

# RECENT DEVELOPMENTS IN DEGRADABLE POLYMERS FOR ORTHOPEDIC REPAIR

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## INTRODUCTION

The first degradable sutures were developed nearly four decades ago.<sup>1</sup> These materials are made from polymers that fulfill their function within the body and then are degraded. With this advance, removal of sutures from a patient once the wound has healed becomes unnecessary.

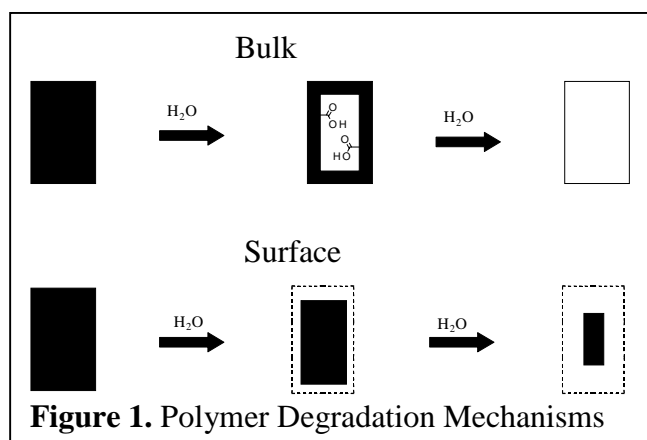
Researchers have developed degradable polymers similar to those used as sutures for fixation of bone defects or fractures. In many cases, for a broken or fractured bone to heal correctly, a patient will require implantation of hardware such as pins, rods, screws, plates, or injection of cements.<sup>1a,2</sup> Many commercially used materials for these applications are nondegradable including polymers, metals, and ceramics which often have serious side effects like inflammation<sup>3,4</sup> or irritation.<sup>4</sup> These side effects sometimes necessitate removal of the implant. Nondegradable implants also prevent the bone from growing into the space where the implant is. This leads to weakened bones and often re-fracture.<sup>1a,3</sup> Implants made of degradable polymers have many advantages over their nondegradable counterparts.<sup>1a</sup> They eliminate the need for second surgery to remove the implant after it has served its function. They allow bones to grow into the polymer matrix so that as the polymer degrades, the bones can strengthen and begin to carry the load. Also, degradable implants may contain drugs that enhance bone growth helping to heal fractures.<sup>5,6</sup> The distinct advantages of degradable polymer implants have led to considerable interest and research in this area.

The usefulness of a degradable polymer for orthopedic applications depends on its ability to fulfill the following criteria:<sup>1a</sup> (1) The degradation rate of the polymer must match the rate at which the bone grows into the polymer. (2) The polymer should facilitate bone growth or at least not inhibit it. (3) The polymer and its degradation products must be biocompatible to prevent adverse reactions. (4) The mechanical properties of the polymer must fit the application and remain until the final stages of degradation.

## POLYMER DEGRADATION MECHANISMS

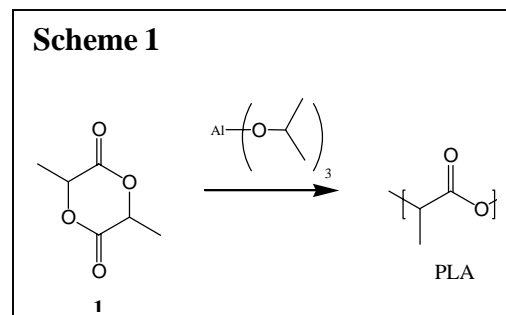
A key consideration in the design and evaluation of a degradable polymer is its degradation mechanism (Figure 1).<sup>1a,7</sup> Bulk degradation is the mechanism invoked for most traditional degradable

polyesters. It is characterized by water entering the polymer bulk where hydrolysis causes degradation. The degradation products are usually carboxylic acids, which decrease the pH of the bulk of the polymer. This leads to autocatalysis and a further drop in pH. As the polymer is hollowed out it will finally break apart releasing the acid groups that had been confined to the interior. This is called acid bursting and can result in inflammation and a decrease in mechanical properties in earlier stages of degradation. On the other hand, surface erosion (Figure 1), results in the thinning of the device over time, while retaining integrity of the polymer bulk.<sup>1a,7</sup> Surface erosion usually occurs in cases where the polymer is significantly hydrophobic, a property that keeps water from entering the bulk. Surface eroding polymers are also less likely to result in inflammation due to acid burst, because the degradation products are washed away from the surface at a constant rate.



