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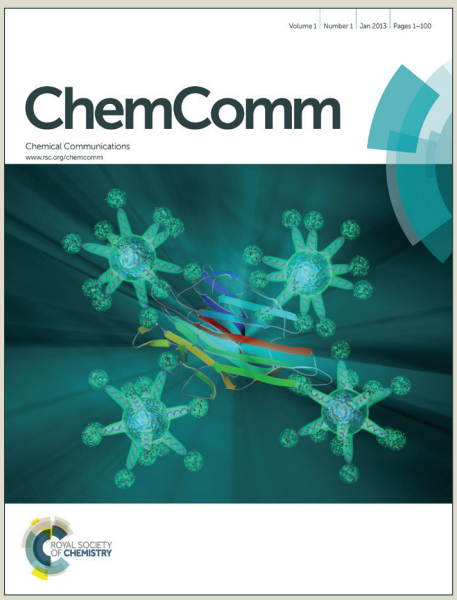

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Photodegradable and Size-Tunable Single-Chain Nanoparticles from a Single Main-Chain Coumarin-Containing Polymer Precursor

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A polyester bearing coumarin moieties in the main chain was used to prepare photodegradable single-chain nanoparticles (SCNPs) of variable sizes. While the intra-chain photodimerization of the chromophore determines the size of SCNPs, the photocleavage occurring under UV irradiation at a different wavelength breaks down the ultra-small nanoparticles.

Functional polymer nanoparticles have attracted much attention because of their potential applications in many areas such as energy, biosensors and high performance materials.[1] However, preparing well-defined polymeric nanoparticles with sizes below 20 nm is still challenging. In recent years, single-chain nanoparticles (SCNPs), being formed by one polymer chain via a unimolecular coil-to-particle transition, have gained increasing interest because their ultra-small sizes (1.5-20 nm) could lead to unique properties potentially useful for drug delivery, nano-reactor and bio-mimic systems.[2-5] For instance, when employed as a drug carrier, such small sizes allow SCNPs to avoid uptake by the reticuloendothelial system and also prevent rapid renal exclusion.[2]

SCNPs are prepared via intramolecular crosslinking[6] or collapse[7] and both covalent and non-covalent associations can be exploited to compress a single coil of polymer chain into a nanoparticle.[8] A number of SCNP preparation methods have been reported based on the use of various chemistries for intra-chain crosslinking, including photochemical reactions,[9] dynamic bonding,[10] polymerizations,[11] Diels−Alder reaction,[12] metal complexation,[13] click chemistry[14] and host–guest interaction.[15] In most cases, pendant reactive moieties were used for intra-chain crosslinking. In addition to developing efficient preparation methods, the ability for effective control of the size of SCNPs is also of major importance for practical applications. Obviously, the size of SCNPs can be varied by changing the molecular weight of the used polymer precursor.[16] A study also showed the size control by adjusting the content of crosslinkable units in a polymer chain, which determines the intra-chain crosslinking density.[17] In other words, the preparation of SCNPs of variable sizes requires the synthesis of various polymer precursors with either different molecular weights or different compositions. Notably, in a recent study of preparing SCNPs through photodimerization of pendant anthracene units,[9b] Frank et al. showed continuous shift of the size exclusion chromatograpy (SEC) peak to longer retention times with increasing UV irradiation time, suggesting that SCNPs of varying sizes can be obtained from a single sample.

Herein we report a facile method that allows photodegradable SCNPs of variable sizes to be obtained from a single polymer precursor containing photocrosslinkable units in the chain backbone. As shown in Fig. 1, the method is based on the use of a polyester precursor bearing coumarin moieties in the main chain structure. We demonstrate that with the polymer dissolved in dilute solution, SCNPs can be obtained by the intra-chain photodimerization of coumarin groups upon >320nm UV light irradiation, and that the size of SCNPs is tunable by varying the dimerization degree of coumarin moieties that is controlled by the UV irradiation time. Moreover, the polymer structure design also allows the photocleavage of coumarin to occur under 254 nm UV irradiation, which results in chain scission.[18] The latter photochemical reaction was utilized to impart the function of photodegradability to SCNPs for the first time.

