

# Triggered Release of Encapsulated Cargo from Photoresponsive Polyelectrolyte Nanocomplexes

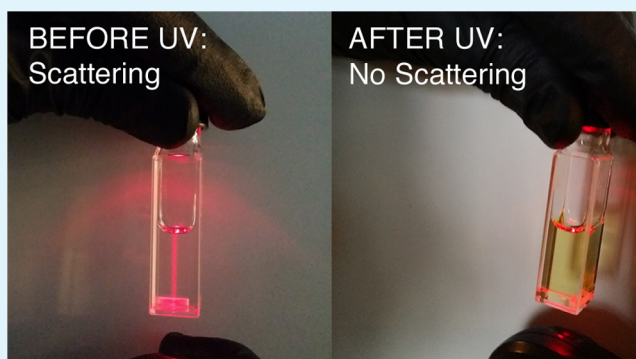
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## S Supporting Information

**ABSTRACT:** Combining the numerous advantages of using light as a stimulus, simple free radical random copolymerization, and the easy, all-aqueous preparation of polyelectrolyte complexes (PECs), we prepared photolabile PEC nanoparticles and demonstrated their rapid degradation under UV light. As a proof of concept demonstration, the dye Nile Red was encapsulated in the PECs and successfully released into the surrounding solution as the polyelectrolyte nanocomplex carriers dissolved upon light irradiation.



**KEYWORDS:** polyelectrolyte complex, nanoparticles, nitrobenzyl, triggered release, photodegradable

## INTRODUCTION

Polyelectrolyte complexes (PECs) and coacervates are association complexes between oppositely charged polyelectrolytes that form spontaneously upon mixing solutions of polyanions and polycations under appropriate aqueous conditions. The ion pairing between the oppositely charged polymers, resulting in the release of counterions, together with van der Waals and hydrophobic interactions, provide the driving force for assembly. The formation of PECs can be highly sensitive to parameters such as polymer structure, charge density along polymer chains, polyelectrolyte concentration, mixing ratio between polycations and polyanions, mixing order, salt type, and ionic strength.<sup>1–5</sup> The association complexes formed by mixing oppositely charged polyelectrolyte solutions may be precipitates (solid–liquid macrophase separation), coacervates (liquid–liquid phase separation), or colloidal nanoparticles. PECs have been used as carriers to deliver drugs,<sup>6,7</sup> enzymes,<sup>8</sup> proteins,<sup>9</sup> and DNA,<sup>10,11</sup> and used in other applications such as solar cells,<sup>12</sup> chemical sensors,<sup>13</sup> and membranes.<sup>14,15</sup>

Responsive materials that degrade on demand upon exposure to applied stimuli have received tremendous interest. Much of the designed responsive characteristics of polymers results from their self-assembly into supramolecular assemblies or their covalent functionalization, resulting in response to stimuli including temperature,<sup>16,17</sup> magnetic field,<sup>18,19</sup> redox,<sup>20</sup> pH,<sup>21</sup> enzymes,<sup>22,23</sup> and light.<sup>16,24,25</sup> Light has unique characteristics because it allows control over the location, timing, and dosage of delivery of cargo.<sup>24,26,27</sup> Light-responsive functional materials

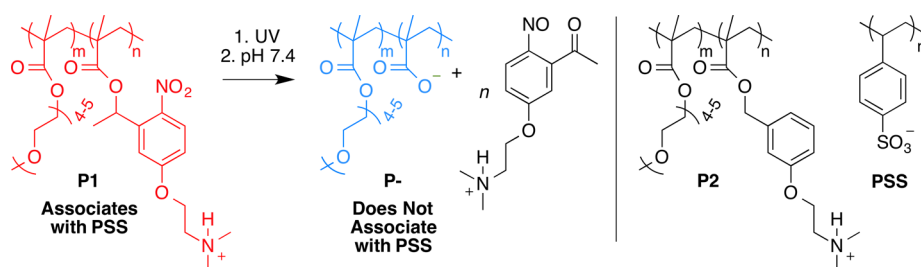
therefore find wide application in drug delivery,<sup>24</sup> tissue engineering,<sup>28,29</sup> and memory devices.<sup>30</sup> Our group has been interested in light responsive materials comprising polyelectrolyte multilayers (PEMs),<sup>27,31</sup> functional conjugated materials,<sup>32</sup> and gels.<sup>33,34</sup> The photoresponsive PEMs we recently reported comprise polycations with photocleavable benzylic ester pendants that yield carboxylic acid groups upon irradiation with light.<sup>27,31</sup> This charge-generating characteristic renders PEMs soluble in part due to the disruption of ion pairing between polyelectrolytes.

