self-immolative polymer **82** (see Figure 72) modified with different end caps to create polymers responsive to the indicated triggers.

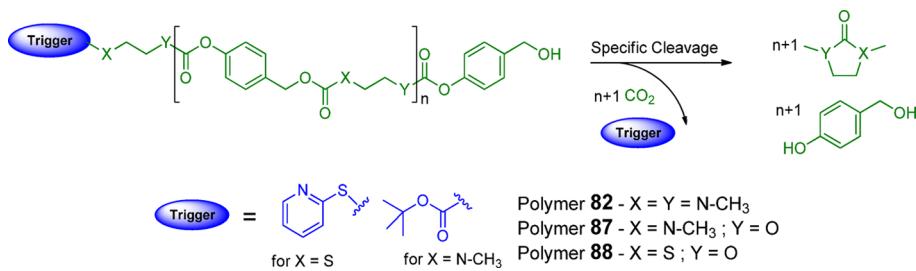


Figure 76. Structures and disassembly of self-immolative polymers 82, 87, and 88.

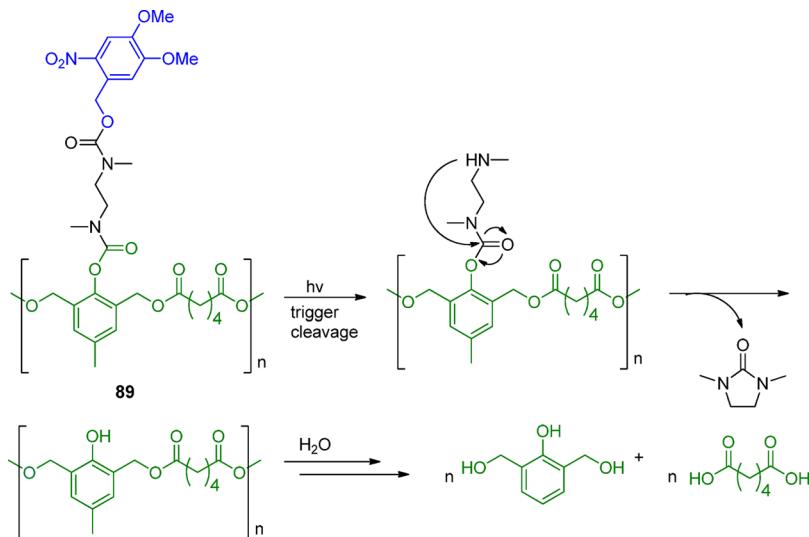


Figure 77. Mechanism of degradation of light-sensitive polymer 89, which is composed of multiple units of 4,5-dimethoxy-2-nitrobenzyl alcohol as triggers. The triggering group can be removed by one-photon excitation (UV range) or two-photon excitation (NIR range).

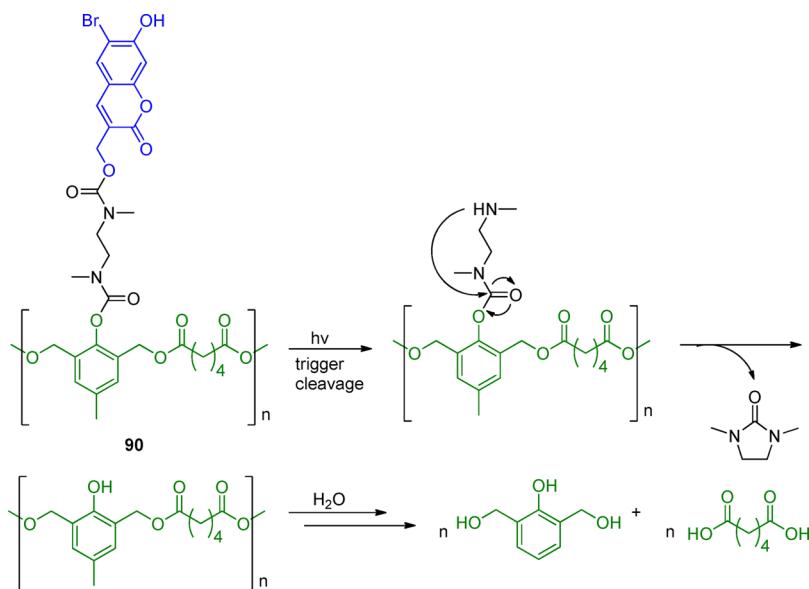


Figure 78. Degradation mechanism of light-sensitive polymer 90, which contains multiple 6-bromocoumarin units as triggers.

method, encapsulating Nile red, a small hydrophobic dye. After irradiation, the fluorescence intensity of Nile Red drops drastically as a result of disassembly of the nanoparticles and release of the dye into the aqueous solution.

Several self-immolative polymers composed of boronic ester trigger units without an ethylenediamine spacer were synthesized by Almutairi and co-workers.⁸⁴ The triggers were linked either

directly (**91**) or as pendant benzylic boronic esters (**92**) to form the polymers (Figure 79). Polymer **92** degraded more rapidly than polymer **91** upon cleavage initiated by H₂O₂, as shown by NMR spectroscopy and gel-permeation chromatography. These polymers were also evaluated as components for the assembly and disassembly of nanoparticles using Nile Red as the payload. After trigger cleavage, the fluorescence intensity of Nile red

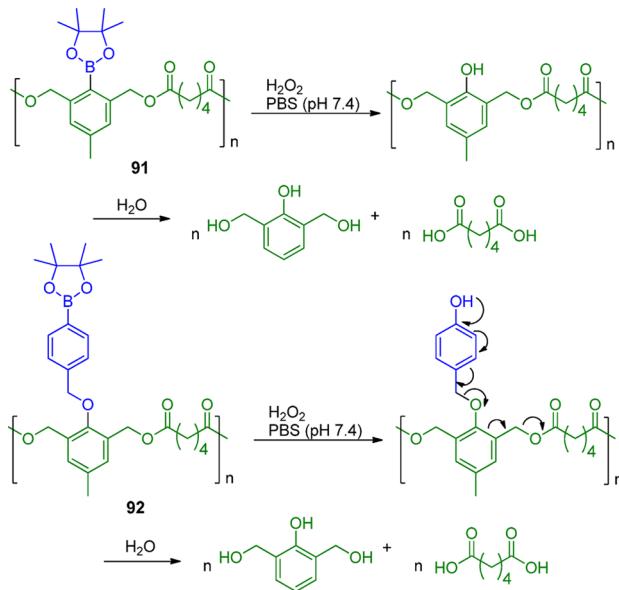


Figure 79. Polymers **91** and **92** form nanoparticles that deliver a payload upon trigger cleavage with H_2O_2 as a result of degradation of the polymer.

dropped drastically as a result of nanoparticle disassembly. Nanoparticles formed from polymer **91** released only 50% of the Nile red after exposure to 1 mM H_2O_2 for 26 h, whereas nanoparticles formulated from polymer **92** released the same amount of dye within 10 h under the same conditions. Nanoparticles formulated from polymer **92** were also degraded in biologically relevant concentrations of H_2O_2 and released their payload more effectively (by 2-fold) when exposed to activated neutrophils than did polymer **91**.