Our main-chain coumarin-containing copolymer was synthesized by reacting a coumarin diol with adipic acid and polypropylene glycol (PPG, M=425 g/mol) under carbodiimide/DPTS-catalyzed conditions (details in Supplementary Information). The coumarin diol was synthesized using a reported method.[18] The obtained polymer, abbreviated as CAPPG, has M_n=13220 g/mol (about 15 repeating units) and a polydispersity index PDI (M_w/M_n)=1.64 according the SEC measurements using polystyrene (PS) standards. With the polymer structure (Fig.1), the coumarin groups in the main chain can enable both UV light-induced

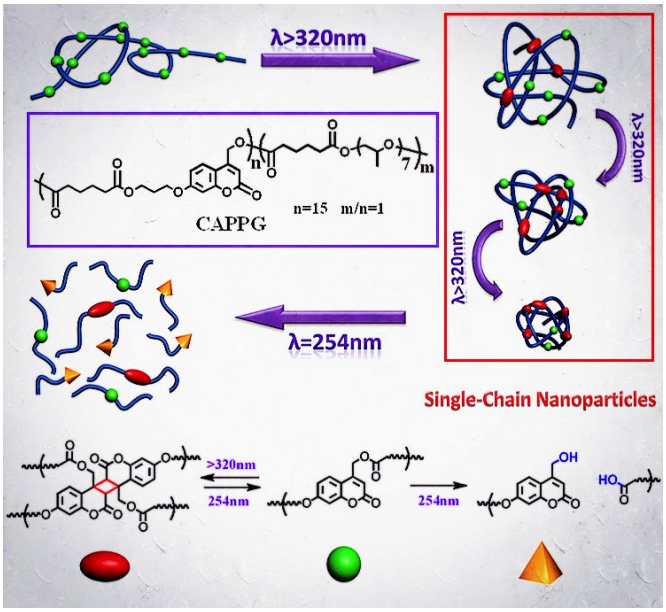

Fig.1 *Schematic illustration for the preparation of variable-size SCNPs using a single polymer precursor based on intra-chain photodimerization of coumarin moieties and the photodegradable feature of the SCNPs.*

chain cross-linking (>320 nm) and chain scission (254 nm) via photodimerization and photocleavage of the chromophore, respectively.[18,19] Since a homopolymer prepared through condensation of the same coumarin diol and adipic acid was shown to biodegradable and biocompatible,[18] CAPPG should behave the same way considering that it is basically derivative of that polymer with the addition of the biocompatible PPG.[20]

SCNPs of CAPPG were obtained by the intra-chain photodimerization of coumarin groups, with a dilute polymer solution (0.2 mg/mL, in $CHCl_3$) exposed to >320 nm UV light (900 mW/cm^2). The occurrence of the photodimerization was observable from the decreasing absorbance of the coumarin groups around 322 nm (Fig.2a); the increase over irradiation time in the dimerization degree (DD) of coumarin was monitored by UV-vis absorption spectra and calculated according to $DD=1-A_t/A_0$, with A_0 and At being the initial absorbance and the absorbance after irradiation time t at 322 nm, respectively. The result (inset of Fig.2a) shows that in the dilute CAPPG solution and under the used conditions, the photodimerization of most coumarin groups occurs within the first 60 min UV irradiation and prolonged times up to 120 min further raised the dimerization degree slightly, reaching an apparent maximum level of 87%. The simple control over the photodimerization degree by changing the UV irradiation time offers the possibility to optically tune the intra-chain crosslinking density and, consequently, the size of SCNPs. The nanoparticles formed by single polymer chain of CAPPG were first proved by means of SEC that is sensitive to changing hydrodynamic volume associated with the single chain coil-to-particle transition. As seen in Fig. 2b, as compared with the CAPPG precursor without UV irradiation, the elution band of the polymer shifts continuously to longer elution times with increasing the >320 nm UV irradiation time, indicating a continuously increased intra-chain crosslinking density and, consequently, reduced hydrodynamic volume. The absence of peaks at shorter retention times implies that only photoinduced intra-chain crosslinking takes place (SEC traces of full retention time scale in Fig.S2). Figs. 2c and 2d show images of SCNPs (120 min UV irradiation) recorded by atomic force microscopy (AFM) and transmission electron microscopy (TEM), respectively. Well-separated nanoparticles, below 10 nm in diameter, were observable by casting a very dilute polymer solution (0.02 mg/mL).

On the other hand, photodegradability of SCNPs is an interesting feature that may find applications in light-controlled delivery.[21] Also shown in Fig.2b is the SEC trace of the SCNPs with the highest crosslinking density (DD=87%) that was subsequently exposed to 254 nm UV light for 3h. It is visible that the SCNPs are degraded into smaller fragments giving rise to a broad elution band at longer elution times corresponding to lower molecular weight species (apparent M_n decreases from13220 g/mol for the precursor to 1385 g/mol) after 254 nm UV irradiation. Photocleavage of the coumarin-4-yl methyl esters should be at the origin of the photodegradation of SCNPs because it results in chain scission.[22] The possible photocleavage of the cyclobutane functionality in the dimer can only diminish the intra-chain crosslinking density.

