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Poly(butyl cyanoacrylate) Nanoparticle Containing an Organic PhotoCORM

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Abstract:

Carbon monoxide (CO) is a gasotransmitter, which has shown therapeutic effects in recent studies. Photo carbon monoxide releasing molecules (PhotoCORMs) allow the delivery of CO to be controlled by light. In this work, a new organic photoCORM DK4 is studied. DK4 is a diketone type photoCORM, which releases two CO molecules under visible light and simultaneously generates a fluorescent anthracene derivative. However, this type of CORM suffers from a deactivating hydration reaction and often needs to be incorporated in polymers or micelles. The two highly hydrophobic tert-butyl groups of DK4 protect it from the hydration reaction. DK4 functions in 1% DMSO aqueous solution, in which other DKs are deactivated. DK4 was incorporated in a poly(butyl cyanoacrylate) (PBCA) nanoparticle. PBCA has been used as a tissue adhesive and has been extensivly studied for brain delivery of drugs. The PBCA/DK4 nanoparticle showed good photoactivity and low cytotoxicity, and thus is a promising material for studying the biomedical effects of CO.

Key Words: carbon monoxide releasing molecule; PhotoCORM; poly(butyl cyanoacrylate); nanoparticle

1. Introduction

Carbon monoxide (CO) is a gasotransmitter produced naturally during heme catabolism. The production of CO plays a vital role in many physiological functions in the mammalian body, such as anti-inflammatory, anti-apoptotic, anti-coagulative, anti-hypertensive, and cell protective effects.[1] However, it is well known that CO is toxic at high concentrations. The high affinity of CO for hemoglobin reduces the availability of O_2 in tissues causing death by asphyxiation. Previous work suggests that low concentrations of CO are not acutely toxic to humans.[1] When the cellular concentrations are considered, the rate and amount of CO production by Heme Oxygenase 1 within the body is in nanomolar levels.[2] However, in the past decade, inhaled, small-quantities of supplemental CO gas has been demonstrated in pre-clinical disease models to have therapeutic effects including reducing inflammatory and cardiovascular disorders.[3]

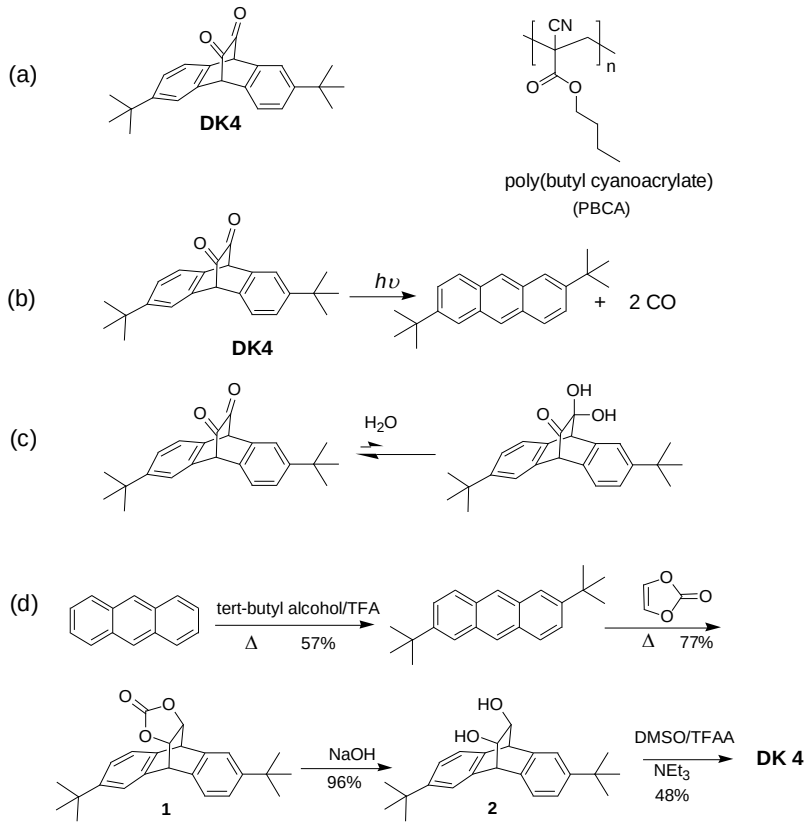
The recent synthesis of CO-releasing molecules (CORMs), a group of compounds capable of releasing controlled quantities of CO in cellular systems, provides a promising delivery approach to reduce the safety concerns of systemic, inhaled CO gas. The potential to control the release of CO to a specific target is the major advantage of CORMs over gaseous CO as a therapeutic agent. The majority of CORMs studied contain transition metals including both essential trace elements (manganese, iron, cobalt) and non-physiological metals (ruthenium, tungsten, rhenium).[1,4] Some nonmetallic CORMs have also been developed in recent years.[5-11] CO release from these CORMs were triggered by protonation, thermal release, ligand exchange, ligand substitution, enzymatic reaction and light.[1,5] In recent years, CORMs have also been incorporated into organic and inorganic nanoparticles to improve biocompatibility, control of CO release, and response to magnetic field and near infrared light.[12-17] In this work, we incorporated a new organic photoCORM into a nanoparticle of poly(butyl cyanoacrylate) (PBCA), which is used as tissue adhesive and has been studied for delivery of drugs to treat neural disorders such Alzheimer disease.[18-20] The biocompatibility of the photoCORM loaded nanoparticles were also tested.

