Photo-sensitive PMMA microgels: light-triggered swelling and degradation †‡

Daniel Klinger and Katharina Landfester*

Received 7th July 2010, Accepted 5th October 2010 DOI: 10.1039/c0sm00638f

Two classes (type A and type B) of novel photolabile divinyl functionalized crosslinkers based on onitrobenzyl derivatives were synthesized and investigated with regard to their photolytic performance upon UV irradiation. The systematic variation of the molecular structure resulted in different degradation rates depending on the irradiation conditions. Thus, the successive and independent cleavage is enabled by either adjusting the applied wavelengths or irradiation times. The respective molecules were used to build up photodegradable PMMA microgels by free radical copolymerization with MMA in a miniemulsion polymerization process. UV light-induced degradation of the swollen microgels was monitored by time dependent turbidity measurements and the resulting kinetics were found to correlate with the photolysis rates of the respective crosslinkers in solution. The irradiation wavelength-controlled selective partial cleavage of type B crosslinking points was achieved by UV irradiation with $\lambda > 315$ nm and resulted in particles with extensively increased volumes consisting of highly swollen networks. In addition, the irradiation time-controlled selective complete degradation of particles containing type B crosslinkers was accomplished. By using broadband UV light containing wavelengths of $\lambda < 315$ nm, the successive complete particle disintegration of type B and type A microgels was observed. Hence, the specific performance of the synthesized microgels can be precisely triggered by means of the used UV light wavelengths, doses and intensities, thus representing a great potential as new light-responsive nanoscaled materials.

Introduction

In recent years, much effort has been focused on the preparation of nanoscaled materials with a controlled chemical functionality by exploiting specific macromolecular designs.¹ Especially stimuli responsive nanoparticles, nanofibers, and nanostructured polymeric thin films represent complex multifunctional systems. Such materials are able to change certain properties in response to particular external triggers and can be applied in numerous fields such as sensors,² optics, colloidal crystals³ and biomedical fields including drug delivery systems⁴⁻⁶ and biotechnology.⁷ Various techniques are well-established to form a broad variety of polymeric architectures on a submicron scale. The selective fabrication of spherical nanostructures for example can be achieved by self-assembly processes such as micellar aggregation of amphiphilic block copolymers⁸⁻¹⁰ or layer-by-layer deposition of polyelectrolytes on template particles.11,12 Furthermore, reactions in stabilized heterophases such as emulsions, suspensions, or miniemulsions¹³⁻¹⁵ represent powerful tools for the formation of polymer particles.

In many applications it would be desirable to have stable nanoparticles that can maintain their structural integrity in a variety of environments including different types of solvents and the dry state. Contrary to non-crosslinked stimuli-responsive micellar aggregates,^{8–10} microgels as intramolecularly crosslinked polymer particles would allow diverse processing routes in different media and applications in various fields such as drug delivery,⁶ sensors,² catalysis,¹⁶ chemical separation¹⁷ and enzyme immobilization.¹⁸

Regarding delivery applications in general, the release from gels is determined by diffusion of the embedded compounds out of the network.¹⁹ A specific molecular design of the polymeric network structure allows the incorporation of stimuli sensitive properties into the gel, thus enabling a release controlled by external triggers which can be obtained by two approaches. In the first approach, stimuli responsive polymers change the physicochemical properties of the network upon application of an external trigger, in many cases temperature,¹ and thus induce controlled swelling and deswelling of the particles.

In the second approach, the use of cleavable crosslinking points in a gel represents a method for triggering the complete decomposition of the network architecture using external stimuli. Here, especially acid degradable microgels synthesized with crosslinkers containing various acid-labile moieties such as tertiary esters or acetals have been an active research area for delivery systems in organic²⁰ and aqueous²¹ media.