The potential for preparing photoresponsive polycations with nitrobenzyl ester groups linking cationic side chains with the polymer backbone offers the possibility to “charge-shift” polycations to oppositely charged polyanions using light. Sullivan, Epps, and co-workers<sup>11</sup> have reported using a charge-shifting cationic diblock copolymer prepared via atom transfer radical polymerization (ATRP) to bind negatively charged DNA for photoinduced nucleic acid delivery. In this paper, we prepared a charge-shifting polycation (**P1**) via free radical random copolymerization of photolabile, positively charged monomers with the hydrophilic neutral monomer oligo(ethylene glycol) methacrylate. Dilute, nonstoichiometric aqueous mixtures of cationic **P1** and anionic poly(styrene sulfonate) (PSS) yield suspensions of nanoparticles with diameters of 50–100 nm. Upon irradiation, photolysis of the

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**Figure 1.** Left: Photoinduced charge-shifting of positively charged **P1** to negatively charged **P-**. Right: Chemical structures of control polycation **P2** and polyanion **PSS**.

nitrobenzyl groups changes the **P1** into polyanion **P-** (Figure 1). The resulting lack of ion pairing complementarity between **P-** with **PSS** causes the nanoparticles to dissolve, and the triggered release of the encapsulated guest Nile Red.

## EXPERIMENTAL SECTION

**General Considerations.** All synthetic manipulations were performed under standard air-free conditions with an atmosphere of argon gas with magnetic stirring. Flash chromatography was performed using silica gel (230–400 mesh) as the stationary phase. NMR spectra were acquired on a Bruker Avance III 500 spectrometer. Chemical shifts are reported relative to residual protonated solvent. Polymer molecular weights were determined using a Shimadzu gel permeation chromatography (GPC) system equipped with a Tosoh TSKgel GMHhr-M mixed-bed column and guard column using the UV detector. The column was calibrated with low polydispersity poly(styrene) standards (Tosoh, PS Quick Kit) with 2% triethylamine in THF as the mobile phase eluting at 0.75 mL/min. Methacryloyl chloride was freshly distilled and used immediately. All other reactants and solvents were purchased from commercial suppliers and used without further purification. Dry THF and dry  $\text{CH}_2\text{Cl}_2$  were obtained from an Innovative Technologies PureSolv 400 solvent purifier.

All solution optical spectra were acquired of samples in quartz cuvettes (NSG Precision Cells). Electronic absorbance spectra were acquired with a Varian Cary-100 instrument in double beam mode using a solvent-containing cuvette for background subtraction spectra of solution samples. Fluorescence emission spectra were obtained by using a PTI Quantum Master 4 equipped with a 75 W Xe lamp. Fluorescence spectra were corrected for both the output of the lamp and for the response of the photomultiplier tube detector to different wavelengths. Solutions used in the fabrication, processing and response of PECs were all aqueous solutions unless otherwise mentioned. Dynamic light scattering (DLS) and zeta potential results were collected using a Malvern Zetasizer Nano-ZS. AFM and SEM images were obtained using a Veeco D3100S-1 and a Phenom G2 Pure Table Top SEM (operating at 5 kV), respectively.

Detailed synthetic procedures can be found in the Supporting Information.