2. Results and Discussion

Previously, our group has reported a type of photoCORM with cyclic diketone (DK) structures.[9] The DK photoCORMs can efficiently release two molecules of CO under visible light and simultaneously generate a fluorescent anthracene, which allows the CO release to be monitored

by fluorescence spectroscopy and UV-vis spectroscopy. The clean photoreaction yields well-defined products and both the previously reported DKs and the anthracene photoproducts showed low cytotoxicity. However, the DK PhotoCORMs are hydrated in aqueous conditions, which diminishes its photoactivity. The hydration is a reversible reaction so it does not decompose the DK. If the equilibrium favors the hydrated form, which is not photosensitive, the rate of the photoreaction is significantly reduced since the hydrated form must change to the dehydrated form to react. Therefore DKs need to be incorporated in micelles [9] or polymers [21] to avoid hydration for biological uses. In fact, previous work showed that photo-induced CO release increased with the hydrophobicity of the DK.

In this work, we studied a DK molecule with two highly hydrophobic tert-butyl groups (DK4 in Scheme 1). Although this molecule has been reported before, [22] it has never been studied as a CORM. In addition, we used a different synthetic route, which led to the DK4 with good yield. As shown in Scheme 1, di-t-butyl anthracene was prepared from anthracene and t-butyl alcohol following a literature procedure. [23] Then it was heated with vinylene carbonate in xylene to form the Diels Alder adduct **1**. Compound **1** was then hydrolyzed by NaOH to yield the dihydroxy intermediate **2**. DK4 was synthesized from **2** using Swern oxidation.



Scheme 1. (a) Structures of DK4 and PBCA, (b) photoreaction of DK4, (c) the potential hydration reaction, and (d) synthesis of DK4.

DK4 is not soluble in water, but is well dissolved in dimethyl sulfoxide (DMSO) and other common organic solvents such as tetrahydrofuran (THF). The UV-vis spectrum of DK4 in DMSO is shown in Figure 1. It is similar to other DKs reported before. [9] The n-π transition band of the diketone appears between 400 and 550 nm with the maximum absorption at 465 nm. Upon irradiation by a 470 nm LED for 5 min, the absorption of the n-π transition diminished to zero, indicating a quantitative reaction. A typical absorption band of anthracene derivatives with three peaks between 300 nm and 400 nm appeared. Among the three peaks the middle peak at 358 nm was the highest and the peak at 379 nm was the second highest. The spectrum is identical to that of di-tert-butyl anthracene, which is the expected photoproduct. (Figure 1) Previous studies on DKs have shown that the formation of the anthracene derivatives is accompanied by the release of CO. [9,24] (Scheme 1) Therefore, CO release can be conveniently monitored by the formation of the anthracene.