The Cheng group reported an analogous polymer with aniline instead of phenol building blocks. The disassembly of polymer **93** was based on self-immolative azaquinone methide elimination (Figure 80).⁸⁵ A variety of polymers were synthesized with

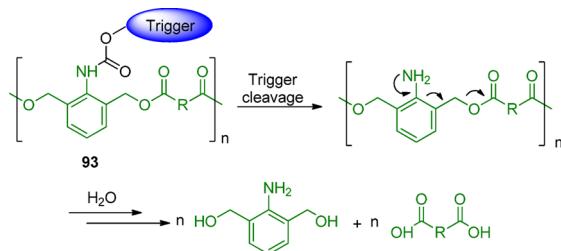


Figure 80. Mechanism of degradation of polymer **93**, which is composed of multiple trigger units and azaquinone methide moieties.

different triggers. The polymers were used to prepare dye- and drug-containing nanoparticles from which the encapsulated molecules could be rapidly released upon trigger-induced degradation.

None of the systems described above incorporated a drug or diagnostic agent as the monomer that is released upon degradation of the polymer. Cheng and co-workers used their self-immolative polymer design⁸⁵ and integrated a drug moiety as a monomer of the polymeric backbone.⁸⁶ The selected drug, CPT, is monofunctional and therefore cannot be used as a monomer without modification. Thus, the bifunctional derivatives 10-hydroxycamptothecin (HCPT) and 9-aminocamptothe-

cine (ACPT) were selected to serve as monomers for polymers **94** and **95**, respectively. These drugs were incorporated along with a self-immolative linker, capped with a trigger, using carbonate/carbamate bonds to yield the polymer (Figure 81). Once the trigger is cleaved, the linkages on both sides of the self-immolative units rapidly degrade, facilitating depolymerization, and the drug molecules are released.

Li and co-workers reported the synthesis of an amphiphilic self-immolative polymer containing mPEG-5000 and functional amino building blocks that disassembles through H_2O_2 -triggered degradation in quinone methide eliminations.⁸⁷ The degradation of polymer **96** (Figure 82) results in release of its amino building blocks, which are capable of trapping the highly active quinone methides. The addition of the PEG allows control of the nanoparticle assembly (as it makes the polymer amphiphilic) and impacts the rate of degradation upon oxidation and cleavage of the trigger.

Jia and co-workers also exploited this polymeric structure to synthesize azomethine-based self-immolative polymers **97** and **98**.⁸⁸ The polymers bear multiple boronate triggers that can be cleaved by H_2O_2 (Figure 83). The polymers are also very labile toward acidic hydrolysis because of their imines. Nanoparticles encapsulating Nile red were constructed from the polymers. Upon exposure to H_2O_2 , the fluorescence intensity due to Nile red declined over time as a result of the nanoparticle disassembly. Oligomer **98** degraded more rapidly than **97** in the presence of H_2O_2 , especially in a weakly acidic environment.

Yaguchi and Sasaki reported the synthesis of a self-immolative poly(olefin sulfone). The degradation of poly(olefin sulfone) has been widely reported.^{89–93} Because of the sulfonyl's electron-withdrawing properties, the backbone protons can be removed by an amine base in heated solutions, leading to random backbone scission and depolymerization of the polymer (Figure 84). Yaguchi and Sasaki incorporated the amine base into the polymer as a pendant and capped it with a UV-induced trigger, yielding polymer **99** (Figure 85).^{94–97} Upon irradiation and trigger cleavage, the amine base is generated, and subsequent heating of the irradiated polymer induces degradation. Thus, the depolymerization requires both irradiation and heat rather a single stimulus. Although the polymer may be categorized as a self-immolative polymer because it bears multiple triggering units, it is unique because the polymer degrades from the trigger cleavage site to its tail without the need to remove all of the triggering groups. Another such polymer is described in section 3.4. It should be noted that when the triggering occurs along the backbone and not at the head of the polymer, the polymer remains intact.

3.3. Self-Immolative Poly(phthalaldehyde)s

Another well-known class of self-immolative polymers is constructed from poly(phthalaldehyde) (PPHA). These unique polymers (such as general polymer **100**), reported by Seo and Phillips,⁹⁸ are polymerized from *o*-phthalaldehydes capped at the end with a trigger to yield a plastic material. Upon trigger cleavage with a specific stimulus, the resulting hemiacetal-terminated polymer depolymerizes rapidly to generate the monomeric units (Figure 86). Seo and Phillips based their work on the poly(phthalaldehyde) used by Ito and Willson (and further developed by Fréchet and Willson) in photoresist chemistry.^{99–103} Upon exposure to UV light in the presence of a photoacid, one of the acetal linkages is cleaved, and the hemiacetal is formed. The polymer then degrades because the ceiling temperature of poly(phthalaldehyde) without an end-

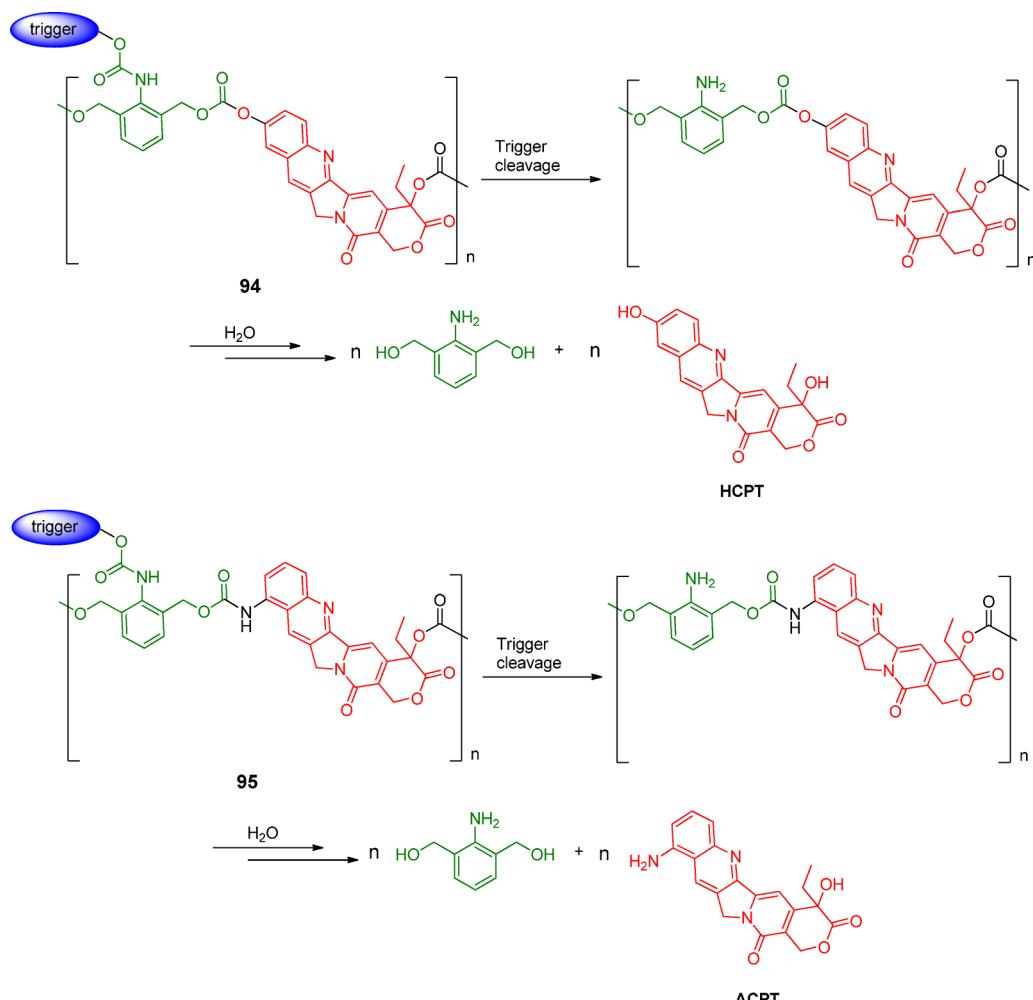


Figure 81. Proposed degradation that releases drugs from self-immolative polymers **94** and **95**. These polymers have multiple trigger units that react with a specific stimulus. In these polymers, the drugs are the building blocks of the polymer rather than pendant groups.