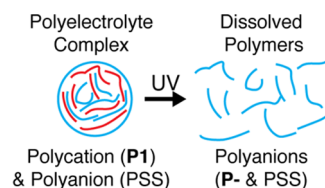
**Preparation of PEC Solutions.** Buffered solutions (30 mM pH 7.4 phosphate buffer) with various concentrations (0.34 or 1.02 mM, based on charged repeat unit) of **P1** and **PSS** were prepared. A PEC solution was prepared by rapidly mixing solutions of **P1** and **PSS** while stirring vigorously. The solution was stirred for ~1 min after mixing. All PEC solutions prepared were filtered through a 0.45 nm hydrophilic PTFE filter (A ChemTek Inc.) prior to dynamic light scattering (DLS) measurements, unless otherwise mentioned.

**Preparation of a Nile Red (NR)-Loaded PEC Solution.** To prepare a NR loaded colloid solution, we added 5.0  $\mu\text{L}$  of acetone solution of NR (0.01%, w/v) into 2.0 mL of **P1** or **P2** solution (0.20 mg/mL) in pH 7.4 30 mM phosphate buffer). The polycationic solution was then quickly added into 2.0 mL **PSS** solution (0.21 mg/mL, pH 7.4, 30 mM phosphate buffer). A fluorescence spectrum of the NR loaded PEC solution was collected, then 2.0 mL of the solution was irradiated with 365 nm UV light and the other 2.0 mL of solution was kept in the dark.

**Irradiation Experiments.** In each irradiation experiment, 2.0 mL of photolabile PEC solution was prepared and filtered as described above. 1.0 mL of the sample was transferred into a cuvette (light path = 10 mm), and subjected to measurement of size by DLS, after which the solution was kept in the dark. The other 1.0 mL was placed under 365 nm UV light for a certain time and also subjected to measurement of size by DLS.

## RESULTS AND DISCUSSION

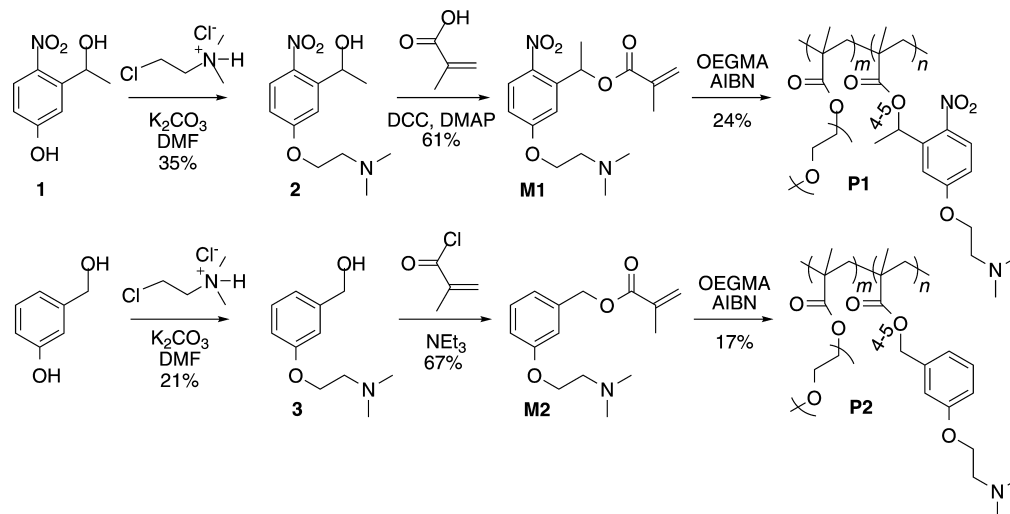
We designed photodegradable polycation **P1** with the cationic to anionic charge-shifting characteristic shown schematically in Figure 1. This methacrylic polycation contains both hydrophilic oligo(ethylene glycol) and tertiary amine side chains linked to the polymer backbone through  $\alpha$ -methylated *ortho*-nitrobenzyl (ONB) ester linkers. Photolysis of the ONB esters cleaves the benzylic C–O bonds through a radical mechanism, separating the amine groups from the polymer and leaving behind carboxylic acid pendants bound to the polymer backbone. At near-neutral pH values, therefore, photolysis events convert pendants of **P1** from having positive formal charges to negative formal charges. As ion pairing of cations and anions is largely responsible for the association of oppositely charged polyelectrolytes in aqueous media, we hypothesized that such a chemical change would disrupt these interchain interactions and cause such polyelectrolyte complexes to dissolve (Figure 2). We also designed control polymer **P2**, which has a structure similar to **P1**, but does not contain nitro groups, and therefore is not photolabile.



