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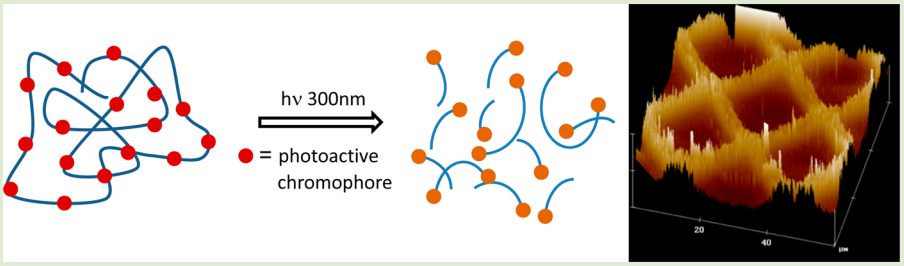
Photoinduced Polymer Chain Scission of Alkoxyphenacyl Based Polycarbonates

Shuangyi Sun, Elaheh A. Chamsaz, and Abraham Joy*

Department of Polymer Science, The University of Akron, Akron, Ohio 44325, United States

Supporting Information



ABSTRACT: We report the design and development of a new class of alkoxyphenacyl based photodegradable polycarbonates. These polymers incorporate the photoactive moiety in the backbone and, when irradiated at 300 nm, undergo controlled chain scission. Micropatterned thin films of these polymers were fabricated by photolithographic techniques. The use of these photodegradable polymers for controlled release applications was demonstrated by the release of Nile Red from polymeric nanoparticles. In addition, these polymers are mechanically robust, thermally stable, and hydrolytically degradable.

Photoresponsive materials have several advantages over other stimuli responsive materials due to the spatial and temporal control of the input.[1] Photoactivation can be used to control various polymer properties such as release or capture of additives,[2] light activated bending,[3] modulation of refractive index,[4] or phase behavior.[5] Photoactivation can also be used to bring about polymer backbone scission. Historically photodegradable polymers were designed to decrease the environmental burden of plastics. Such photodegradable copolymers of vinylic monomers and carbon monoxide are commercially available and are used mostly in agricultural applications.[6] In addition, over the past decade or so several photodegradable polymers have been designed, including polymers containing in-chain metal−metal bonds, photolabile dendrimers, and copolymers of methymethacrylate.[7] Currently there is a strong need in biomedical applications for polymers that are both photodegradable and biodegradable. Polymers with such properties would be responsive to the photochemical input and at a later stage undergo hydrolysis in the aqueous biological environment. Such materials are being investigated as drug delivery devices and as platforms with phototunable physical and mechanical properties.[8] Anseth et al. have designed nitrobenzyl ether based poly(ethylene glycol) (PEG) hydrogel systems whose moduli and the resultant effect on cell behavior can be tuned by photoirradiation.[9] Kasko et al. have synthesized hydrogels that are amenable to creating positive and negative features by two photon irradiation.[10] Zhao et al. reported a micellar system from nitrobenzyl ether based polyurethanes that degrade upon photoirradiation.[11] Almutairi et al. have reported a quinone methide nanoparticle system that upon light activation undergoes a cascade of cyclization and rearrangement reactions resulting in degradation of the polymer.[12] These examples point to the advantages of photoresponsive polymers, and a broader portfolio of photoactive materials would address the increasing need for photoresponsive materials in biomedical applications. We report here a new class of photodegradable polycarbonates that undergo controlled degradation to oligomers upon irradiation at 300 nm. Additionally these polycarbonates are biodegradable and have a high thermal and mechanical stability. Due to the combination of photochemical, hydrolytic, thermal, and mechanical properties of these polymers, they could be useful for many biomedical applications such as in controlled drug delivery and in creating devices with micropatterned architectures. Since their absorbance is in the range of 270−320 nm, these polymers will be most useful in applications where light is not directed at cells and tissues.[13] Topical applications such as cosmetics and wound dressings and patterning of surfaces outside the body and subsequent implantation of the patterned device would be potential applications.[14]