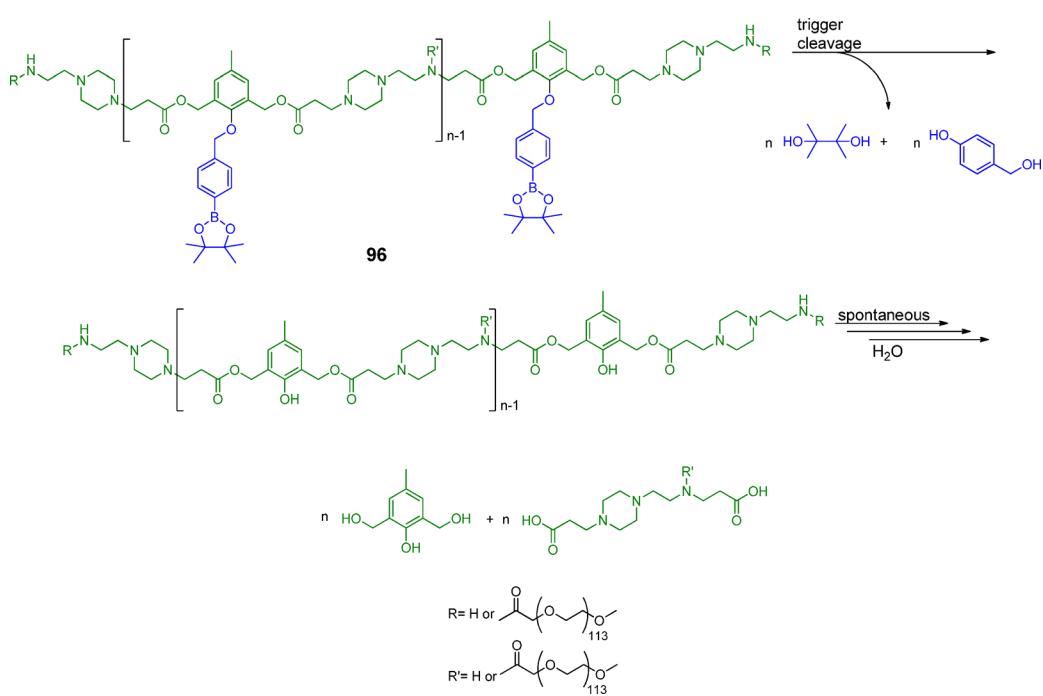


Figure 82. Disassembly of amphiphilic self-immolative polymer **96**, which was used to assemble nanoparticles that degrade upon oxidation with H_2O_2 .

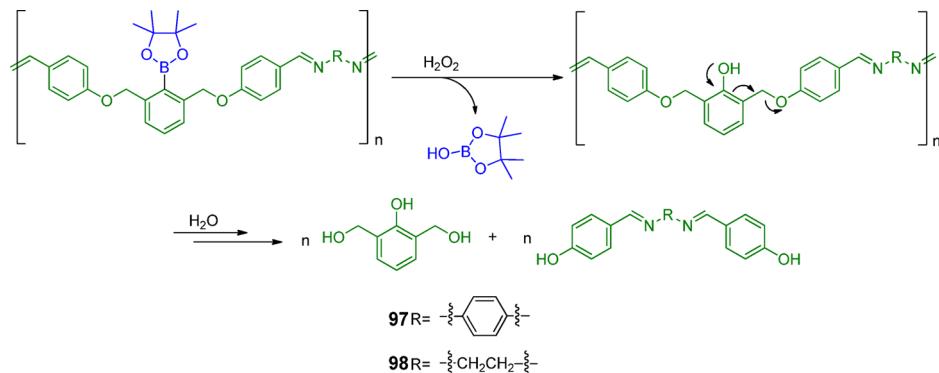


Figure 83. Degradation mechanism of H_2O_2 -sensitive azomethine-based polymers **97** and **98**, which contain multiple trigger units released through quinone methide eliminations.

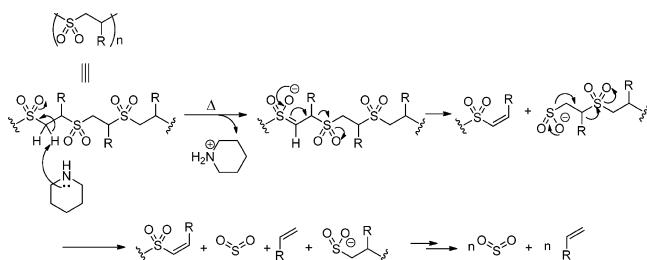


Figure 84. Mechanism of base-induced poly(olefin sulfone) degradation.

capping group (i.e., the hemiacetal form in Figure 86) is -40°C . In the presence of an end-capping group, however, the polymer is stable up to 180°C . Different triggers were applied and evaluated for stimuli-responsive degradation of these polymers.

The Phillips group has demonstrated several applications based on the ability of PPHA to transform from a solid plasticlike material to a liquid very quickly and efficiently upon trigger cleavage. Stimuli-responsive plastics were prepared by placing a cylinder of self-immolative poly(phthalaldehyde) within a film of poly(phthalaldehyde) with an end cap that cannot be removed under the same specific stimulus.⁹⁸ When fluoride is added, only the self-immolative poly(phthalaldehyde) depolymerizes, leaving a cylindrical hole in the plastic sheet.

Self-powered microscale pumps were also prepared by making insoluble polymer films from the self-immolative polymer.¹⁰⁴ These films depolymerize to release soluble monomeric products when exposed to a specific analyte, creating a concentration gradient that pumps fluids and insoluble particles away from the bulk polymer by a diffusiophoretic mechanism. These pumps

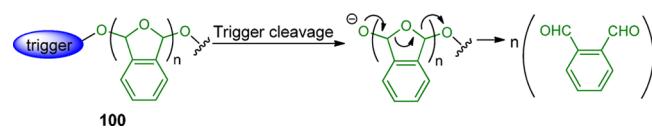


Figure 86. Mechanism of the head-to-tail depolymerization reaction when the trigger on poly(phthalaldehyde) **100** is cleaved via reaction with a specific stimulus.

may be produced from PPAs with different end caps that respond to a variety of analytes from small molecules to enzymes.

Phillips and co-workers also developed microcapsules that, upon specific stimulus, release their contents through head-to-tail depolymerization of the end-capped poly(phthalaldehyde) that forms the capsule membrane.¹⁰⁵ Such microcapsules amplify the applied signal, and the rate of the response can be tuned both by changing the length of the polymer and by altering the thickness of the capsule membrane. Microfluidic flow-focusing was used to encapsulate different payloads in the polymer microcapsules (such as fluorescein isothiocyanate-labeled dextran). The release of the payload is correlated with microcapsule degradation.

Phillips and co-workers also improved the synthesis of the trigger-functionalized depolymerizable poly(phthalaldehyde) to make it reproducible and scalable.¹⁰⁶ Different triggers were attached at the ends of the linear polymer, generating polymer **101**; degradation of polymer **101** can be induced by either of two stimuli (Figure 87).