As described above, hydration is a problem for using DKs as PhotoCORMs. Previous work showed that when DKs were dissolved in 1% DMSO in water, the n-π transition band of the diketone disappeared and the DKs became inactive under irradiation. [9] To test whether DK4 can be protected from hydration due to the hydrophobic t-butyl groups, a solution of DK4 in 1% DMSO in water was prepared. The UV-Vis spectrum of the solution is shown in Figure 1. Unlike other DKs, the n-π transition band in the visible range can still be observed. Upon irradiation, the band disappeared and the absorption bands of the anthracene product showed in the spectrum. However, the position of the two peaks red-shifted to 366 and 387 nm. The shape of the absorption band was also different from that of the DMSO solution (Figure 1). The peak at 387 nm was higher than that at the 366 nm. We attribute this change to the formation of aggregation or even small particles due to the low solubility of the photoproduct (di-t-butyl anthracene) in water. In fact, the baseline was high, especially at the lower wavelengths, which is commonly observed when there are small particles in the solution. To confirm this, DMSO was added to the irradiated solution until the DMSO/water ratio was 3:1. The position of the two peaks shifted back to 357 nm and 378 nm, and the former was higher than the latter as in the spectrum of the DMSO solution (Figure 1b). In addition, the release of CO was confirmed by a direct measurement using a CO meter (Experimental section). The results showed that the hydration of DK4 is much lessened comparing to previously developed DKs and it is photoactive in 1% DMSO in water.

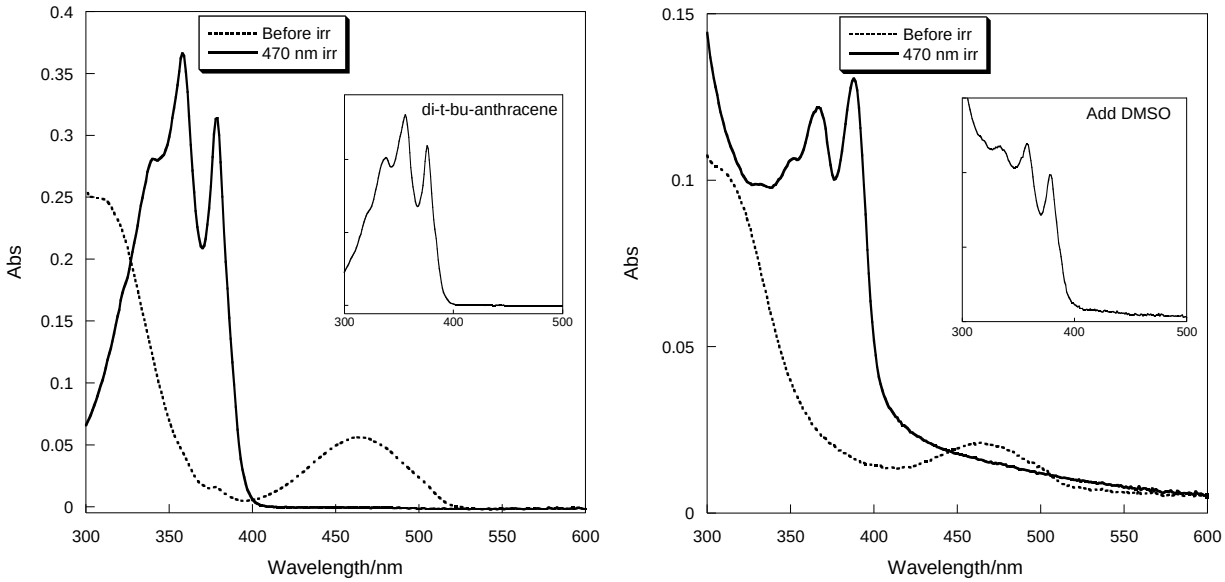


Figure 1. UV-Vis spectra of DK4 in DMSO (9×10^{-5} M) before and after irradiation [left, inserted figure: spectrum of di-t-butyl anthracene (the expected photoproduct)], and in 1% DMSO aqueous solution (4×10^{-5} M) before and after irradiation [right, inserted figure: spectra of the irradiated solution after addition of DMSO].