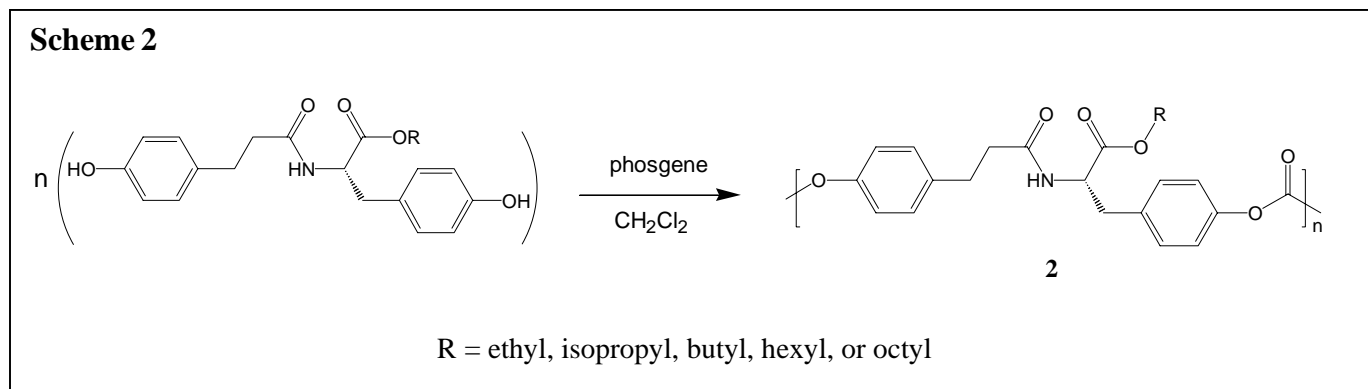
## POLYESTERS

Poly(lactide) (PLA) is a degradable polyester used clinically in medical devices such as sutures and some orthopedic implants.<sup>1a</sup> Copolymerization of lactide (**1**) with other hydrophilic monomers is a way to tune the properties of the resulting polyester.<sup>1a,5</sup> PLA is formed by ring opening polymerization with a metal catalyst such as aluminum isopropoxide (Scheme 1).<sup>8a</sup> Degradable polyesters such as PLA have some distinct advantages over nondegradable materials. For example, PLA is used commercially as orthopedic pins and screws. PLA also has sufficient mechanical strength for in vivo uses. In addition, PLA and poly(lactide-co-glycolide) support sufficient cell growth to be used commercially. Polyesters such as PLA also have a major disadvantage.<sup>4</sup> Most of these hydrophilic polyesters degrade by a bulk degradation mechanism.<sup>10,11</sup>



