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Programmable Microcapsules from Self-Immolative Polymers

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Abstract: For the autonomous repair of damaged materials, microcapsules are needed that release their contents in response to a variety of physical and chemical phenomena, not just by direct mechanical rupture. Herein we report a general route to programmable microcapsules. This method creates core−shell microcapsules with polymeric shell walls composed of self-immolative polymer networks. The polymers in these networks undergo a head-to-tail depolymerization upon removal of the triggering end group, leading to breakdown of the shell wall and subsequent release of the capsule's liquid interior. We report microcapsules with shell walls bearing both Boc and Fmoc triggering groups. The capsules release their contents only under conditions known to remove these triggering groups; otherwise, they retain their contents under a variety of conditions. In support of the proposed release mechanism, the capsule shell walls were observed to undergo physical cracking upon exposure to the triggering conditions.

Autonomous repair of damaged devices remains an ongoing challenge in the field of materials science. One approach is the release of compartmentalized chemicals via rupture of microcapsules by crack propagation.[1] Beyond repair of structural materials, restoration of other functions such as optical and electronic properties could benefit from the triggered release of a healing fluid,[2] but the technology for rupturing microcapsules is currently limited by the need for direct, mechanical interaction between the capsule and the damage. In ideal self-healing systems, capsules could release healing agent in response to various physical, chemical, or biological signals. Nature uses this approach in a number of healing and regulatory systems where small concentrations of a chemical signal are turned into large-scale responses.[15] Synthetically, the concept of stimuli-triggered release was first demonstrated with lipid vesicles.[3] However, polymeric microcapsules are stronger, more chemically resistant, and able to contain larger volumes[4] than liposomes, making them attractive for materials applications. "Triggerable" microcapsules that are ruptured by light, enzymes, or chemical reduction[5] have been reported. Here we present a general approach to programmable microcapsules that release their core when triggered by a specific event that ruptures the shell wall.

As other triggerable shell walls require specific syntheses, we sought to develop a general method for core−shell microcapsules by embedding a chemical trigger in the shell wall (Figure 1). The capsule shell wall is constructed from self-immolative polymer networks that undergo a head-to-tail depolymerization upon removal of a triggering end group.[6] The "trigger" is a carbamate-based protecting group, making this method highly general. In this work, we have synthesized capsules that are sensitive to either HCl or piperidine, but many other variations can easily be imagined.

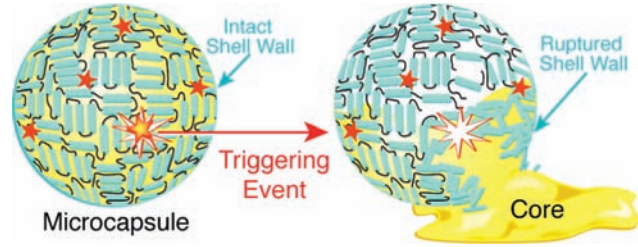
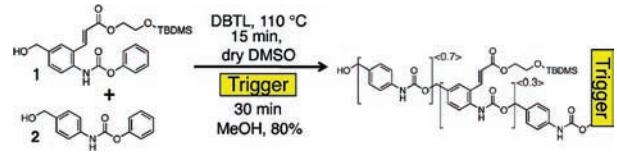


Figure 1. Schematic of a programmable microcapsule. The capsule shell wall is a self-immolative cross-linked polymer network (blue) with a loaded trigger (star). The capsule releases its contents upon activation from a triggering event. This event removes the head of the polymer (star), initiating a head-to-tail depolymerization and release of the core contents.

Scheme 1. Synthesis of Self-Immolative Polymers



Construction of the self-immolative polymer followed methods similar to those of Sagi et al.[6] Briefly, monomer **1** bearing a *tert*-butyldimethylsilyl (TBDMS)-protected[9] pendant alcohol and a masked isocyanate was created. This was then mixed with the phenyl carbamate of aminobenzyl alcohol (**2**) in a 3:7 ratio and polymerized by addition of catalytic dibutyl tin dilaurate (DBTL) to create a metastable polyurethane. Trigger-loaded polymers were created by capping the terminal isocyanate through addition of an unique alcohol to form a carbamate protecting group [**SI-6**, **SI-7**, where **SI-*n*** refers to compound ***n*** in the Supporting Information (SI)]) (Scheme 1). The linear polymers were characterized by NMR spectroscopy and gel-permeation chromatography (GPC) (see the SI).