Concerning the use of microgels in the aforementioned applications, it is desirable to have materials responding to a broad variety of triggers such as pH, temperature, enzymes, specific ions, solvent composition or light. Among the different stimuli, light represents an outstanding position as it can be applied in a very precise manner by selecting suitable wavelengths, polarization directions and intensities in a non-contact approach, respectively.^{22,23} Furthermore, light offers the possibility to change the polymer properties in very confined spaces

Max Planck Institute for Polymer Research, Ackermannweg 10, 55128 Mainz, Germany. E-mail: landfester@mpip-mainz.mpg.de

[†] This paper is part of a Soft Matter themed issue dedicated to the International Soft Matter Conference 2010.

[‡] Electronic supplementary information (ESI) available: Kinetic UV-Vis measurements and HPLC elugrams of the photoreaction of the crosslinking molecules in THF solution. Molecular structures of the proposed secondary dimeric photoproducts. See DOI: 10.1039/c0sm00638f

and hence, e.g., can be used to create patterns in polymer thin films with nanometre precision. Photochemistry in combination with polymeric gels is well established for the formation of crosslinks by the application of UV light.^{24,25} While the reversibility of the [2 + 2] cycloaddition reaction of coumarin, anthracene and cinnamovl derivatives is well examined to prepare stimuli responsive macroscopic gels,^{26,27} only little attention has been paid to the formation of photosensitive gel particles in the nano- or micrometre size range.^{28,29} In addition, cleavage of crosslinks obtained from [2 + 2] cycloadditions requires harsh irradiation conditions such as UV-C light ($\lambda =$ 200-280 nm), whereas the photolysis rates and absorption bands of o-nitrobenzyl derivatives such as esters, carbonates or carbamates are known to be adjustable by the molecular structure of the chromophore.^{30,31} Hereby, a potential rapid and quantitative cleavage upon irradiation with UV-A light ($\lambda > 300$ nm) enables their use in biomedical related applications.^{7,32}

The good photolytic properties of the chromophore have been employed in various applications such as photolabile supports for solid phase organic synthesis,^{30,33} linkers for chemical proteomics,³⁴ or degradable linkers to bridge fluorophores to DNA.³⁵

Another group of applications uses o-nitrobenzyl derivatives as protecting groups for a broad variety of materials. Early investigations in this context were based on the photogeneration of functional moieties in low molecular weight compounds.^{36,37} In the field of macromolecular chemistry, the attachment of o-nitrobenzyl esters to a polymer backbone allows the preparation of photoresist materials for surface patterning.^{38,39} Here, it was shown that high photolysis rates of this chromophore are maintained in polymeric matrices^{32,40} and even in solid state.^{37,41} On the other hand, soft hydrogel materials in the macroscopic size range containing o-nitrobenzyl groups as photocleavable crosslinking points allowed the formation of three-dimensional channels upon focused irradiation. Cell migration in the matrix was therefore enabled without influencing cell vitality.7 However, the used crosslinking molecule contains a PEG spacer with a molecular weight of $M_{\rm n} \approx 3400$ g mol⁻¹, thus resulting in a big initial mesh size for the hydrogel which hinders an effective embedding of smaller functional compounds.

The particularly good performance of the photoreaction under various conditions represents a versatile tool for more complex applications in the nanometre size range as well.^{32,42} Recently investigated approaches include the design of targeting nanoparticles⁴ and the preparation of photoresponsive nanocarriers using *o*-nitrobenzyl esters as capping groups on dendrimers⁴³ or hyperbranched polyglycerol nanocapsules.⁴⁴

The aim of this work is the synthesis of two classes (type A and type B) of novel photolabile divinyl functionalized crosslinkers based on *o*-nitrobenzyl moieties, which will be used to build up photodegradable PMMA microgels. Investigations on the cleavage behavior will be focused on controlling the independent degradation of the different types of gel particles by means of irradiation wavelengths and times applied. A dissimilar photolytic reactivity should in principle enable the successive decomposition of one specific type of microgel after the other in a mixed dispersion of the two, thus giving access to subsequent release of different functional compounds. Moreover, the low molecular weight structure of the crosslinkers should cause an initial small mesh size of the resulting gel, allowing the embedding of relatively small molecules.