**Figure 2.** Schematic of the light-triggered disruption of nanoscale PECs.

Our syntheses of charge-shifting polycation **P1** and photo-inert control polymer **P2** were straightforward (Scheme 1). Low yields of monomer **M2** resulted from its rapid self-polymerization upon synthesis. Free-radical random copolymerization, using AIBN as initiator, of either **M1** or **M2** with 1 mol equiv of commercially available oligo(ethylene glycol) methacrylate ( $M_w \approx 300$  g/mol, OEGMA) gave **P1** ( $M_n = 5.1$  kDa,  $M_w = 7.0$  kDa, GPC) or **P2** ( $M_n = 3.5$  kDa,  $M_w = 4.7$  kDa, GPC) respectively. The molar ratio of incorporation of OEGMA units and **M1** units in **P1** was 45:55 as determined by  $^1\text{H}$  NMR spectroscopy. We chose OEGMA as a comonomer in **P1** and **P2** because: (i) it is neutral and will not interfere with

Scheme 1. Synthesis of Photoreactive Polymer P1 and Photoinert Control Polymer P2



the ionic interactions, (ii) polyethylene glycol is a widely used nontoxic material to stabilize nanoparticles<sup>35</sup> and (iii) it renders P1 soluble in water—the homopolymer of M1 had limited water solubility even after protonation.

We then explored conditions for the fabrication of nanoscale colloidal polyelectrolyte complexes by mixing aqueous solutions of P1 with aqueous solutions of the strong polyanion PSS. In particular, we investigated the influence of the ratio of oppositely charged repeating units (P1/PSS) on the PECs obtained. Results from dynamic light scattering (DLS) of the resultant suspensions (Table 1) show that nanoparticles with

**Table 1.** Influence of P1/PSS Mixing Ratios on the Size Distributions of Prepared PECs<sup>a</sup>

[PSS] (mg/mL)	[P1] (mg/mL)	P1:PSS <sup>b</sup>	diameter <sup>c</sup> (nm)	PDI	zeta potential (mV)
0.070	0.20	1	7700 ± 2200 <sup>d</sup>	0.40	0 ± 5
0.070	0.60	3	52 ± 1	0.18	+ 13 ± 1
0.21	0.20	0.33	87 ± 2	0.16	- 31 ± 3

<sup>a</sup>All measurements are the average results of three independent experiments. <sup>b</sup>Molar ratio of charged units. <sup>c</sup>Z-average diameter. <sup>d</sup>PEC solutions with stoichiometric polycation/PSS ratios were not filtered before measurements because the light scattering intensity were too low after filtration.

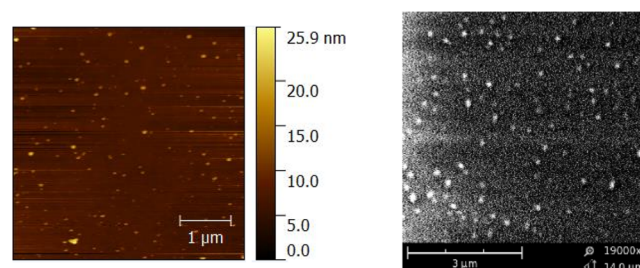
relatively narrow size distributions (PDI < 0.2, with Z-average diameters between 50 and 100 nm) were obtained by using nonstoichiometric ratios of either the cationic or anionic functional groups. When [PSS] = [P1], however, macroscale aggregates formed, even though the overall concentration of polymer was lower under these mixing conditions.

This observation, in addition to the sign of zeta potential corresponds to the sign of the excess polyelectrolyte component, is consistent with known behavior of such complexes:<sup>1,3,36</sup> nonstoichiometric mixing ratios of polycations and polyanions yield complexes that consist of a charge neutral core and a shell enriched in the excess polymer, stabilizing the colloid via electrostatic repulsion between particles. These nonstoichiometric PECs are also stable over our observation time of 3 days and upon dilution with DI water or buffer solution of the same concentration (Table 2). AFM and SEM images (Figure 3), as well as visual observation of the Tyndall

effect (see TOC graphic) are also consistent with nanoparticle formation.