Depolymerization of the linear polymers was monitored by GPC. Polymers terminated with a Boc[10] or Fmoc[11] trigger were exposed to conditions known to remove that group (Boc, 1:1 TFA/CH_2Cl_2; Fmoc, 10% piperidine in THF) as well as orthogonal, unreactive conditions (e.g., Boc exposed to 10% piperidine in THF). The depolymerization reaction was allowed to proceed over 48 h. In the presence of triggering conditions, the polymers showed a large molecular weight reduction. They did not, however, show the same reduction in the opposing triggering conditions (Figure 2). These

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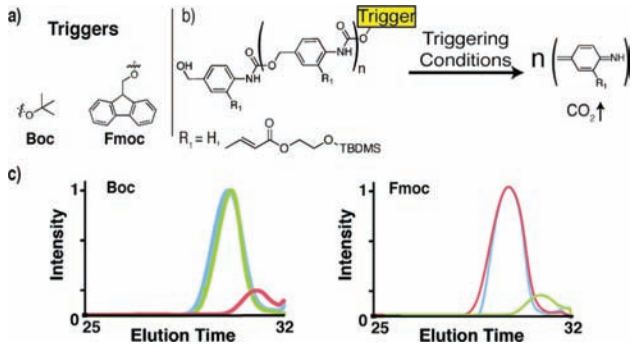

Figure 2. Triggered depolymerization of polymers. (a, b) Scheme depicting (a) the triggers and (b) the polymers and disassembly chemistry. (c) GPC traces showing disassembly of the polymers after removal of the triggers. Green: 10% piperidine, THF, 15 min. Red: 1:1 TFA/CH_2Cl_2, 15 min. Blue: unexposed polymer.

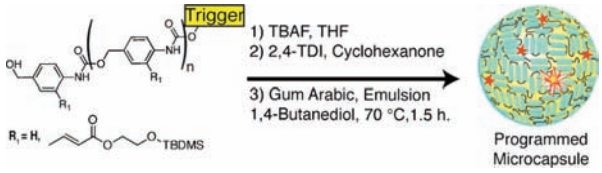

Figure 3. Synthesis of microcapsules. The trigger-loaded polymer was treated with TBAF in order to remove the TBDMS protecting group. The free alcohols were then reacted with 2,4-TDI to form a prepolymer for microcapsule formation. Microcapsules were formed by an interfacial polymerization reaction between the isocyanates and 1,4-butanediol.

results show that removal of the trigger group initiates depolymerization of the linear polymer.

The trigger-loaded polymers were transformed into microcapsules by conversion into a reactive prepolymer.[12] The TBDMS group was removed from the polymers (**SI-10**, **SI-11**), and the polyols were cross-linked and converted to isocyanates by reaction with excess 2,4-toluene diisocyanate (2,4-TDI) in cyclohexanone (Figure 3). A molecular weight increase was observed by GPC (see the SI).

Microcapsules were synthesized via an interfacial polymerization method as previously described.[8] To a solution of water with gum arabic (surfactant and viscosity modifier) was added trigger-loaded "prepolymer" (**SI-8**, **SI-9**) dissolved in the core solvent [ethyl phenylacetate (EPA)]. Butanediol was added to the resulting emulsion as a chain extender, and the solution was heated to 70 °C for 1.5 h (Figure 3). We synthesized **Boc** and **Fmoc** microcapsules, whose shell walls consisted of polymer networks terminated with Boc and Fmoc groups, respectively. Capsules were routinely produced in the 5−40 μm size range. The size and shell-wall morphology were determined by fluorescence, optical, and scanning electron microscopy (Figures 4 and 6). We found that the capsules have a distinctive "wrinkled" appearance. This morphology did not occur under identical capsule formation conditions using the control polymer Desmodur L75, a commercially available prepolymer composed of cross-linked 2,4-TDI (affording microcapsules designated as **Control**), indicating that it is unique to the trigger-loaded polymer (Figure 6). Additionally, the capsule shell wall was fluorescent, indicating the presence of the trigger-loaded polymers at the shell wall.[13]

We hypothesized that the capsules loaded with a given trigger would rupture upon exposure to conditions specific to the removal of that group (hereafter called triggering conditions). **Boc** and **Fmoc** microcapsules were both exposed to 4 M aqueous

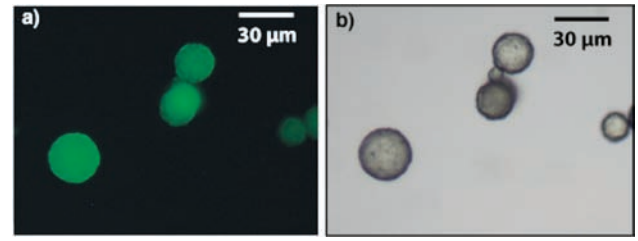

Figure 4. Microcapsule morphology. (a) Fluorescence microscopy images and (b) optical microscopy images of **Boc** microcapsules.

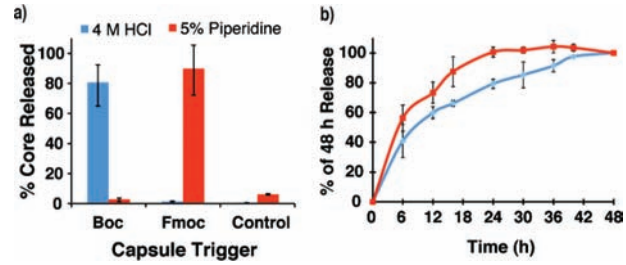

Figure 5. Release of core contents. (a) Percentage of core released after 48 h in triggering solution for capsule sizes of 5−40 μm. Blue: 4 M aqueous HCl with 10% EtOH. Red: 5% piperidine in THF. Percentage of core released was calculated as the integral of the GC peak relative to that for manual rupture. (b) Release profile of the two triggers (Boc, Fmoc) in their respective triggering solutions. The final data point was set to 100% to facilitate interpretation.