Next, we incorporated DK4 in PBCA nanoparticles. As described above, incorporating CORMs in nanoparticles can improve their biocompatibility and achieve better control of CO delivery. PCBA is a well-known biocompatible polymer. It has previously been used to deliver drugs to pass the blood-brain barrier. PBCA nanoparticles are commonly prepared by anionic emulsion polymerization.[19,20] It combines the polymerization, nanoparticle formation and drug incorporation in one step. However, much work needs to be done for optimizing the conditions and achieving good reproducibility. We synthesized PBCA using a nonconventional free radical polymerization (Experimental Section). The competing anionic polymerization was quenched by addition of dichloroacetic acid. This method allows us to prepare a relatively large scale of PBCA, which can be used many times for the preparation of the DK4/PBCA nanoparticles. In addition, it is possible to copolymerize common acrylates (not only cyano-acrylates) with BCA, which could be useful for tuning the nanoparticle properties.

The PBCA nanoparticle containing DK4 was prepared by addition of an acetone solution of DK4 and PBCA in a quickly stirred 1% Pluronic F-127 solution in water. The details are given in the Experimental Section. The nanoparticle was characterized by the dynamic light scattering (DSL) method. The average size was measured to be 326 nm. After irradiation, the size was about the same (351 nm). Since a size of around 200 nm or less is preferred for drug delivery,[25] the nanoparticle suspension was filtered through a 2 μm filter. DSL showed that the average size was 214 nm before irradiation and 216 nm after irradiation. (Figure 2) The zeta potential of the nanoparticle was -28.4 mV indicating a moderate stability.