Phillips and co-workers also investigated the response of the poly(phthalaldehyde) in the solid state.¹⁰⁷ Solid-state materials composed of these polymers respond most efficiently to a stimulus in solution when the triggers on the polymer are at the solid–liquid interface rather than buried inside the solid-state

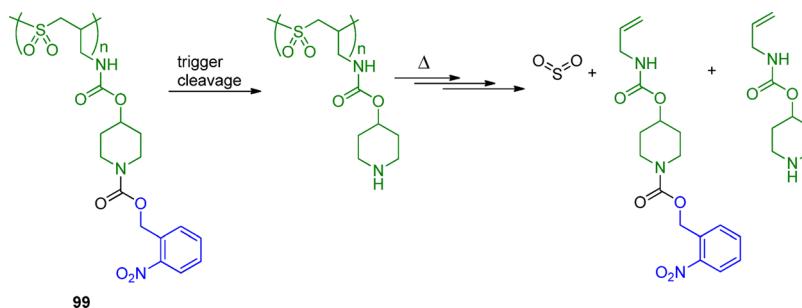


Figure 85. Self-immolative poly(olefin sulfone) degradation upon trigger cleavage via UV irradiation, which unmasks an amine base that allows heat-induced degradation.

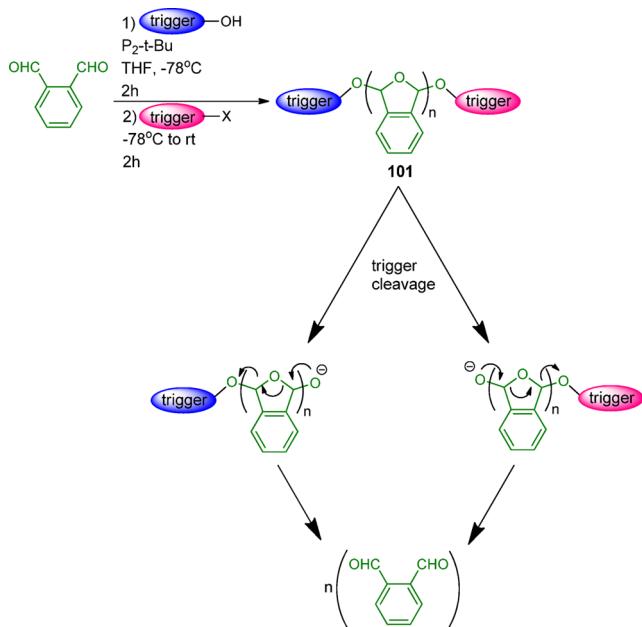


Figure 87. Synthesis and head-to-tail depolymerization of dual-triggered polymer **101** upon specific stimuli.

material. Phillips and co-workers have defined approaches for improving the likelihood that the triggers are accessible at the solid–liquid interface. In water this occurs when (i) the triggers are hydrophilic and (ii) when the polymer is shorter rather than longer (thus increasing the density of the triggers that are at the solid–liquid interface). The test system chosen was a microscale pump made up of the polymer. By measuring the flow rate initiated by depolymerization of the polymers within the films, the researchers were able to determine the rate of depolymerization and thus the ease of access of molecules in solution to the triggers.

Moore and co-workers reported the polymerization of copolymers made up of *o*-phthalaldehydes and other monomers such as benzaldehydes^{108,109} and glyoxylates¹¹⁰ (polymers **102** and **103**, respectively; Figure 88). The polymers reported did not possess a moiety for triggered depolymerization, as Phillips et al. described, and could be depolymerized only via acetal hydrolysis or mechanical degradation. Nonetheless, these polymers are a potentially important new depolymerizable polyaldehyde family, since combinations of different self-immolative monomers allow production of polymers with various mechanical and physical

properties and straightforward incorporation of various pendant functionalities.

Additionally, Moore and co-workers reported a study of poly(*o*-phthalaldehyde) as a test of potential systems that may undergo repair by depolymerization–repolymerization to imitate repair in biological systems.¹¹¹ Macroyclic poly(*o*-phthalaldehyde) **104** is a metastable polymer; its stability is due not to the capping of the chain ends but rather to the macrocyclization process (Figure 89). This polymer undergoes

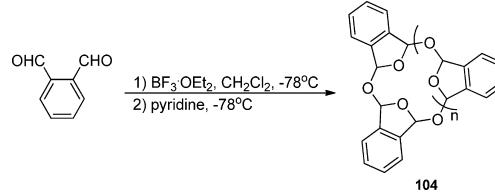


Figure 89. Strategy for polymerization of *o*-phthalaldehyde to yield the macrocyclic poly(*o*-phthalaldehyde).

mechanically triggered heterolytic depolymerization to its monomers. The obtained monomers can undergo repolymerization upon treatment with a chemical initiator, effectively completing a depolymerization–repolymerization cycle.

Recently, Phillips and co-workers reported a new type of polymer that is a member of the poly(phthalaldehyde) family: poly(4,5-dichlorophthalaldehyde) (PCl_2PA) (polymer **105**; Figure 90a).¹¹² The *p*-chloro groups on the polymer have a

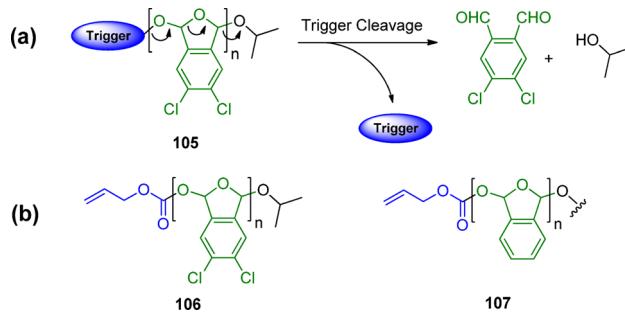


Figure 90. (a) Mechanism of the head-to-tail depolymerization when the trigger on PCl_2PA **105** is cleaved via reaction with a specific stimulus. (b) Comparable polymers: Alloc- PCl_2PA **106** and Alloc-PPHA **107**.

stabilizing effect due to their electron-withdrawing properties. Alloc- $\text{PCl}_2\text{PA-OiPr}$ (**106**) (Figure 90b) is stable in air at 23°C

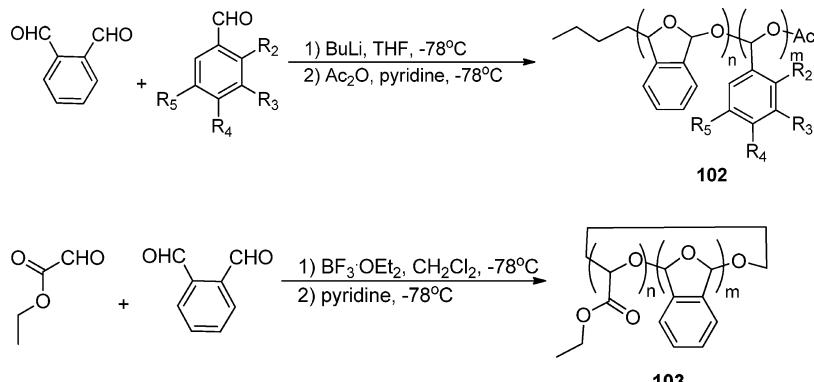


Figure 88. Synthesis of copolymers based on PPHA that may be used to produce self-immolative polymers.