Polycarbonates have several advantages and are actively investigated for many biomedical applications.[15] Aromatic polycarbonates have been investigated as bone pins with high tensile strength.[16] Drug delivery devices and antibacterial polymers have been designed from aliphatic polycarbonates.[17] The polycarbonates described here are based on the alkoxyphenacyl photoactive moiety. Anderson and Reese first described the photochemistry of this chromophore.[18] Sub-

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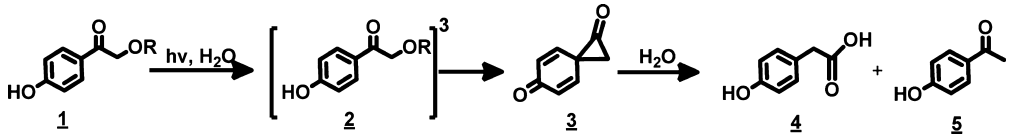
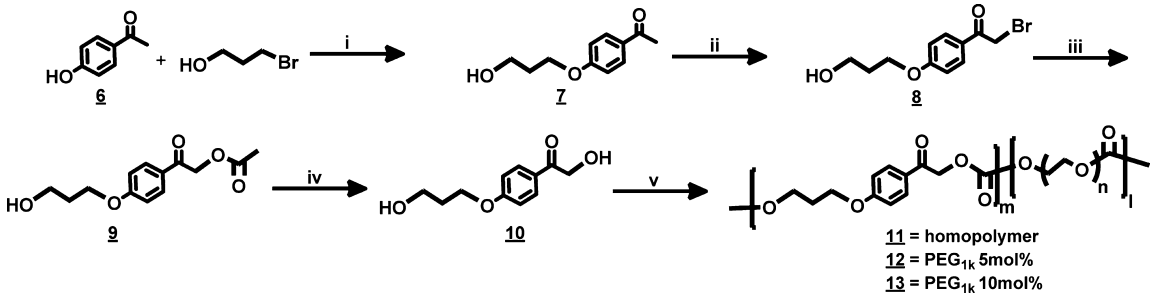
Scheme 1. Mechanism for Photo-Rearrangement of Hydroxyphenacyl Esters[20]



Scheme 2. Synthesis of the Photodegradable Polymers[a]



[a](i) K_2CO_3/18-crown-6, acetone reflux. (ii) $CuBr_2$, EtOH, $CHCl_3$ (over two steps: 75% yield). (iii) NaOAc, CH_3COOH, H_2O (99% yield). (iv) 1. NaOH, MeOH, 2. $NaHSO_4$ (46% yield). (v) Triphosgene, $CHCl_3$, pyridine, PEG_{1k}.

Table 1. Physical Properties of the Homopolymer and Copolymers

Composition	M_n (g/mol)[a]	M_w[a] (g/mol)	PDI[a]	T_g[b] (°C)	T_d[c] (°C)	Modulus, E[d] (MPa)	Stress at yield (σ_y, MPa)	Strain at yield (ε_y, %)
Homopolymer (**11**)	12900	29525	2.3	63	271			
5% PEG_{1k} (**12**)	22698	26252	1.2	9	250	173	8.5	14
10% PEG_{1k} (**13**)	8810	10352	1.2	1	248	59	4.9	22

[a]Result from GPC. [b]Result from DSC. [c]Result from TGA. [d]Result from uniaxial tension.