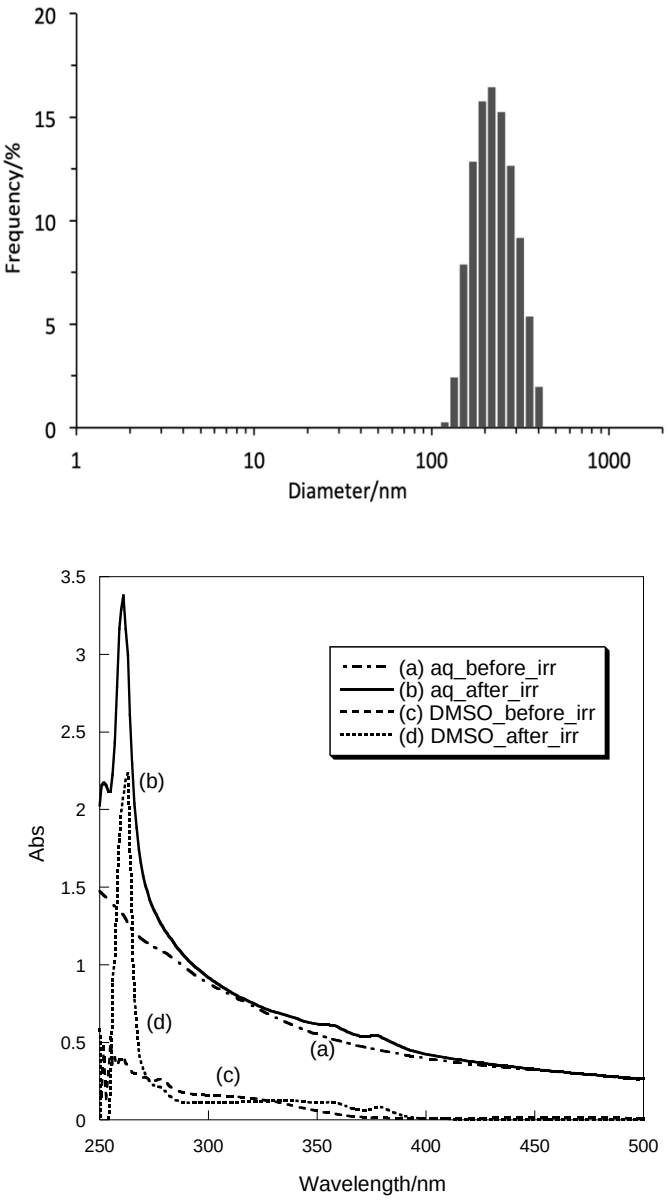


Figure 2. Size distribution of the PBCA/DK4 nanoparticle measured by DSL (up) and UV-Vis spectra of the nanoparticle in water and in DMSO before and after irradiation (down).

A suspension of the nanoparticles was irradiated by 470 nm light and its UV-Vis spectra were studied. A shallow bump appeared between 400 and 550 nm before irradiation. (Figure S1) The baseline was high, especially at the lower wavelengths, due to background light scattering of the nanoparticles. Upon irradiation, the bump disappeared and the anthracene peaks at 261 nm and between 300 to 400 nm appeared as expected (Figure 2). To evaluate the photoreaction

efficiency, a different sample from the same batch of the nanoparticle suspension was dried under nitrogen. Then DMSO with the same volume as that of the sample before drying was added to the residue to prepare a DMSO solution with the same concentration of DK4 as that of the aqueous sample. Since both the polymer and the DK4 are soluble in DMSO, the DMSO solution contained the dissolved polymer and DK4 but not the nanoparticle. The DMSO solution was irradiated and UV showed the anthracene absorption peaks. The peak absorption at 263 nm was 2.23, which was 1.9 units higher than the absorption before irradiation. For comparison, the absorption change of the aqueous suspension of the nanoparticle was 2.0 (Figure 2), which is about same as that of the DMSO solution. The result shows that the photoreaction of DK4 in the nanoparticle was as effective as that of a DK4 solution in DMSO. As described above, the photoreaction of DK4 in DMSO is nearly quantitative. Therefore, the photoreaction of DK4/PBCA nanoparticle is nearly quantitative.

The cell toxicity of DK4 incorporated within PBCA nanoparticles was determined by delivering a single-dose of the DK4/PBCA nanoparticle suspension to endothelial cells (ECs) seeded on tissue culture polystyrene (TCPS). DK4-loaded nanoparticles were tested both for the non-activated and pre-activated conditions. For pre-activated nanoparticles, the CORM was activated and CO released prior to adding the nanoparticles to the cells. This allows evaluation of the potential toxicity after the photoreaction. We prepared 0, 0.5, 5, and 50 μg/mL of DK4 loaded nanoparticles (DK4+NP) in sterile EC complete growth media. Figure 3 shows the DNA analysis results for density of ECs seeded on TCPS treated with varying concentrations of DK4 nanoparticle solutions (6 samples/condition). There was no significant difference in cell density between conditions, even with a dose of nanoparticles up to 50 μg/mL, which indicates negligible toxicity even at this relatively high dose. There is variability in the biocompatibility of different nanoparticle formulations in other studies. For example, some iron oxide nanoparticles formulations have demonstrated toxicity at the levels we tested in this study.[26] Overall, the results indicate good biocompatibility for DK4/PBCA nanoparticles. Live/Dead confocal images of ECs after 11 days of culture with high and low doses further supported this conclusion. (Figure 3) There was almost 100% cell viability, as indicated by the presence of calcein-AM stained live cells but no ethidium homodimer stained dead cells. While the photo-product of DK4 is fluorescent, it does not absorb the 488 nm light that was used to excite the fluorescence of the live/dead stains. Thus, it did not provide background fluorescence.