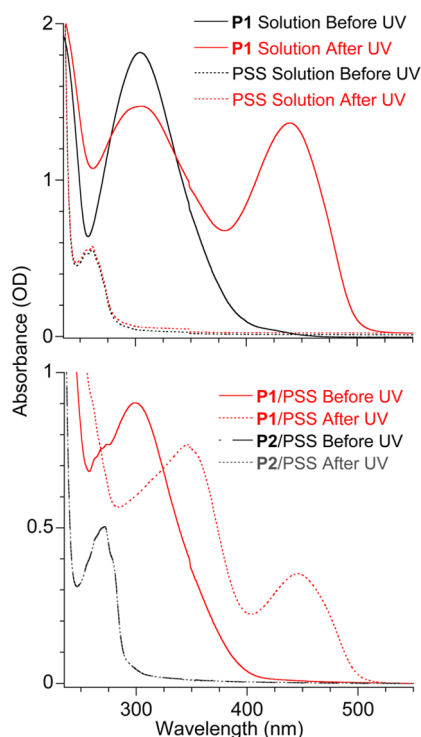
**Table 2.** Sizes and Zeta Potentials of PECs upon Dilution by 50% (v/v)

		1:3 P1:PSS		3:1 P1:PSS	
		before dilution	after dilution	before dilution	after dilution
diluted by water	<i>d</i> (nm)	89	85	50	51
	PDI	0.15	0.16	0.16	0.17
	$\zeta$ (mV)	-27	-29	+14	+14
diluted by 30 mM pH 7.4 buffer	<i>d</i> (nm)	88	86	53	53
	PDI	0.16	0.15	0.18	0.15
	$\zeta$ (mV)	-33	-30	+14	+11



**Figure 3.** AFM and SEM images of the polyelectrolyte nanocomplexes (PSS:P1 = 3:1, by charged repeating units). Sample preparation: one drop of PEC solution was applied onto a plasma cleaned watch glass using a pipet, and the bulk of the droplet was wicked away using a paper towel. The sample was gently rinsed with 1–2 drops of deionized water to rinse away salt from the buffered solution, then dried using a mild flow of clean compressed air before AFM or SEM measurements.

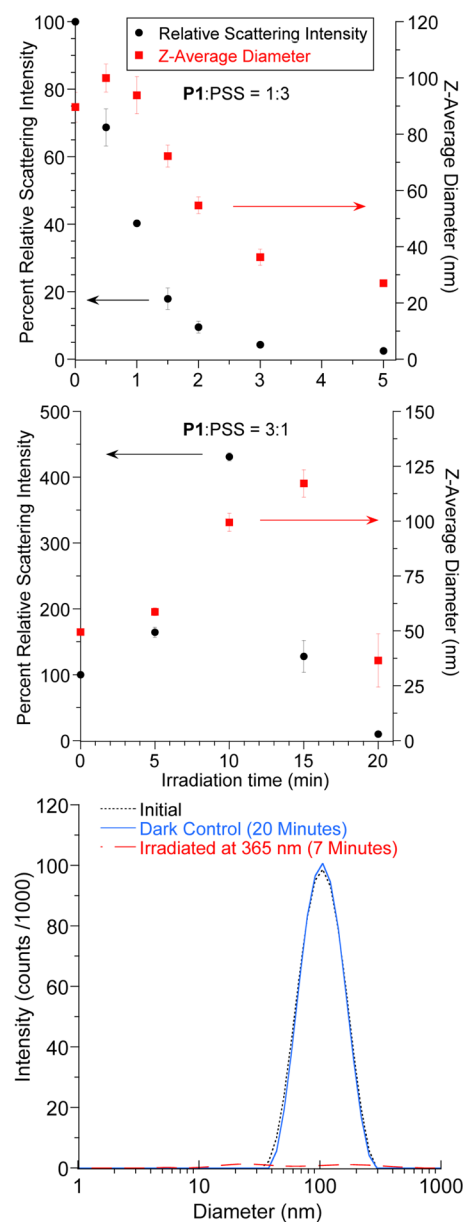
UV/vis spectrophotometry of P1 in solution and its complexes with PSS provided evidence for photolysis of the nitrobenzyl groups upon irradiation with UV light. After UV irradiation at 365 nm (20 mW/cm<sup>2</sup>), the characteristic absorption peak of the nitrobenzyl groups in P1 at 310 nm (Figure 4, top) decreased by ~20%, while a new peak at approximately 450 nm emerged, which we attribute to the expected arylnitroso ketone and other secondary photo-