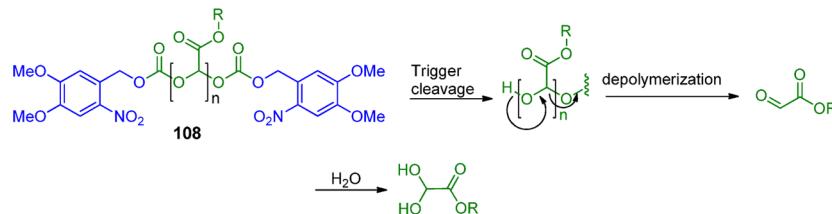


Figure 91. Mechanism of the head-to-tail depolymerization reaction that occurs after the trigger on polyglyoxylate **108** is cleaved via reaction with a specific stimulus.

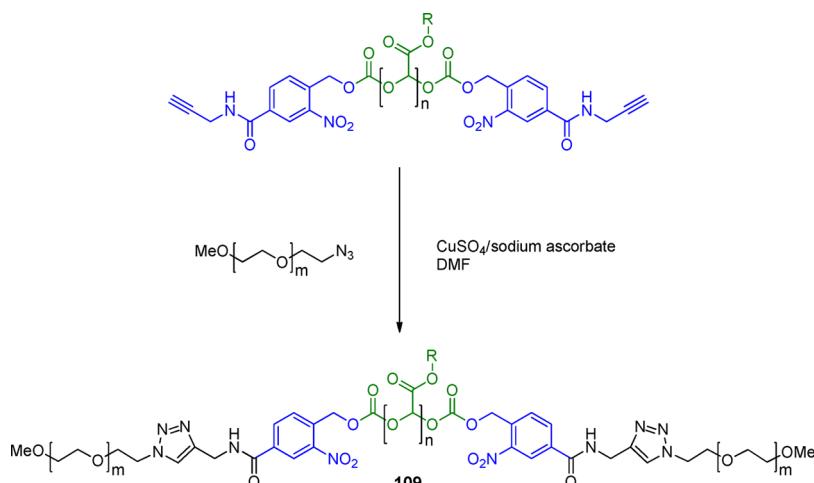


Figure 92. Synthesis of mPEG–polyglyoxylate–mPEG triblock copolymer **109**.

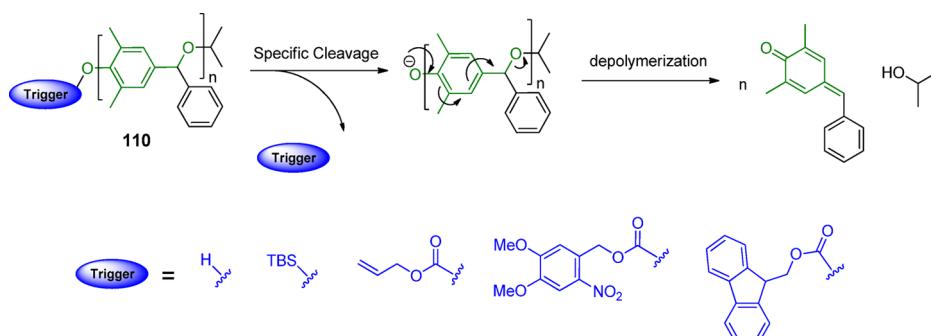


Figure 93. Disassembly pathway of self-immolative polymer **110**.

with less than 1% degradation over 130 days. In contrast, Alloc-PPHA (**107**) is 95% degraded under the same conditions. The stability of **106** allows its use in the assembly of three-dimensional macroscopic polymeric materials, which can undergo patterning by selective laser sintering. These macroscopic polymeric materials are self-powered, multi-stimuli-responsive, and sustainable. It should be noted that the higher stability of PCl₂PA versus PPHA does not prevent PCl₂PA from depolymerizing completely upon trigger cleavage at room temperature both in solution and in the solid state.

DiLauro and Phillips further examined the differences in PPHA and PCl₂PA stability and background degradation.¹¹³ Both polymer types were synthesized with different triggers, and their degradation was compared under diverse conditions. Comparable PPHA and PCl₂PA polymers (with the same trigger, such as polymers **107** and **106**) were stored under protection from light at 23 °C in THF-*d*₈ and monitored over time by ¹H NMR spectroscopy for the appearance of monomers. After 6 days, PPHA polymers that were end-capped via a

carbonate linkage were degraded by 5–19%, and the comparable PCl₂PA polymers were not detectably degraded (less than 1%). The added stability afforded by the chlorine substitution is more pronounced when the polymers are exposed to mild acid in THF rather than to pure THF. When exposed to 100 equiv of benzyl alcohol for 6 days in THF-*d*₈ (in the dark), PPHA depolymerizes 30-fold more per day than the comparable PCl₂PA. Thermogravimetric analysis of the two also shows this pattern, indicating that PCl₂PA is more stable than PPHA by approximately 40 °C.

More recently, Gillies and co-workers reported the synthesis and characterization of self-immolative polyglyoxylate polymer **108** with a similar mechanism of disassembly.¹¹⁴ Polymerization of alkyl glyoxylate followed by end-capping with the trigger 4,5-dimethoxy-2-nitrobenzyl alcohol provides polyglyoxylate **108**, which depolymerizes upon cleavage triggered by UV light (Figure 91). Different alkyl glyoxylates (e.g., ethyl glyoxylate, benzyl glyoxylate) were polymerized by themselves or together to yield random copolymers. Additionally, a UV-responsive trigger bearing an alkyne was utilized to allow conjugation to a

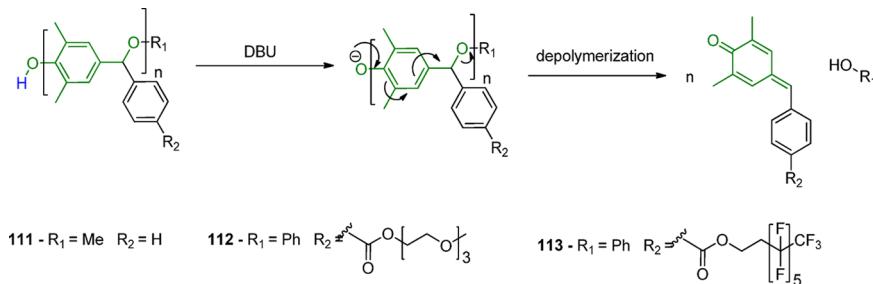


Figure 94. Design and disassembly pathway of base-responsive self-immolative poly(benzyl ether)s with different bulk material properties.

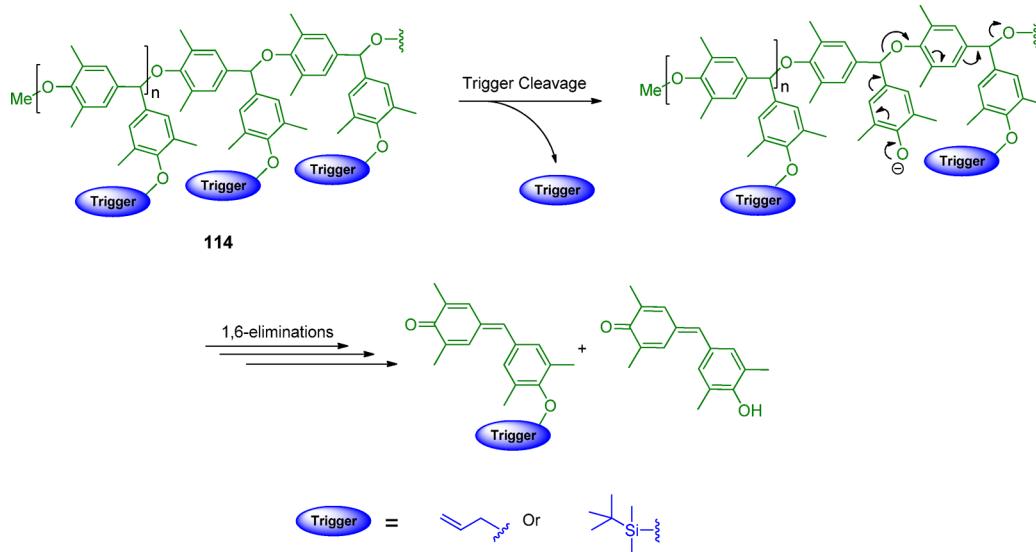


Figure 95. Design and disassembly pathway of multitrigger self-immolative polymer 114.

hydrophilic polymer (e.g., mPEG-azide) via azide–alkyne “click” cycloaddition (Figure 92). This yields an amphiphilic self-immolative triblock copolymer (polymer 109) that self-assembles into micelles in aqueous solution, which can be degraded upon UV irradiation.