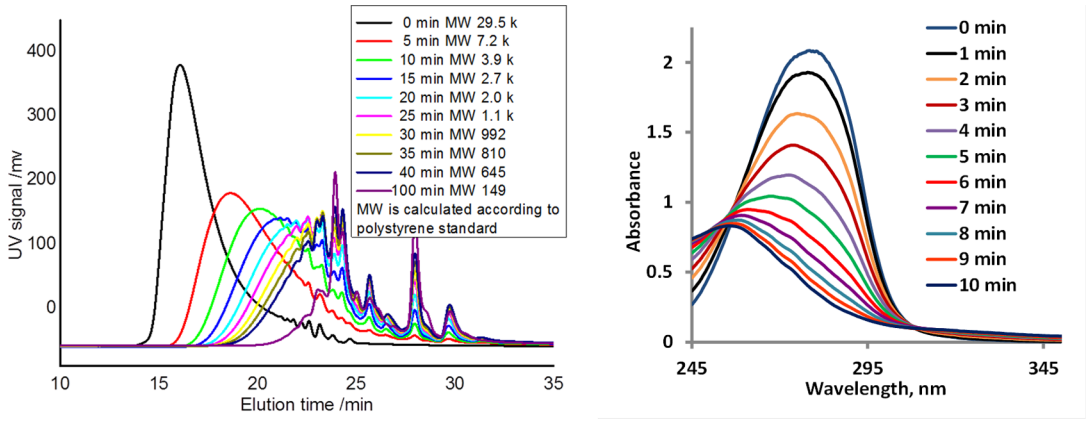


Figure 1. GPC traces showing decrease in molecular weight (M_W) with increasing irradiation time (left) and UV spectrum showing the change in λ_{max} with an increase in photodegradation of the polymer (right).

sequently Givens et al. developed the hydroxyphenacyl functionality as a very efficient photoprotecting group for acids, phosphates, and thiols.[19] Givens et al. reported that solution irradiation of hydroxy and alkoxy phenacyl esters undergo a Favorski type rearrangement to yield the phenylacetic acid derivative and the reduced acetophenone as the major products.[20] The initial excitation of the phenacyl chromophore produces the singlet excited state followed by rapid singlet−triplet intersystem crossing to generate the triplet state.[21] The phenacyl triplet undergoes a rearrangement reaction to give hydroxyphenylacetic acid (**4**) by formation of an intermediate spirodienedione (**3**) or undergoes fragmentation to yield the reduced acetophenone product (**5**) (Scheme 1).

We hypothesized that photodegradable polymers could be designed by incorporating this photoactive unit in the polymer backbone. In 1980, Huang and Byrne reported the synthesis of a poly(arylene keto ester) that contained an analogue of the phenacyl unit in the backbone.[22] However, photolysis of polymer suspensions did not show a molecular weight loss, which the authors suggested was due to the very low solubility of the polymer in most of the solvents.

The phenacyl photochemistry is tolerant to numerous modifications α to the ketone but requires a hydroxyl or alkoxy substitution in the p-position.[19a,23] Additionally, it has been shown that the phenacyl photochemistry is tolerant to extension of the phenolic group with an alkyl spacer.[24] Taking these factors into consideration, we synthesized alkoxyphenacyl based polycarbonates by the route shown in Scheme 2.

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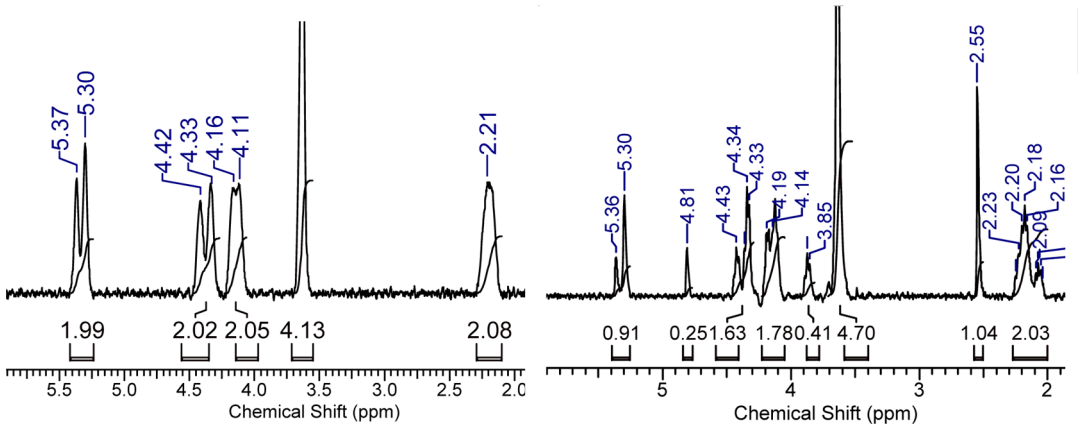