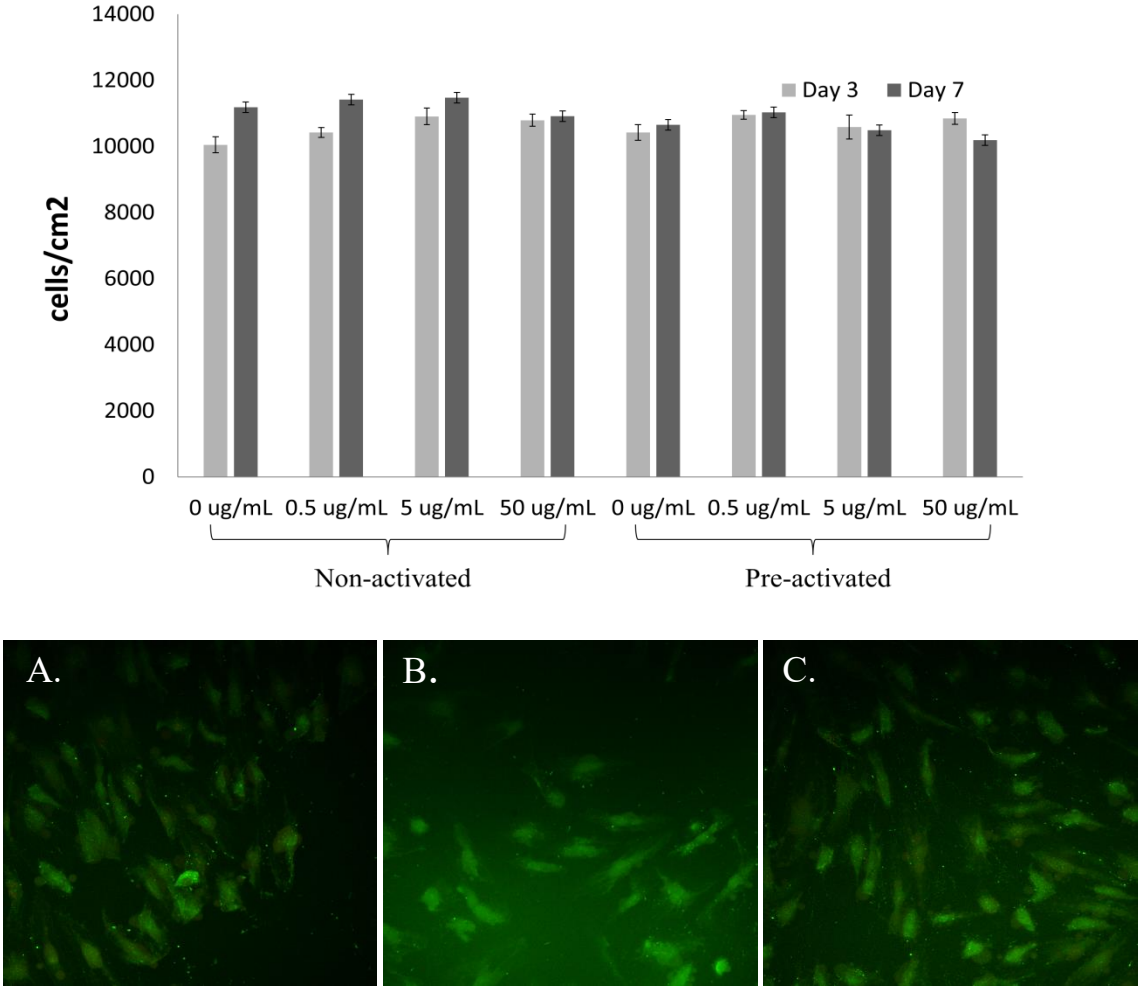


Figure 3. Top: DNA Analysis of Endothelial Cells seeded on TCPS treated with varying concentrations of DK4 Nanoparticle solutions (*n=6*). No significance was determined. **Bottom:** Live/Dead (green / red) confocal images of endothelial cells with varying dose at A) no drug delivery of 0 μg/mL; B) low dose of 0.5 μg/mL, and C) at high concentration of 50 μg/mL for DK4 Nanoparticle solution at Day 11.