3.4. Self-Immulative Poly(benzyl ether)s

The Phillips group reported the design and synthesis of a class of self-immolative polymers based on poly(benzyl ether)s. Self-immolative polymer 110 disassembles completely from head to tail when exposed to specific stimulating conditions (Figure 93). Controlled depolymerization is achieved by incorporating a stimuli-responsive end cap on the polymer’s terminal headgroup. Cleavage of the end cap by a specific analyte generates a phenolate that undergoes a cascade of 1,6-elimination reactions to release the quinone methide monomers. These new benzyl ether polymers exhibit high stability in acid, base, and heat, which usually cause unwanted degradation by side reactions.¹¹⁵ The quinone methide monomer is less favorable enthalpically than the phenol repeating unit in the polymer. Hence, the monomers were synthesized with extended conjugation to a phenyl group, providing an enthalpic driving force for disassembly of the polymer by 1,6-eliminations.

A year after, the Phillips group reported the synthesis of several self-immolative poly(benzyl ethers) with different substituents on the benzyl monomer, yielding different bulk material properties (Figure 94).¹¹⁶ These polymers were capped at the terminus head with a hydrogen atom, thereby making them base-responsive materials. The hydrogen atom serves as a model trigger and can be replaced with a variety of analyte-responsive

groups. Incubation of 111–113 with 1,8-diazabicycloundec-7-ene (DBU) leads to complete disassembly from head to tail at room temperature, thus releasing the original building blocks. Moreover, following the depolymerization process, they recovered the released monomers with sufficient purity to enable repolymerization. This work displays a design principle for new generations of polymeric materials in which polymers are designed for both required bulk material properties and ease of recycling. Additionally, they suggested two idealized strategies for isolating and recycling polymeric materials.

As noted in section 3.3, Phillips and co-workers investigated the degradation of self-immolative polymers in the solid state and the correlation between the rate of disassembly and the density of triggers at the solid–liquid interface. Recently the group demonstrated another method to increase trigger accessibility at the solid–liquid interface by adding multiple triggering units per polymer chain (in a similar manner to the polymers shown in section 3.2). In most cases, the triggering moiety constitutes less than 1% of the number of atoms in self-immolative polymeric materials; therefore, statistically, few triggers are displayed at the solid–liquid interface. Recently, the Phillips group reported a poly(benzyl ether) that was synthesized from a monomeric unit similar to that used in polymer 110, with the addition of a conjugated phenol group, capped with a trigger (Figure 95).¹¹⁷ This self-immolative polymer 114 bears multiple triggers along its backbone and degrades from the trigger cleavage site to its tail without the need to remove all of the triggering groups. This is similar to the degradation of poly(olefin sulfone) described in section 3.2. The released quinone methide unit exhibits a

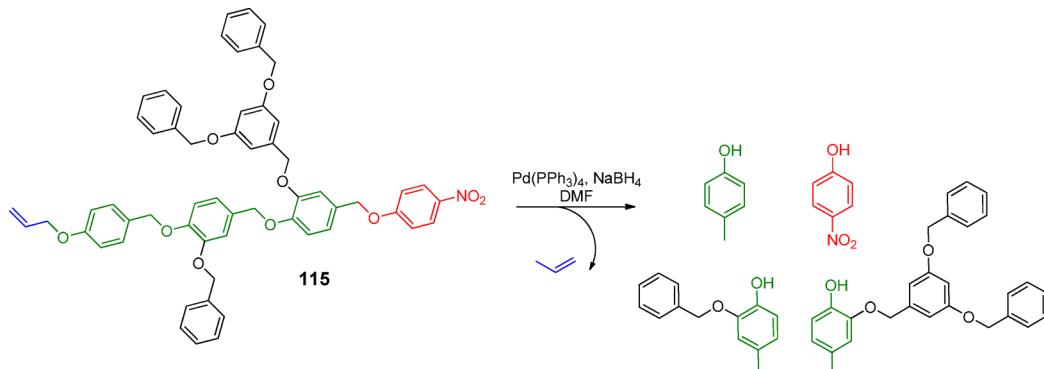


Figure 96. Structure and disassembly of self-immolative oligomer **115** bearing first- and second-generation Fisher dendrons.

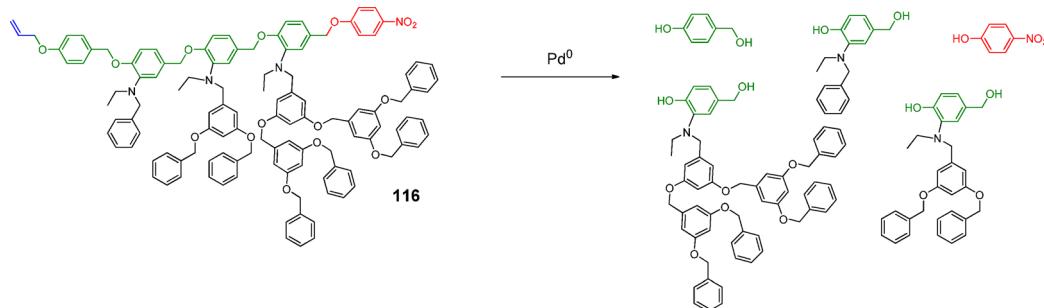


Figure 97. Design and disassembly of self-immolative oligomer **116** bearing a third-generation Fisher dendron.

maximal emission at a wavelength of 574 nm, thus providing a visible color change that corresponds to the disassembly of the self-immolative polymer.

3.5. Self-Immolative Oligomers

McGrath and co-workers reported the integration of Fisher-type dendrons with a self-immolative oligomer backbone equipped with an allyl ether protecting group (polymer **115**; Figure 96).¹¹⁸ This self-immolative oligomer backbone was composed of 4-hydroxybenzyl alcohol units conjugated by ethereal linkages between the phenol and the benzyl alcohol; each unit was conjugated to a different generation of benzyl(aryl ether) dendrimer through an ascending generation. At the terminal benzyl alcohol, 4-nitrophenol was conjugated as a reporter group. Removal of the allyl ether protecting group with Pd⁰ initiates a cascade of 1,6-elimination reactions, thus resulting in disassembly of the oligomer.

The McGrath group also reported the iterative synthesis of self-immolative oligomers with ascending generations of benzyl(aryl ether) dendrimers and demonstrated their disassembly (Figure 97).¹¹⁹ In contrast to self-immolative oligomeric system **115**, the benzyl(aryl ether) dendrimers in self-immolative oligomeric system **116** were conjugated to an aniline and not a phenol. The disassembly process of **116** through sequential 1,6-eliminations is initiated by allyl deprotection with Pd⁰. Gram quantities of self-immolative oligomers such as **116** can be obtained using iterative synthesis.