Experimental section

Materials

All chemicals were purchased from Sigma Aldrich and used without further purification unless otherwise stated. Methyl methacrylate (MMA), diethylene glycol dimethacrylate (DEGDMA) and divinylbenzene (DVB) were purified over basic aluminium oxide to remove contained inhibitor.

Instrumentation

¹H (300 MHz) and ¹³C NMR (75 MHz) spectra were measured using a Bruker spectrometer. UV-vis measurements were performed using a Perkin Elmer Lambda 25 UV/VIS spectrometer. A NICOMP zetasizer measuring at a fixed scattering angle of 90° was used to determine particle size distributions by dynamic light scattering (DLS). The measurements were carried out at 25 °C on diluted dispersions in the respective solvents. Irradiations were either carried out by using a 365 nm emitting UV-LED with a maximum power of 150 W or an OSRAM HBO 100 W/2 mercury short arc lamp, either combined with a UG-11 and a W-320 filter resulting in an output of wavelengths $\lambda = 315-390$ nm or used without any filters resulting in a broadband spectrum of emitted light. HPLC measurements were conducted using an Agilent quaternary gradient pump (series 1100) combined with an Agilent photodiode array detector (DAD series 1200). A Gemini 1530 (Carl Zeiss AG, Oberkochem, Germany) with an In-Lens detector was used to take scanning electron micrographs (SEMs). The samples were prepared by drop-casting of diluted dispersions on a silicon wafer.

Synthesis of photolabile molecules

Two different photolabile molecules were synthesized according to procedures described in the literature.

(2-Nitro-1,4-phenylene)dimethanol (2NPDM). The procedure of Piggott and Karuso³⁴ was followed. Briefly, 5 equivalents of a 1 M borane-THF complex solution in THF were added under nitrogen to a stirred ice-cooled solution of 1 equivalent of 2-nitroterephthalic acid in anhydrous THF. After complete addition, the reaction mixture was allowed to warm to room temperature for 1 h and then stirred overnight at 40 °C. Destruction of the excess borane by dropwise addition of water was followed by removal of the organic solvent under reduced pressure. The resulting aqueous phase was extracted three times with ethyl acetate, the organic layers were combined, dried with anhydrous magnesium sulfate and the solvent was removed under reduced pressure. Recrystallization of the obtained yellow solid from chloroform yielded (2-nitro-1,4-phenylene)dimethanol as yellowish needles. Yield 90%; mp 91-93 °C; elemental analysis calc. for C₈H₉NO₄: C, 52.46; H, 4.95; N, 7.65; found: C, 52.40; H, 5.09; N, 7.69%; ¹H NMR (DMSO-d6): $\delta = 8.05$ (s, 1H), 7.81 (d, 1H, J = 8.0 Hz), 7.68 (d, 1H, J = 8.0 Hz), 4.93 (s, 2H), 4.69 (s, 1H). ¹³C NMR (DMSO-d6): $\delta = 146.70, 142.86, 136.41, 131.35, 128.24,$ 121.66, 61.52, 59.77. MS (FD) m/z 183.7 (M⁺).