## TYROSINE-DERIVED POLYCARBONATES

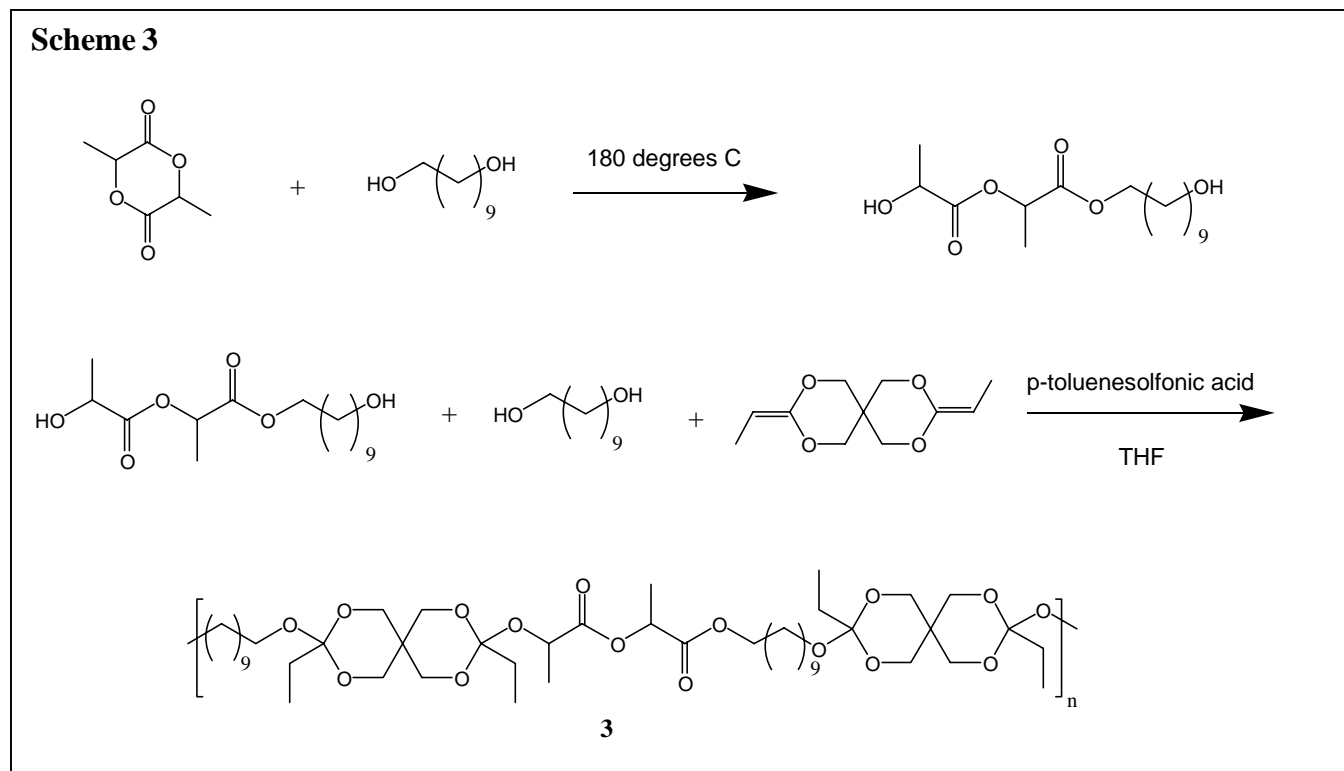
Recognizing the problems associated with bulk degrading polyesters, current efforts are focused on polymers that degrade by surface erosion.<sup>1a,7</sup> For example, Kohn and coworkers have synthesized tyrosine-derived polymers with carbonate linkages in the polymer backbone (Scheme 2).<sup>2d,12</sup> Polymer **2** has three groups per repeating unit that can potentially be hydrolyzed: amide, ester, and carbonate. Studies have shown<sup>12a</sup> that the carbonate group hydrolyzes at a faster rate than the ester group, and the amide bond is not labile in vitro. The products of the hydrolysis of carbonate groups are two alcohols and carbon dioxide. Thus significant degradation is achieved without a corresponding decrease in pH. This alleviates the problem of acid bursting<sup>4</sup> seen in polyesters. The pendant ester group on the chain accomplishes two objectives: (1) in the later stages of degradation, the ester bonds are hydrolyzed into acids. Hydrophilic acid groups provide the necessary solubility for the degradation products to be eliminated from the implant area; (2) the pendant ester moiety also contains a hydrophobic R-group that leads to a surface erosion mechanism. With degradation times as long as 900 days, no significant water uptake was measured in **2**<sup>d</sup> indicating the polymer's hydrophobicity and its strong resistance to water entering polymer bulk. Polymer **2** has been reported to have sufficient mechanical properties for load bearing bone fixations<sup>4,12b</sup> and has been shown to be biocompatible in vivo.<sup>4</sup> In one study, polymer **2** was implanted into canine specimens where it promoted significant bone growth.<sup>4</sup>