HCl with 10% EtOH and to 5% piperidine in THF, conditions known to trigger the Boc and Fmoc protecting groups, respectively. In order to monitor the triggered release of the microcapsules' content, we measured the amount of core contents (EPA) released after 48 h using gas chromatography (GC)[12] after immersion in each of the different triggering solutions. The results are presented as the percentage of core released relative to that released upon manual rupture of the capsules (Figure 5a). Capsules released their core contents upon exposure only to the conditions specific to the trigger removal, while capsules exposed to conditions in which the trigger is unreactive showed little to no release of core contents. Additionally, control capsules without a self-immolative shell wall (**Control**) did not show release under any triggering conditions.

Release profiles of **Boc** and **Fmoc** microcapsules were monitored by GC over the same 48 h period. Release of core material is displayed as a percentage of the final 48 h data point (Figure 5b). **Fmoc** capsules exposed to 5% piperidine released their content slightly faster than **Boc** capsules exposed to 4 M HCl, with complete release in 24 h. This effect may be a result of the solvent dependence of the azaquinone methide elimination.[14] We will investigate this phenomenon in future work.

We examined the capsules' shell morphology to confirm that rupture of the shell wall was the mechanism of release (Figure 6). Following exposure to the triggering conditions, SEM was used to visualize changes in shell-wall morphology. Microcapsules exposed to their matching triggering conditions appear cracked and in some instances deflated, whereas capsules exposed to the nonmatching triggering conditions appear unaffected. In great contrast, the morphology of the control capsules was unaffected under either set of triggering conditions (Figure 6). Combining these observations with the core release data, we conclude that triggering conditions caused a chemically specific depolymerization of the polymer shell wall coincident with release of the core contents.

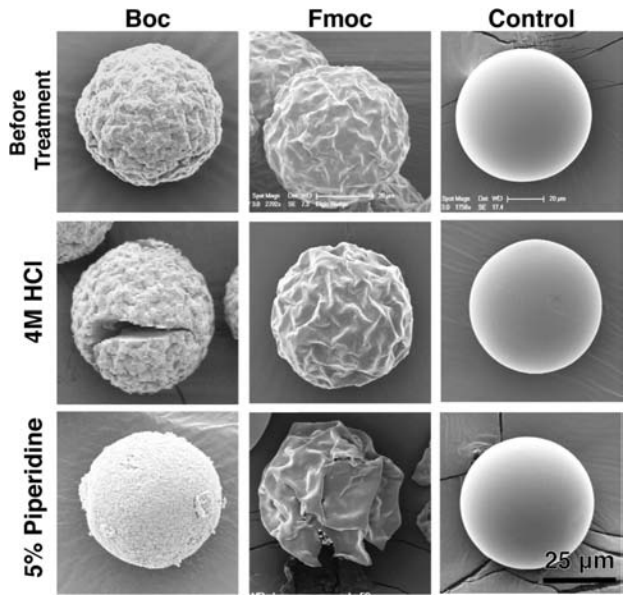

Figure 6. Changes in shell-wall morphology. Capsule shell walls are shown before and after 48 h exposure to triggering solutions. Triggered capsules bear a distinct cracking pattern on the outsides of their shell walls.

In view of the time scale on which the linear polymer depolymerizes (Figure 2), it is surprising that the capsule shell walls remain intact under these conditions. The enhanced capsule stability may be due to the solid-phase nature of the shell wall. Moreover, introduction of trace quantities of units that disrupt the depolymerization reaction cannot be ruled out at this time. Further research on enhancing the rate of capsule rupture is ongoing and will be reported in due course.

In conclusion, we have outlined a general route to programmable microcapsules. We have demonstrated the synthesis of trigger-loaded self-immolative polymers and their subsequent transformation into core−shell microcapsules. We have shown that both the polymer and capsules depolymerize only when exposed to matching triggering conditions and that nontriggering conditions do not cause the capsules to release their core contents or to change their morphology. There are potentially over 100 protecting groups that are synthetically amenable to our method[7] and still others that could be triggered enzymatically.[8] We envision that this will allow the rapid prototyping of capsules that can be made to release their contents upon activation by various chemical, physical, or biological stimuli. These types of "on-demand" chemical systems could find use in diverse areas ranging from drug delivery to self-healing Li ion batteries that are safer and longer-lasting.

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Supporting Information Available: Experimental procedures, synthesis of small molecules and polymers, triggering conditions, UV−vis spectra, controls, additional GPC traces, TGA and GC data, and details of the synthesis of capsules. This material is available free of charge via the Internet at http://pubs.acs.org.

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