3. Conclusion

The results show that DK4 is a promising organic photoCORM. The two hydrophobic t-butyl groups protect it from hydration, and allow it to react in a 1% DMSO/water solution. The well-defined photoreaction and efficient release of two molecules of CO makes DK4 a useful molecule for the study of CO. For example, it may be used to prepare a standard CO solution

with low concentration. DK4 was incorporated into PCBA nanoparticles. The unconventional synthesis of PCBA and PCBA/drug nanoparticles is convenient for preparation of many batches with good consistency. The nanoparticles showed good photoactivity and low cytotoxicity. Given that PBCA has been applied to brain drug delivery, the PBCA/DK4 nanoparticle may be used for studying the effects of CO on brain cells, which will be investigated in the future.

4. Experimental Section

4.1 General Method

Unless otherwise noted, reagents and solvents were commercially available and used as received without any further purification. The starting material di-t-butyl anthracene was prepared following a literature procedure.[23] UV-vis spectra were obtained from a Varian Cary 60 Scan UV-Vis spectrophotometer. NMR spectra were determined in deuterated solvents on a Bruker av400 NMR spectrometer. Chemical shifts were reported in delta (δ) units, parts per million (ppm) downfield from TMS.

4.2 Synthesis of DK4 (Scheme 1)

Synthesis of compound 1. The compound **1** was prepared by a Diels Alder reaction. A solution of di-t-butyl anthracene (1.0 g, 3.5 mmol) and 2 mL of vinylene carbonate in dry xylene (4 mL) was refluxed in autoclave at 180 ^{o}C for 3 days. After that the solvent was removed in vacuo. The crude product was collected by filtration and washed with cold hexane. The final product was a white sold after drying (1.0 g, 77%). 1H NMR (400 MHz, CDCl3, δ ppm): δ = 7.38 (s, 2H), 7.38-7.22 (m, 4H), 4.87 (t, 2H), 4.64 (d, 2H), 1.29 (s, 18H).

Synthesis of compound 2. Compound **1** (1.0 g, 2.6 mmol) was added to a mixture of 1, 4-dioxane (10 mL) and 4 M NaOH (10 mL). The mixture was reflexed under nitrogen for 2 h, then cooled down to room temperature. The solution was then neutralized by 1 M HCl, diluted with water and extracted with dichloromethane (DCM) twice. The combined organic phases were dried by Na_2SO_4. The solvent was removed in vacuo, and the crude product was washed with cold hexane to yield a white sold (0.9 g, 96%). 1H NMR (400 MHz, CDCl3, δ ppm): δ = 7.38 (d, 1H), 7.32 (d, 1H, J=8 Hz), 7.31-7.14 (m, 4H), 4.35 (s, 2H), 4.04 (s, 2H).

Synthesis of DK4. Under nitrogen, trifluoroacetic anhydride (0.62 mL, 4.2 mmol) was added dropwise to a mixture of anhydrous DMSO (0.4 mL, 0.5 mmol) and anhydrous DCM (22

mL) at -78 °C. After stirring for 10 min, a solution of **2** (0.52 mg, 1.5 mmol) in anhydrous DCM/DMSO (2:1; 6 mL) was added to the above mixture over 20 min, and stirred for additional 2 hours at the same temperature. Next, triethylamine (1.4 mL, 10.0 mmol was added dropwise and stirred for 2 hours. Then the mixture was warmed to room temperature and poured into 50 mL of 2 M HCl. DCM was added to the mixture, and the organic phase was separated dried with Na_2SO_4. The solvent was removed by vacuo, the crude product was purified by column chromatography (Hexane: ethyl acetate 5:1) in the dark to yield a yellow solid (0.21g, 48%). 1H NMR (400 MHz, $CDCl_3$, δ ppm): δ = 7.461 (s, 2H), 7.40 (s, 4H), 4,944 (s, 2H), 1.3 (s, 18H) IR: 1735 cm^{-1} (C=O stretch). HRMS (ESI) $M+Na^+$ (369.1798, cal. 369.1831).