## POLYORTHOESTERS

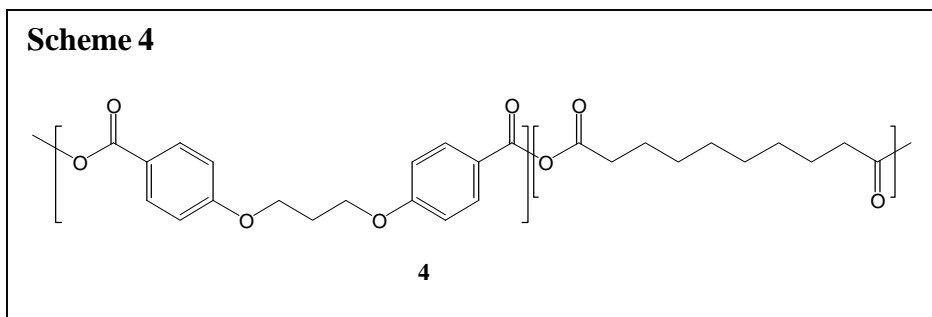
Polyorthoesters (POE) also have been identified as degradable polymers suitable for orthopedic applications. Heller and coworkers have synthesized a specific family of POE (Scheme 3).<sup>13</sup> Polymer **3** degrades by surface erosion.<sup>10,13</sup> With the addition of lactide segments in **3** tunable degradation times ranging from 15 to hundreds of days can be achieved<sup>13</sup>. Most previous POE that have been synthesized contained acidic additives that were used to aid in degradation. This was necessary because POE degrade at slightly acidic pH, whereas the body is slightly basic. Such additives lead to toxicity

concerns. Polymer **3**, however, is self-catalyzing, and it can degrade easily without the presence of acidic additives. This is due to the lactide segments in the chain that produce carboxylic acids upon hydrolysis catalyzing the