Similar oligomers based on either *p*-quinone methide species (oligomers **117** and **118**) or *o*-quinone methide species (oligomers **119** and **120**) as illustrated in Figure 98 have also been reported.¹²⁰ Cleavage of the trigger induces a cascade of eliminations based on either 1,6- or 1,4-eliminations, respectively. The disassembly of these oligomers through 1,4-eliminations proceeded as efficiently as that through the 1,6-eliminations.

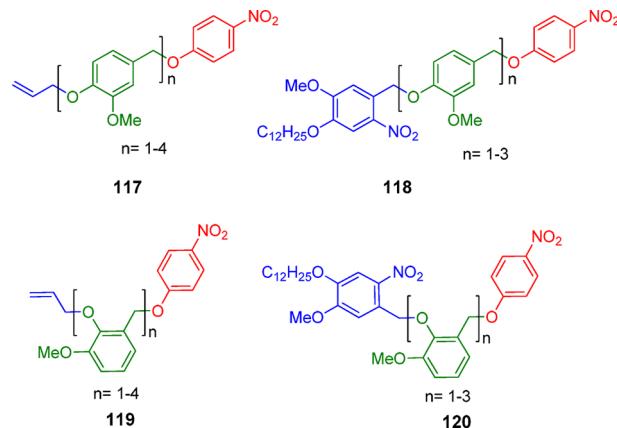


Figure 98. Self-immolative oligomers based on *p*-quinone methide or *o*-quinone methide.

3.6. Self-Immolative Polymers Disassemble through Cyclization Reactions

Another mechanism for achieving head-to-tail self-immolative depolymerization of a linear polymer was reported by Gillies and co-workers.¹²¹ The polymer disassembly mechanism involves trigger cleavage followed by self-cyclization of the monomers. Polymer **121** is composed of alternating *N,N'*-dimethylethylenediamine and 2-mercaptopropanol monomers linked through carbamate or thiocarbamate (Figure 99). Upon trigger cleavage under reducing conditions, the thiol of 2-mercaptopropanol is exposed, leading to sequential cyclizations of the monomers to 1,3-oxathiolan-2-one and *N,N'*-dimethylimidazolidinone.

The Gillies group reported the construction of self-immolative poly(ester amide) **122**,¹²² which contains multiple triggering units on the polymer backbone and disassembles via intramolecular cyclizations (Figure 100). Poly(ester amide)s are of

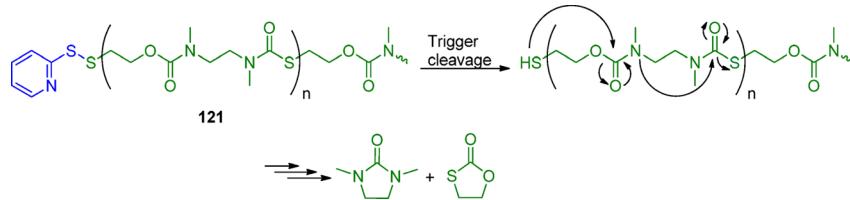


Figure 99. Mechanism of head-to-tail depolymerization of biodegradable linear polymer **121** based on the cyclization of 2-mercaptopropanoate derivatives to 1,3-oxathiolan-2-one and of *N,N'*-dimethylethylenediamine to urea upon trigger cleavage.

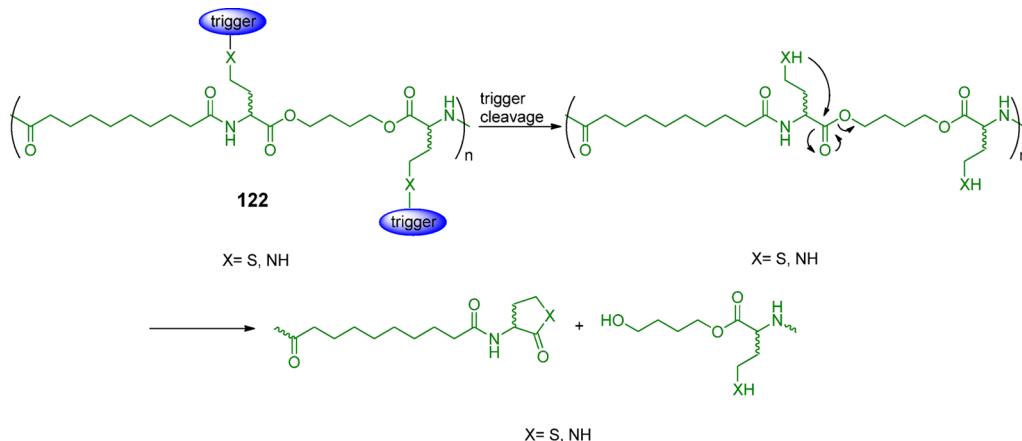


Figure 100. Degradation of poly(ester amide)s via cyclization of pendant functional groups of amino acid monomers upon trigger cleavage.

interest because the structures and properties of these polymers can be readily tuned through the integration of a wide variety of monomers, making them suitable for a diverse range of applications. Either L-2,4-diaminobutyric acid (DAB) or homocysteine (HCY) have been incorporated into the backbone of the polymer, and γ -pendant groups have been capped with triggers. Upon trigger cleavage, the pendant γ -amines or γ -thiols of DAB or HCY esters are revealed, leading to intramolecular cyclizations to give five-membered lactams and thiolactones, respectively. The degradation of these polymers was evaluated both in solution and in films, validating that stimuli-triggered degradation was more rapid than background ester-hydrolysis-based disassembly.

Similarly, Almutairi and co-workers developed self-immolative poly(DL-lactide-*co*-glycolide) (PLGA).¹²³ PLGA is an FDA-approved polymer. Because of this and the fact that its hydrolytic degradation is slow and offers minimal control over the degradation kinetics, it is of interest in the field of self-immolative polymers. The modified PLGA **123** contains pendant nucleophiles protected with photocleavable groups as triggers (Figure 101). Upon trigger cleavage, the pendant nucleophiles are revealed, which leads to intramolecular cyclizations to give five-membered lactams, lactones, and thiolactones and the complete degradation of the polymer. Nanoparticles were produced by the single emulsion method, encapsulating Nile red, a small hydrophobic dye. After irradiation, the fluorescence intensity of Nile red decreased drastically as a result of nanoparticle disassembly and release of the dye into aqueous solution.

Almutairi and co-workers also developed a self-immolative poly(ester amide), which depolymerizes via intramolecular cyclizations based on ornithine lactamization (Figure 102).¹²⁴ Spontaneous cyclization of ornithine in peptides is well-known, making it a candidate monomer for self-immolative polymers. Ornithine-based poly(ester amide) **124** was synthesized with the

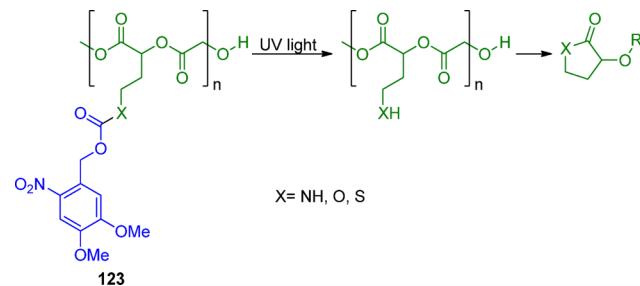


Figure 101. Degradation of self-immolative PLGA via cyclization of pendant functional groups of amino acid monomers upon trigger cleavage.