4.3 Synthesis of PBCA

To a test tube was added 2 mL of BCA, 20 mg of dichloroacidic acid, and 12 mg of AIBN. The mixture was thoroughly degassed and then heated at 60 ^oC overnight. The resultant polymer was dissolved in small amount of THF. The THF solution was dropped into methanol to precipitate the PBCA as a white solid.

4.4 Synthesis of DK4/PBCA nanoparticles

To synthesize the DK4/PBCA nanoparticles, 5.0 mg of DK4 and 20 mg of PBCA were dissolved in 1.0 mL acetone. The solution was added dropwise using a syringe needle to aqueous solution of pluronic F127 (1.0%, 30.0 ml) stirred at 700 rpm. After addition, the mixture was stirred in a ventilation hood for an hour to evaporate the acetone. The resultant nanoparticle suspension was diluted to 200 mL and stored at in a refrigerator and at 4 ^oC. The procedure was conducted in the dark and the final suspension was protected from light using alumina foil.

4.5 Measurement of CO release from DK4 under irradiation

A solution of DK4 in a mixture of DMSO (5%) and water (0.250 mM, 2.5 mL) was prepared in the dark. The solution in a glass vial was then put in a glass container with a Drager Pac3500 CO detector. The container was sealed and the solution was irradiated by a 470 nm LED light outside the container. The reading of the meter was recorded after 20 min. Calculations from average of three separate experiments shows that 88.0 ± 9% of CO (two for each molecule) was released. The uncertainty is estimated from that of the weight, volume, and CO concentration

measurement. The number of released CO, N_{CO} (mol) was calculated using the following equation [27]:

$$N_{CO} = \frac{pV_g}{RT} + cV_l = p(\frac{V_g}{RT} + \frac{V_l}{k})$$

where p is partial pressure of CO (CO detector readings); $V_{g\ is}$ volume of the gas phase (373 mL); $V_{l\ is}$ liquid phase (2.5 mL); R is 0.08205 $L{\cdot}atm{\cdot}mol^{-1}{\cdot}K^{-1}$); T is Temperature; c is CO concentration in the liquid phase; k is Henry's law constant of CO in water (1052.63 $L{\cdot}atm{\cdot}mol^{-1}$ at 25 °C).

4.6 Cell culture analysis

Primary human umbilical vein endothelial cells (HUVECs) were cultured in standard cell culture conditions (95% air, 5% CO_2, and 37 °C). Culture media was Endothelial Cell Growth Medium MV with ECs growth supplement and 1% penicillin/streptomycin. For nanoparticle biocompatibility, ECs were seeding at a density of 5,000 cells/cm^2 on TCPS and single doses of DK4+NP suspensions were added after 24 hours of seeding to allow for attachment of cells before treating. The biocompatibility of nanoparticles were tested both with (pre-activated) and without (non-activated) activation of the nanoparticles prior adding to the cells. Pre-activation was performed with a 470 nm LED light for 5 min. Regular media changes were performed every 2 days until the end points. The DNA Assay was used to measure cell density at days 3 and 7 following standard procedures. It is a cell-permeant nuclear counterstain that emits blue fluorescence when bound to dsDNA. Significance was determined using one-way ANOVA with Tukey comparison for six samples per condition ($p<0.05$). Cells were also stained with a Live/Dead stain (calcein-AM / ethidium homodimer) and imaged at day 11 with a Nikon D-Eclipse confocal microscope. For calcein-AM, a 488 nm laser and 515 ± 30 nm bandpass filter were used. For ethidium homodimer, a 561 nm laser and 605 ± 75 nm bandpass filter were used.

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Graphic Abstract:

A new organic photoCORM encapsulated in poly(butyl cyanoacrylate) nanoparticle showed nearly quantitative CO release under visible light and low cytotoxicity.