Figure 2. NMR spectra (in $CDCl_3$) before (left) and after (right) irradiation of the copolymer (**12**), showing emergence of peaks at 4.8, 3.8, and 2.5 ppm corresponding to the reaction products.

Hydroxyacetophenone was chain extended with a hydroxy terminated spacer. The product was converted to the bromide without purification and then reacted with sodium acetate to yield the acetate protected derivative in high yield. Following deprotection, the alkoxyphenacyl diol **10** (Scheme 2) was reacted with triphosgene to provide the corresponding polycarbonates. Triphosgene has similarly been used to synthesize tyrosine based polycarbonates which have been extensively studied for tissue engineering applications.[25] Although Givens et al. have not reported the use of hydroxyphenacyl carbonates, we reasoned that since the photochemically active moiety remains the same, a comparable photochemistry would be observed. Our results show that this is indeed the case.

The homopolymer and different copolymers with PEG (Table 1) were synthesized and characterized by NMR and gel permeation chromatography (GPC). PEG copolymers are used in biomedical applications as PEG decreases nonspecific protein adsorption and also decreases the Tg of the polymer. These polymers have UV absorption from 250 to 320 nm with a λ_{max} at 280 nm. The extinction coefficient of the homopolymer is 0.79×10^4 M^{-1} cm^{-1} (calculated with respect to the photoactive unit) which is comparable to the values of hydroxyphenacyl esters (1.4×10^4 M^{-1} cm^{-1}).

Photodegradation of the polymers was examined by irradiation in $CHCl_3$ in a Rayonet reactor at 300 nm (16 tubes, 5.34 mW/cm^2). GPC traces of the irradiated samples of the homopolymer (Figure 1) showed that the polymer underwent controlled time-dependent chain scission upon irradiation. Within 5 min of irradiation, there was a loss of three-fourths of the molecular weight (M_W) of the polymer. Further experiments confirmed that all the three polymers listed below undergo similar photodegradation. The UV spectrum of the photodegradation products also shows the expected change in λ_{max} upon irradiation as a result of the phenacyl moiety rearranging to the blue-shifted phenyl acetic acid derivative.

NMR spectroscopy (Figure 2), of irradiation of the copolymer (**12**), showed the appearance of new peaks at 4.8, 3.8, and 2.5 ppm and a decrease of the number of protons corresponding to the CH_2 α to the ketone (5.37 ppm). It is likely that the peaks at 3.8 ppm and 2.5 ppm correspond to the analogous rearranged product (**4**) and the analogous reduced product (**5**), respectively.

As expected, the rate of photodegradation in the solid state was substantially slower than solution photodegradation. While it was difficult to quantify the solid state degradation products (due to their low concentration) it is clear, as detailed below, that the expected photodegradation occurs in the solid state as shown by the results from irradiation of films and nanoparticles of these materials.

A key attribute of these polymers is their thermal stability (Table 1) which would allow the use of high temperature fabrication methods such as compression molding and extrusion. The homopolymer (**11**) has a decomposition temperature of 271 °C and a T_g of 63 °C. To further assess the thermal stability of these polymers, the copolymer (**12**) was molded as a pellet and held at 180 °C for 1 h. The NMR spectrum of this sample was essentially identical to that of the sample prior to heating, demonstrating the stability of these polymers to high temperature (Supporting Information; Figure S1).