We further investigated the relationship between the photodimerization degree of coumarin and the size of SCNPs in

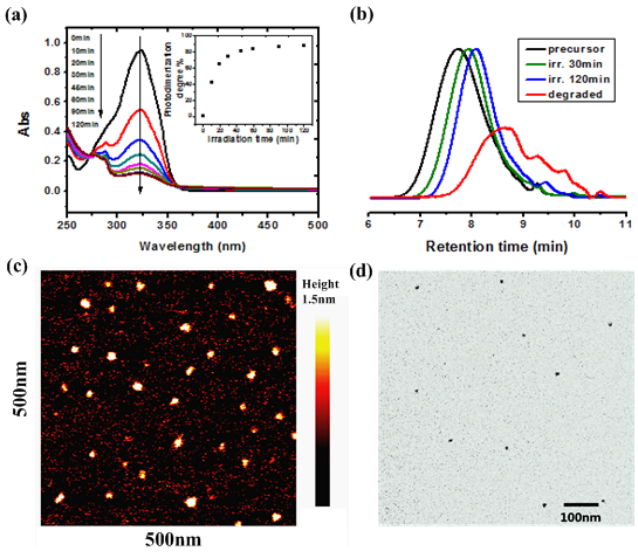

Fig.2 *(a) Absorption spectra of CAPPG in $CHCl_3$ (0.2 mg/mL) recorded after different times of >320 nm UV irradiation showing the intra-chain photodimerization (crosslinking). Inset is the plot of photodimerization degree of coumarin vs. UV irradiation time. (b) SEC traces of the CAPPG precursor, SCNPs of varying photocrosslinking density obtained by exposing the same dilute CAPPG solution (0.2 mg/mL) to >320 nm UV light for different times, and SCNPs of the highest crosslinking density after subsequent 254 nm UV irradiation for 3h. (c) AFM and (d) TEM image of the SCNPs with the highest crosslinking density, cast from a dilute polymer solution in $CHCl_3$ (0.02 mg/mL).*

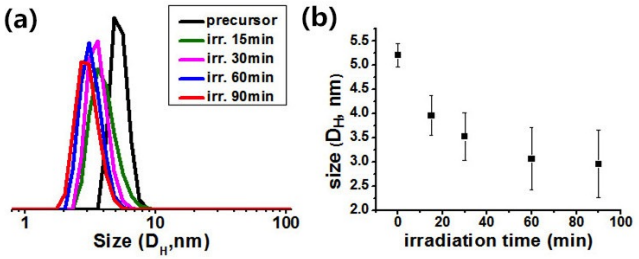

Fig.3: *(a) Number-weighted size distribution of the precursor and SCNPs prepared with different >320 nm UV irradiation times. (b) Average hydrodynamic diameter, D_H, vs. UV irradiation time (from 8 measurements).*

solution by dynamic light scattering (DLS). Knowing that the photodimerization degree increases with increasing UV irradiation time (Fig.2a), SCNPs formed following various UV irradiation times were obtained and the characterization results are shown in Fig.3. Despite the scattering of data, the DLS results show a clear tendency of size decrease upon increasing the UV irradiation time (Figs.3a and 3b). The number-average hydrodynamic diameter decreases from 5.2 nm for uncrosslinked polymer coil to about 3 nm for SCNPs with 87% photodimerization of coumarin. Thus, within the limits of our used SEC and DLS instrumentation, the combined results suggest that the nanoparticles were formed from single CAPPG chains, and that the size of those SCNPs could be controlled, to some extent, by adjusting the intra-chain photocrosslinking density that is determined by the photodimerization degree of the coumarin units in the main chain.

In conclusion, we have demonstrated a facile method that allows the use of a single polymer precursor to prepare photodegradable and size-tunable SCNPs. We showed that by incorporating coumarin moieties into the chain backbone of a polyester, the photodimerization and photoinduced chain scission, which occur at two different UV wavelengths, enable the preparation of sub-10nm SCNPs through intra-chain photocrosslinking (under >320 nm UV) and their subsequent photodegradation (254 nm UV). SEC and DLS results show that the size of SCNPs decreases with increasing the intra-chain photodimerization degree. We expect that inserting coumarin moieties in the main chain of a given polymer represent a general approach for obtaining variable-size SCNPs with the function of photodegradability, without the need for synthesizing different polymer precursors. Owing to the biocompatible and biodegradable nature of the polyesters, they have potential to be exploited for biomedical applications.

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Notes and references

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