**Figure 4.** UV spectral change of the unimixed polyelectrolytes (*top*) and PECs prepared from a 1:3 P1:PSS ratio (*bottom*) after irradiation (365 nm, 20 mW/cm<sup>2</sup>) for 15 min in 30 mM pH 7.4 phosphate buffer.

products. PSS showed no significant change in UV/vis spectra after irradiation under identical conditions. Similar spectral changes (Figure 4, bottom) occurred upon irradiation of a sample of P1/PSS PEC with molar ratio of 1:3, with a stationary state reached after approximately 15 min of irradiation (Figure S1), suggesting the complete photolysis of nitrobenzyl groups from P1. In a control experiment, an analogous photoinert PEC solution prepared with photoinert polycation P2 and PSS was irradiated under the same condition. The photoinert PEC solution showed negligible spectral change upon irradiation.

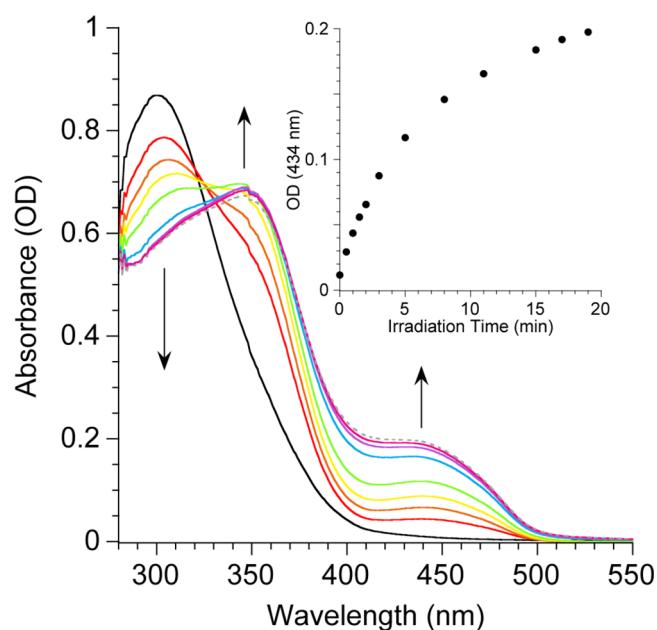
DLS measurements of the nanoscale PECs before and after UV irradiation demonstrated that photolysis of the nitrobenzyl groups did indeed yield PEC dissolution. Figure 5 shows that after 5 min of irradiation at 365 nm (20 mW/cm<sup>2</sup>), the light scattering intensity of the 1:3 P1/PSS complex suspension decreased by more than a factor of 50, together with a decrease in the Z-average particle size. UV/vis absorbance spectra acquired during these irradiation experiments (an example is shown in Figure 6) suggest that approximately 50% conversion of the ONB esters occurs after 5 min of irradiation. Although the complexes prepared using a 3:1 molar ratio of P1:PSS largely dissolved after 20 min of UV irradiation, the light scattering intensity and nanoparticle size of this sample both increased during the first 10–15 min of photolysis. We preliminarily attribute this observation to initial increased complexation between the photolysis products P- and the excess cationic P1 in solution during early stages of photolysis. As the degree of photolysis of P1 increases, however, fewer cationic groups on P1 are available for ion pairing interaction, leading to complex dissolution. Consequently, the light scattering intensity and Z-average size of nanocomplexes observed using DLS decreased. AFM and SEM images of the



**Figure 5.** Dependence of scattering intensity and Z-average particle diameter, as measured by DLS, for P1/PSS polyelectrolyte complexes prepared with 1:3 (*top*) and 3:1 (*middle*) molar ratios upon irradiation at 365 nm (20 mW/cm<sup>2</sup>). Error bars represent one standard deviation of three independent trials. Bottom: Dynamic light scattering data of a 1:3 P1/PSS complex sample before and after irradiation at 365 nm (20 mW/cm<sup>2</sup>) for 7 min.