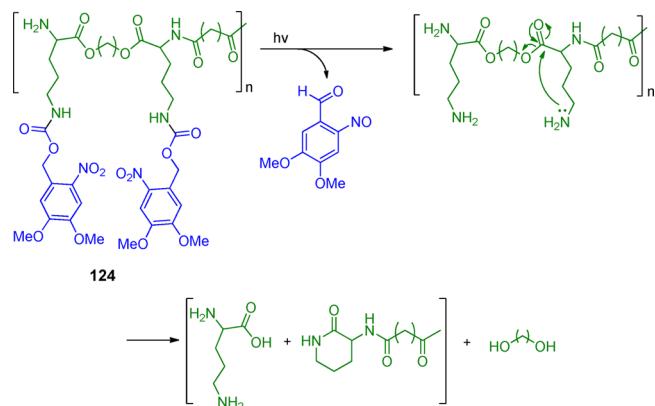


Figure 102. Mechanism of light-induced degradation via intramolecular cyclization of ornithine-based poly(ester amide) **124**. The removal of the light-sensitive groups is followed by a combination of amino-assisted ester hydrolysis and aminolysis, leading to degradation of the polymer.

terminal amine of the ornithine capped with a light-sensitive trigger. Upon irradiation, the amine is exposed, and the

monomer undergoes lactamization, degrading the polymer in the process. The polymers were formulated into nanoparticles encapsulating model payloads, and the payloads were released upon treatment with a stimulus. Nanoparticles were produced by the single emulsion method, encapsulating 10 nm superparamagnetic iron oxide. Irradiated and nonirradiated particles were imaged by transmission electron microscopy. The non-irradiated particles remained intact after 24 h, with iron oxide found only inside the particles. No particles were visible in the irradiated sample; only chunks of material in coexistence with free iron oxide nanoparticles were observed.

De Gracia Lux and Almutairi¹²⁵ reported the synthesis of the analogous self-immolative poly(caprolactone) **125**; the method employed a mechanism similar to the ornithine lactamization. The monomer is equipped with a pendant amine and capped with a trigger. Once the trigger is cleaved, the amine is unmasked, allowing for intramolecular cyclization of the monomer to 2-piperidinone and degradation of the polymer (Figure 103). The

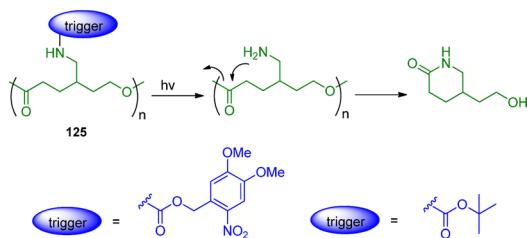


Figure 103. Stimuli-controlled depolymerization of poly(caprolactone) **125** via intramolecular cyclization of the monomers to 2-piperidinones.

degradation of these polymers was evaluated, confirming that stimuli-triggered degradation was more rapid than background ester-hydrolysis-based disassembly. This polymer was also formulated into nanoparticles that encapsulated iron oxide nanoparticles and released the payload upon stimulation.

Li and co-workers synthesized a self-immolative functional poly(4-hydroxybutyrate).¹²⁶ Head-to-tail degradation of poly(4-hydroxybutyrate) **126** occurs via intramolecular cyclization due to the attack of the hydroxyl end group at the ester carbonyl moiety, yielding a lactone (Figure 104). Degradation of the

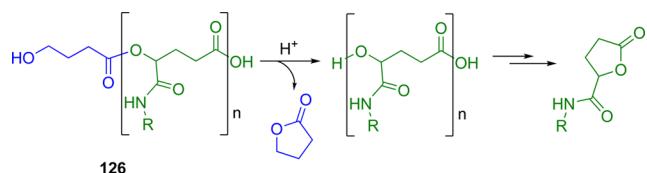


Figure 104. Degradation mechanism of a functional poly(4-hydroxybutyrate) via intramolecular cyclization.

polyester under acidic and neutral conditions was investigated. Under acidic conditions, head-to-tail degradation was observed, though random scission of the ester group also occurred (but at a much lower rate). Under neutral conditions, random scission did not occur, and the polymers degraded solely in a head-to-tail manner.

4. SUMMARY AND PERSPECTIVE

Self-immolative molecular platforms have to date been demonstrated in fields of drug delivery, molecular probes, signal amplification, supermolecular chemistry, and materials chemistry. The number of examples of functional molecular systems

based on self-immolative disassembly grows every year. In this review we have summarized developments made in the last 12 years or so in the synthesis and application of self-immolative molecules that are based on dendritic, oligomeric, and polymeric structures. Two basic disassembly reaction mechanisms are generally employed as tools to construct responsive self-immolative functions: quinone methide eliminations and cyclization reactions. These two tools have been harnessed to design numerous molecular systems that in response to external stimuli undergo programmed disassembly. Systems that allow up to three quinone methide eliminations in one phenol or aniline molecule have opened a door for new branched molecular amplifiers. Such branched molecules can serve as adaptors that achieve release of double or triple payloads in response to a single molecular event. The branched units can be assembled into dendritic structures that disassemble through self-immolative pathways. To further improve this amplification effect, a dendritic chain reaction has been applied. This technique uses simple dendritic molecules to achieve high-generation self-immolative dendrimers. The quinone methide elimination and cyclization disassembly pathways have also been harnessed to achieve head-to-tail disassembly of oligomeric and polymeric molecular structures in response to an analyte-triggered event. Such polymers have been used to construct responsive particles such as microcapsules that discharge their interior contents upon a triggering event. A significant milestone was recently realized with investigations of the degradation of self-immolative polymers in the solid state. The Phillips group demonstrated that the quinone methide disassembly pathway can efficiently occur in the solid state through activation of single or multiple triggering units per polymer chain. Stimuli-responsive polymer domino-like degradation was also achieved with poly(phthalaldehyde) through the “unzipping” effect (which occurs above the ceiling temperature). To further expand this field, there is a need for the development of new self-immolative molecular structures/reactivities. Such developments are most likely already in progress.

Self-immolative molecular amplification is now recognized by the scientific community as an efficient and valuable function relevant to various molecular applications. It is quite certain that this relatively young field of research will continue to grow even as these lines are written.

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Notes

The authors declare no competing financial interest.

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Samer Gnaim was born in 1991 in Baqa El-Garbia, Israel. He received his B.Sc. in Chemistry and Biology from Tel Aviv University in 2013 with distinction. He is currently carrying out a direct Ph.D. studies program

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Doron Shabat studied chemistry at the Technion—Israel Institute of Technology between 1987 and 1990. After obtaining his B.Sc., he continued toward his Ph.D. under the supervision of Prof. Ehud Keinan in the field of catalytic antibodies. Upon completion of his Ph.D. thesis in 1997, he joined a group led by Professors Richard A. Lerner and Carlos F. Barbas, III, at The Scripps Research Institute in La Jolla, California, as a postdoctoral fellow. There he continued to work in the area of catalytic antibodies. In 2000, he returned to Israel to start his independent career in the School of Chemistry at Tel Aviv University as a Senior Lecturer. He was promoted to the rank of Associate Professor in 2005 and to Full Professor in 2008. His research is focused on bioorganic chemistry with particular interests in self-immolative molecular systems and long-wavelength fluorescent dyes for *in vivo* imaging. He is the recipient of the Juludan Prize for 2005, administered by the Technion—Israel Institute of Technology, the Israel Chemical Society's Prize for Outstanding Young Chemists (2005), and the Frost Fellowship administered by The Scripps Research Institute (2012 and 2014).

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