The tensile moduli of the copolymers (with 5 mol % and 10 mol % PEG) were evaluated by uniaxial tensile tests and showed moduli of 173 MPa and 59 MPa, respectively. As a comparison, the Young's modulus of low density polyethylene is about 300 MPa, and that for poly[$(lactic\ acid)_{0.5}$-co-$(glycolic\ acid)_{0.5}$] is 1 GPa.[26] The elastic moduli of the current materials indicate that they can be used for biomedical devices that do not bear high loads. The strain at yield (ε_y) is sufficient to prevent fracture during normal bending.

Incubation of the copolymers **12** and **13** in phosphate buffered saline (PBS) at 37 °C leads to hydrolytic degradation as reflected by the molecular weight loss with the time of incubation. For example, over a period of 28 days, the copolymer with 5% PEG showed increasing molecular weight loss with time and ultimate loss of 61% of molecular weight on day 28 (Supporting Information; Figure S2). As expected, the photochemical degradation is much faster—the polymer undergoes almost complete photodegradation within 30 min (Figure 1), while hydrolytic degradation over 28 days results in a 61% loss for the 5% PEG copolymer.

Controlled delivery of therapeutics from polymeric devices is a promising strategy to increase the bioavailability and decrease drug dosage.[27] In general, drug release from controlled delivery devices occurs by diffusion or is assisted by hydrolytic degradation of the matrix. Compared to traditional dermal patches, it is likely that in these devices the dose can be controlled by the intensity and time of irradiation. As a proof of

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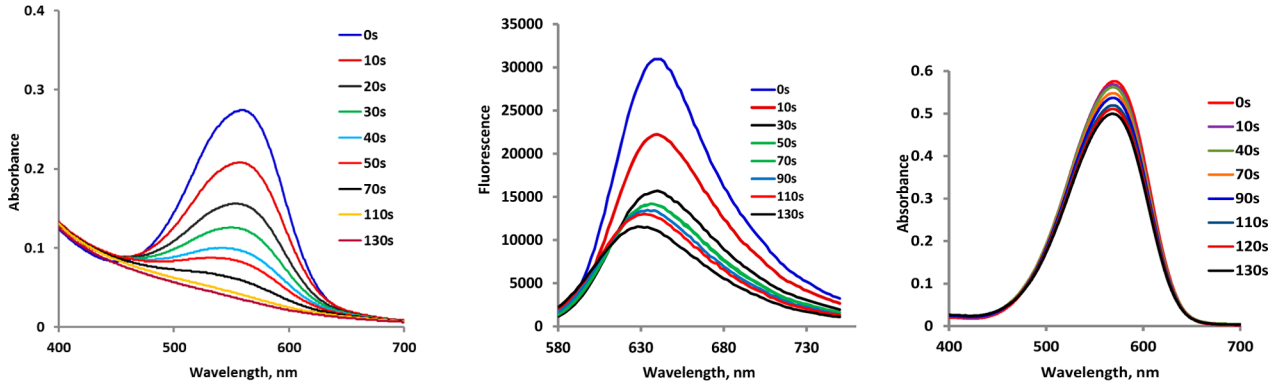

Figure 3. Release of Nile Red from nanoparticles of the 5% PEG copolymer results in decrease in absorbance (left) and fluorescence (center) as a function of time of irradiation. Meanwhile irradiation of Nile Red alone results in only a slight decrease of absorbance at these times (right).