hydrolysis of the orthoester groups. Polymer **3** has also been shown to increase bone growth in comparison with poly(DL-lactide-co-glycolide) thus indicating its biocompatibility.



## POLYANHYDRIDES

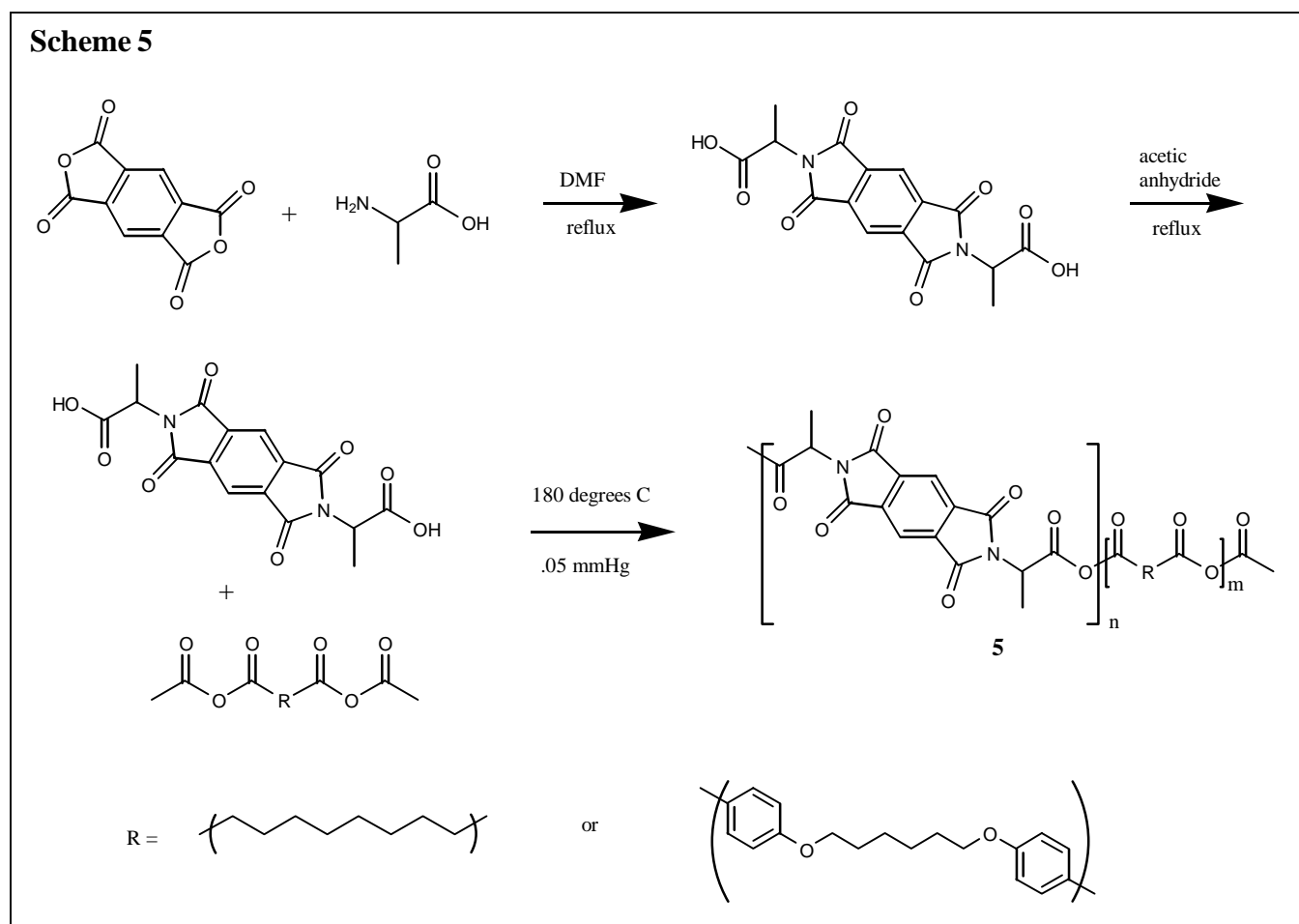
Langer and coworkers have synthesized polyanhydrides for drug delivery applications (Scheme 4).<sup>14</sup> Because **4** has been approved by the FDA, it is the basis of design for some of the polyanhydrides in the following sections. Polymer **4** is used to deliver carmustine, an anticancer drug, to sites in the brain where a tumor has been removed. Copolyanhydride **4** is processed into wafers and then placed in the brain cavity during surgery. Polymer **4** and its degradation products are nontoxic and have a controlled surface erosion degradation mechanism that allows them to deliver drugs at a known rate. Polyanhydride **4** has many characteristics that would