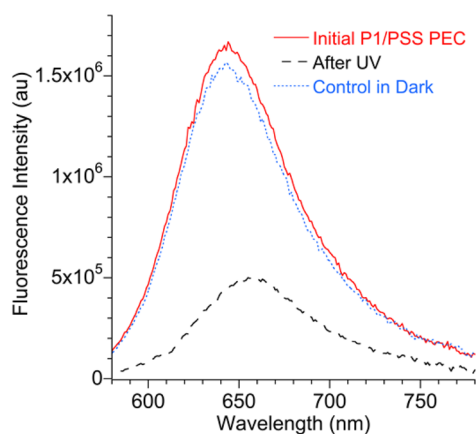
irradiated samples also confirmed the dissolution of the PECs, as no particles were observed of samples that had been irradiated.

In control experiments, the sizes and scattering intensities of P1/PSS nanoparticles prepared with either 1:3 and 3:1 molar ratios kept in the dark for 20 min decreased by less than 1%. Moreover, exposure of analogous PECs comprising P2/PSS in either a 1:3 or 3:1 molar ratio to identical irradiation conditions with UV light induced less than 10% change of the scattering intensities or sizes to the photoinert PECs comprising P2/PSS as determined by DLS (Table S1), and caused no significant change in UV/vis spectra of the sample (Figure S4).



**Figure 6.** Dependence of UV/vis spectra of a suspension of 1:3 P1/PSS nanoparticles on irradiation time. These spectra were acquired as part of the irradiation experiment described in Figure 5.

To demonstrate that these photolabile complexes were capable of releasing encapsulated cargo, we used Nile Red (NR), a hydrophobic fluorescent molecule with a lower quantum yield of fluorescence in water than in less polar environments, as a guest molecule. The fluorescence of a suspension containing P1/PSS (1:3) PECs loaded with NR was monitored before and after UV irradiation. UV irradiation of these PECs for 5 min at 365 nm ( $20 \text{ mW/cm}^2$ ) caused the fluorescence intensity from NR to decrease (Figure 7), which is



**Figure 7.** Phototriggered dissolution of photolabile PECs of P1/PSS (1:3) resulted in the release of cargo molecule (NR) after 5 min of irradiation at 365 nm ( $20 \text{ mW/cm}^2$ ). Figure S3 shows an analogous experiment in which irradiation of photoinert PEC comprising P2/PSS (1:3) did not trigger the release of loaded NR.

indicative of the release of NR into aqueous solution.<sup>26,37</sup> To control for UV-induced photobleaching of NR as an alternative explanation for this result, we irradiated a control PEC sample comprising NR encapsulated within P2/PSS (1:3) nanoparticles. UV irradiation under identical conditions did not

change the fluorescence spectrum or intensity from NR in this sample (Figure S3).

## CONCLUSION

This work demonstrates that nanoscale polyelectrolyte complexes have potential as phototriggered delivery vehicles. The advantages of this approach are (i) the simple preparation procedures, both in terms of polymer synthesis and polymer self-assembly, of these photosensitive PECs, (ii) the stability of these nanomaterials over time, and (iii) rapid degradation and release upon irradiation. One disadvantage of this approach is the need for UV light to induce PEC decomposition, as opposed to more biologically compatible visible or near-infrared light. Current efforts in our laboratory include material design for increasing the wavelengths of light that can disrupt these complexes.

## ASSOCIATED CONTENT

### Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acsami.6b07366.

Additional figures showing results of control experiments, detailed synthetic procedures, and NMR spectra (PDF)

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### Notes

The authors declare no competing financial interest.

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