4-(4-(1-Hydroxyethyl)-2-methoxy-5-nitrophenoxy)butanoic acid (HEMNPBA). The product was prepared based on the synthetic protocols by Holmes.^{30,45} Acetovanillone was suspended together with 1.1 equivalents of methyl 4-bromobutyrate and 1.5 equivalents of potassium carbonate in anhydrous dimethylformamide and stirred under argon for 16 h. Afterwards, the reaction mixture was diluted with an excess amount of water to dissolve all inorganic salts and then extracted with ethyl acetate. Removal of the organic solvent after drying with MgSO₄ yielded the -ester product in quantitative crude yield. Subsequent nitration was achieved by stirring a 3.7% (w/v) solution of the -ester in a mixture of acetic anhydride and nitric acid (1 : 2, v/v) at 0 °C for 3 h. The mixture was precipitated in ice water, filtered and the obtained solid recrystallized from MeOH/H2O yielding 53% of the nitrated product. In the next step, the reduction of the group with excess borohydride was conducted at room temperature for 16 h in MeOH/THF and directly followed by inducing the ester cleavage by addition of NaOH in water and stirring the mixture at room temperature for 7 h. The organic solvents were removed under reduced pressure and the resulting water phase was slowly acidified with diluted hydrochloric acid. The crude product was obtained by extracting the water phase with ethyl acetate and evaporation of the dried organic layers. Recrystallization from ethyl acetate/hexane afforded the photolabile molecule HEMNPBA in 86% yield as a pale yellow solid, mp 165-169 °C; elemental analysis calc. for C₁₃H₁₉NO₆: C, 54.73; H, 6.71; N, 4.91; found: C, 54.73; H, 7.01; N, 4.79%; ¹H NMR (CDCl₃): $\delta = 7.55$ (s, 1H), 7.29 (s, 1H), 5.55 (q, 1H, J = 6.3 Hz), 4.10 (t, 2H, J = 6.1Hz), 3.97 (s, 3H), 3.73 (t, 2H, J = 6.2 Hz), 1.98 (m, 2H), 1.77 (m, 2H), 1.55 (d, 3H, J = 6.3 Hz). ¹³C NMR (CDCl₃): $\delta = 153.67$, 146.38, 138.87, 137.94, 108.62, 108.30, 68.91, 64.65, 61.40, 55.96, 28.89, 25.23, 24.60. MS (FD) m/z 285.0 (M⁺).

Synthesis of photodegradable crosslinkers

Based on the two different photolabile molecules, four different crosslinkers were synthesized. The structures of CL-1A, CL-2A, CL-3A and CL-4B are presented in Scheme 1.

2,2'-(2-Nitro-1,4-phenylene)bis(methylene)bis(oxy)bis(oxomethylene)bis(oxy)bis-(ethane-2,1-divl)bis(2-methylacrylate) (CL-1A). Α solution of hydroxyethylmethacrylate (HEMA) (1.86 g, 14.3 mmol) in anhydrous THF (5 mL) was added dropwise to a solution of carbonyldiimidazole (CDI) (2.39 g, 14.3 mmol) in anhydrous THF (20 mL). After stirring the reaction mixture overnight at room temperature, a solution of 2NPDM (1.31 g, 7.15 mmol) in anhydrous THF (20 mL) together with a 1.75 mol L^{-1} sodium ethanolate suspension (0.2 mL, 0.35 mmol) was added. Additional stirring for 5 d at room temperature was followed by filtration and reduction of the filtrate to dryness under reduced pressure. The residue was purified by column chromatography over silica using CHCl₃/MeOH (20:1) as eluent and yielded CL-1A (1.84 g, 3.72 mmol) as a slightly yellow colored oil. Yield 52%; elemental analysis calc. for C₂₂H₂₅NO₁₂: C, 53.33; H, 5.09; N, 2.83%; found: C, 53.53; H, 5.07; N, 2.81.) ¹H NMR (CDCl₃): $\delta = 8.17$ (s, 1H), 7.68 (s, 1H), 7.67 (s, 1H), 6.12 (d, 1H, J = 5.2 Hz), 5.59 (m, 4H), 5.23 (s, 2H), 4.41 (m, 8H) ppm, 1.93 (d, 6H, J = 3.6 Hz). ¹³C NMR (CDCl₃): $\delta = 167.05, 154.60,$

147.19, 136.79, 135.79, 133.27, 131.96, 128.99, 126.27, 124.60, 67.77, 66.12, 65.82, 62.17, 18.24. MS (FD) *m*/*z* 493.9 (M⁺).