make it suitable for orthopedic repair; however, it does not have the necessary mechanical strength. This has led Langer and coworkers to synthesize modified polyanhydrides with enhanced mechanical properties and surface erosion degradation.<sup>15</sup>

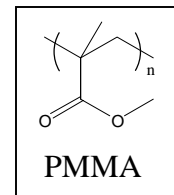
### POLY(IMIDE ANHYDRIDE)S

Polyimides are polymers that are well known for their high thermal and mechanical strength. Langer and coworkers have combined the strength of polyimides and the degradation characteristics of polyanhydrides to obtain suitable materials for orthopedic repair. Poly(imide anhydride)s derived from amino acids such as **5** (Scheme 5)<sup>15</sup> have been synthesized for this purpose. By varying the R-group in **5**, controlled degradation times can be achieved,<sup>16</sup> ranging from 1 to 63 days. It has been reported that **5** degrades by a surface erosion mechanism.<sup>11,17</sup> Polymer **5** has been shown to be biocompatible in vitro<sup>11</sup> for bone repair applications and for drug delivery applications. Increased compression strength of **5** compared to polyanhydrides not containing imide linkages is sufficient to warrant further research into poly(imide anhydrides).



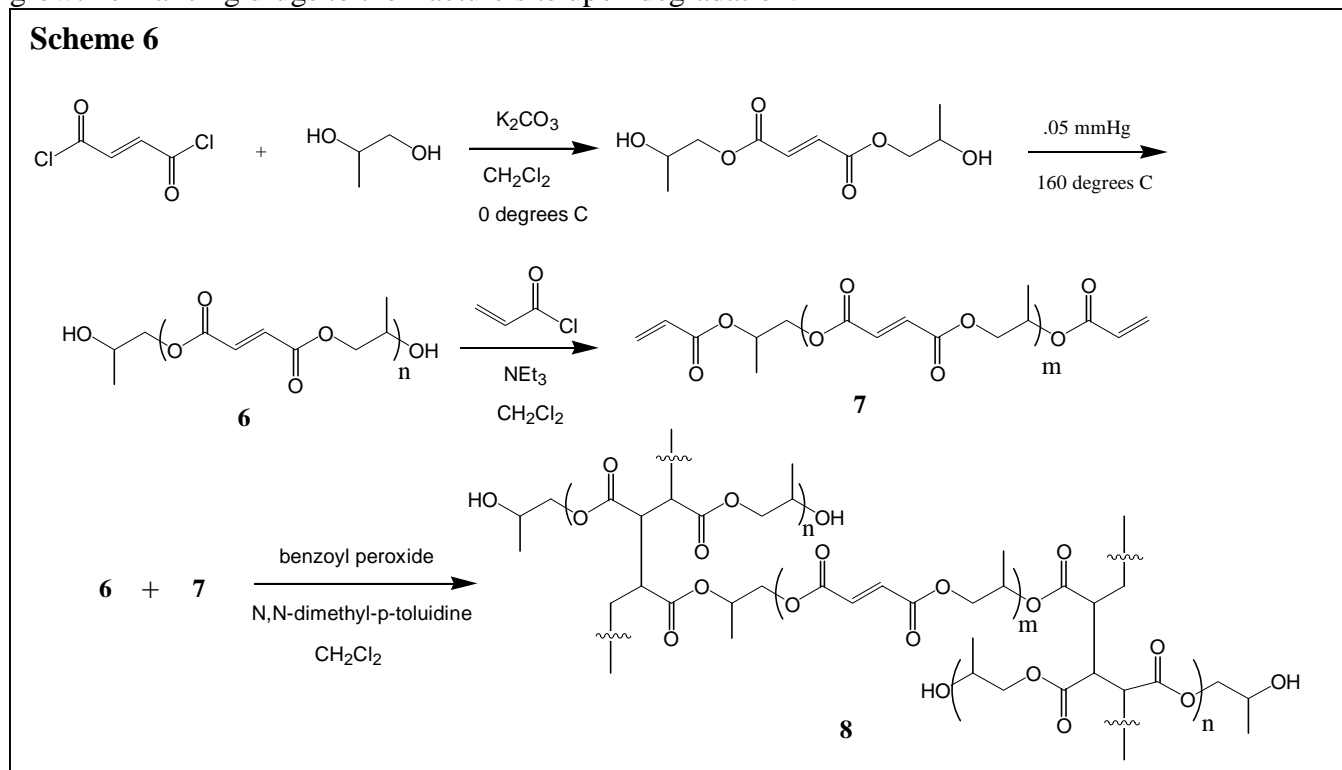
## BONE CEMENT

Bone cement is presently made mostly of the nondegradable polymer polymethylmethacrylate (PMMA).<sup>18</sup> Surgeons internally cement fractures with PMMA by an in situ polymerization reaction. PMMA has several advantages. Injection of the monomer mixture and photo-polymerization allows for a less invasive surgical technique. The mechanical properties of PMMA are sufficient to bear the stress of in vivo loads. There are also some clear disadvantages.<sup>18</sup> For example, it is difficult to control the temperature rise associated with exothermic polymerization. Temperatures at the bone-cement interface often reach up to 90° C causing cell necrosis.<sup>18</sup> In addition, PMMA cements often cause reduced blood flow and irritation.<sup>3</sup>