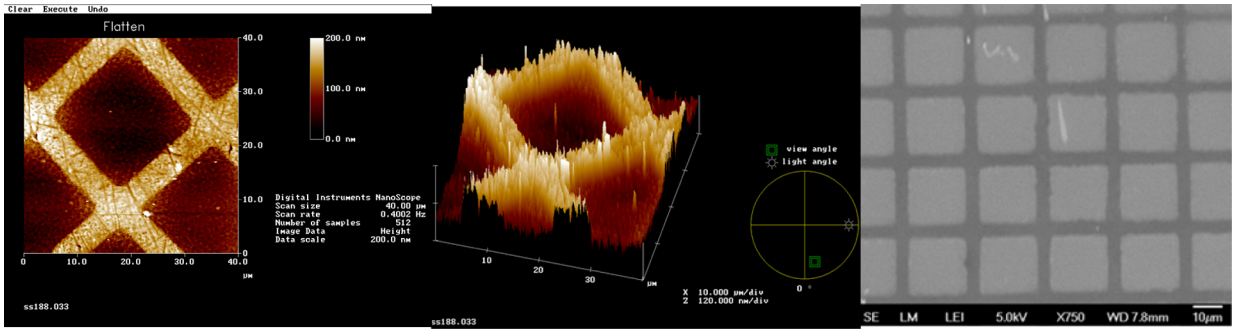

Figure 4. AFM images showing height (left), 3D rendering (center), and SEM image of photopatterned polymer surfaces (right).

concept, Nile Red release from nanoparticles of the copolymer with 5% PEG was examined. Nile Red has been used as a model compound in several controlled release studies.[28]

Aqueous solutions of Nile Red encapsulated nanoparticles were pink and showed the expected fluorescence. Nile Red was released by brief irradiation (0−130 s) and resulted in a decrease of absorbance and fluorescence intensities due to the insolubility of Nile Red in water (Figure 3). Nile Red photobleaches upon extended irradiation but is reasonably stable during the time frame of these experiments (130 s). As a control, irradiation of Nile Red in 1:1 THF:water showed only a slight decrease in absorbance compared to the results for irradiation within the nanoparticles. Currently, there is the limitation that these materials can only be used in applications accessible to 270−320 nm light such as in topical dressings, cosmetics, and ocular implants.[14]

Micropatterned surfaces are useful in numerous applications and are of special utility in studying the fundamental aspects of cell−cell and cell−material signaling.[29] Various cell types are influenced by patterned substrates, and micropatterned surfaces allow tissue-like conditions to be reconstructed and examined in vitro. The photodegradable polycarbonates discussed here can be used to create such micropatterned surfaces which may find utility in biomedical applications. As a proof of concept, polymer films (∼150−200 nm thick) coated on silicon were irradiated through a 1000 mesh transmission electron microscopy (TEM) grid for 30 min and washed thoroughly with MeOH. As shown by AFM (Figure 4), the TEM grid pattern was reproduced on the polymer films. The ridges were 6 μm across, and the degraded squares were 19 μm on each side. These dimensions correspond to the measurements of the TEM grid. The irradiation caused the polymer to degrade away to a depth of ∼120 nm. The SEM results also corroborated the images obtained by AFM and show a larger area of the patterned surface. We are currently working toward translating this patterning process to thicker polymer films with features of ∼1 micrometer depth and 10−20 μm wide. Nerve guidance conduits and small diameter vessels are critical needs in tissue engineering.[30] Although the results demonstrated here are premature for such applications, the use of these photo-responsive materials for creating mico-patterned surfaces for these applications is promising and is currently being explored.

In conclusion, the synthesis and properties of a new class of photodegradable polymers that undergo controlled chain scission upon irradiation at 300 nm are described here. The results demonstrate that the polymers quickly lose their molecular weight upon irradiation but are stable to high temperatures in the absence of light. In addition, these polymers are mechanically robust and biodegradable. These combined properties make them very valuable for many biomedical applications. For example, controlled drug delivery devices such as ocular implants and dermal patches could potentially be designed from such polymers. In addition, polymeric 2D and 3D structures with micropatterned architecture can potentially be fabricated from such polymers. Efforts along these directions are currently underway in our laboratory.

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

Materials, experimental procedures, and figures showing NMR, TGA, DSC spectra and AFM images. This material is available free of charge via the Internet at http://pubs.acs.org.

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AUTHOR INFORMATION

Corresponding Author

*E-mail: abraham@uakron.edu.

Notes

The authors declare no competing financial interest.

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