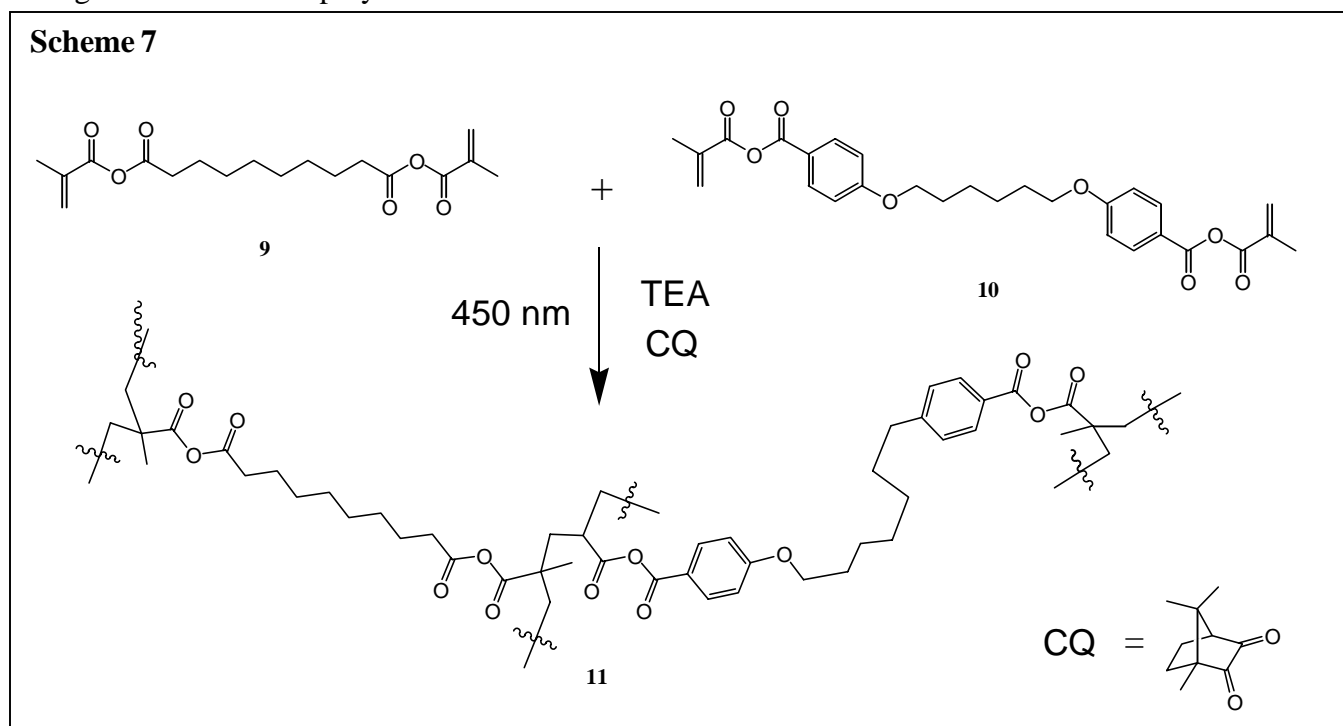
## POLY(PROPYLENE-FUMARATE) NETWORKS

To overcome the disadvantages of PMMA, researchers are developing degradable polymers that can be polymerized in situ during surgery. Mikos and coworkers have synthesized degradable poly(propylene fumarate) networks for bone cement applications (Scheme 6).<sup>19</sup> In general, network polymers exhibit greater mechanical strength than their linear counterparts. Network **8** is formed by initiation with benzoyl peroxide. Polymer **8** is mechanically weaker than PMMA.<sup>19,20</sup> However, by creating networks with higher crosslinking densities, higher strengths may be achieved. Also, the degradation products of **8** are known to be nontoxic.<sup>19</sup> In addition, **8** has been shown to deliver bone growth enhancing drugs to the fracture site upon degradation.<sup>21</sup>



## POLYANHYDRIDE NETWORKS

Anseth and coworkers have reported polyanhydride networks that are formed by photo-initiation and are hydrolytically degraded (Scheme 7).<sup>18</sup> Polymer **11** is based on **4** (Scheme 4).<sup>18</sup> Polymer **11** degrades by a surface erosion mechanism.<sup>18</sup> Photo-initiation can also take place through tissue for an even less invasive surgical technique. By using a mixture of monomers, **9** and **10**, controlled degradation times can be achieved ranging from 3 to 500 days.<sup>18</sup> Also, by using the CQ / TEA initiating system, Anseth has achieved network thicknesses of approximately three cm. Histological studies have also shown that **9-11** are biocompatible.<sup>18</sup> By shuttering the light source used to polymerize, temperature at the bone polymer interface has been controlled to 42° C. Finally, these networks have been shown to form on acceptable time scales from 500 to 1500 seconds, depending on the intensity of the light used to initiate polymerization.



## CONCLUSION

Linear degradable polymers and copolymers have been studied for possible use in degradable orthopedic hardware and cements. These materials have many advantages over current nondegrading technologies, including their ability to degrade at a controlled rate by a surface erosion mechanism. This allows researchers the opportunity to synthesize polymers with a degradation rate similar to that of bone growth. These polymers also appear to be biocompatible, and some even support bone growth. Finally, most of these polymers are shown to possess appropriate mechanical properties for orthopedic

applications, and due to their surface erosion mechanism, maintain these properties through the initial stages of degradation until the bone is ready to accept the load.

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