2,2'-(2-Nitro-1,4-phenylene)bis(methylene)bis(oxy)bis(oxomethylene)bis(azane-diyl)bis(ethane-2,1-diyl) bis(2-methylacrylate) (CL-2A). 2NPDM (1.00 g, 5.5 mmol) was dissolved in anhydrous THF (10 mL) and added dropwise to a solution of 2-isocvanatoethyl methacrylate (1.71 g, 11.0 mmol) in anhydrous THF (15 mL) under nitrogen. The reaction mixture was heated to 65 °C and stirred for 24 h at this temperature. FT-IR measurements showed complete disappearance of the corresponding isocyanato absorption band at 2260 cm⁻¹, thus indicating complete conversion of the latter. The solvent was evaporated and the residue was purified by column chromatography over silica using CHCl₃/MeOH (10:1) as eluent yielding 72% of CL-2A (1.95 g, 4.0 mmol) as a slightly yellow colored oil which slowly solidified at 5 °C. Elemental analysis calc. for C₂₂H₂₇N₃O₁₀: C, 53.55; H, 5.51; N, 8.52.Found: C, 53.75; H, 5.77; N, 8.47%; ¹H NMR (CDCl₃): $\delta = 8.06$ (s, 1H), 7.58 (s, 1H), 7.56 (s, 1H), 6.11 (m, 2H), 5.58 (m, 2H), 5.49 (s, 2H), 5.18 (m, 4H), 4.24 (t, 4H, J =5.4 Hz), 3.51 (q, 4H, J = 5.5 Hz), 1.93 (s, 6H).¹³C NMR (CDCl₃): $\delta = 167.30, 155.80, 147.47, 137.94, 135.91, 132.83, 132.67, 129.16,$ 126.16, 124.14, 65.00, 63.55, 63.28, 40.44, 18.29. MS (FD) m/z 494.6 (M⁺).

Bis(2-(methacryloyloxy)ethyl) '-(2-nitro-1,4-phenylene)bis-(methylene) disuccinate (CL-3A). Mono-2-(methacryloyloxy)ethyl succinate (2.53 g, 11.0 mmol) was dissolved in anhydrous benzene and oxalyl chloride (2.79 g, 2 mmol) was added under nitrogen at room temperature. The reaction mixture was slowly heated to 85 °C and refluxed for 3 h. After cooling to room temperature, benzene and excess oxalyl chloride were removed under reduced pressure. The so obtained acyl chloride was dissolved in anhydrous THF (35 mL) and a solution of 2NPDM (1.00 g, 5.5 mmol) and triethylamine (1.21 g, 12.0 mmol) in THF (15 mL) was added dropwise. After stirring the mixture overnight at room temperature, precipitated solids were removed by filtration and the solution was reduced to dryness. The residue was dissolved in dichloromethane (100 mL), washed three times with water, dried with MgSO4 and evaporated. The resulting red oil was purified by column chromatography over silica using CHCl₃/MeOH (40:1) as eluent and afforded 40% of pure CL-3A (1.34 g, 2.2 mmol). Elemental analysis calc. for C₂₈H₃₃NO₁₄: C, 55.35; H, 5.47; N, 2.31, found: C, 55.24; H, 5.54; N, 2.38%. ¹H NMR (CDCl₃): $\delta = 8.02$ (s, 1H), 7.56 (s, 1H), 7.55 (s, 1H), 6.05 (m, 2H), 5.52 (m, 2H), 5.46 (s, 2H), 5.13 (s, 2H), 4.28 (m, 8H), 2.65 (m, 8H), 1.87 (s, 1H). ¹³C NMR (CDCl₃): $\delta = 171.80, 167.06,$ 147.49, 137.34, 135.89, 132.94, 131.84, 129.32, 126.07, 124.31, 64.67, 63.02, 62.49, 62.26, 28.85, 18.23. MS (FD) m/z 606.8 (M⁺).

2-((1-(4-(4-(2-(Methacryloyloxy)ethylcarbamoyloxy)butoxy)-5-methoxy-2-nitro-phenyl)ethoxy)carbonylamino)ethyl methacrylate (CL-4B). 2-Isocyanatoethyl methacrylate (1.14 g, 7.4 mmol) was dissolved in anhydrous THF (5 mL) and added to a solution of HEMNPBA (1.00 g, 3.5 mmol) and dibutyltin dilaurate (0.11 g, 0.18 mmol) in anhydrous THF (25 mL) under nitrogen. After the mixture was heated to 65 °C and stirred for 48 h at this temperature, FT-IR measurements showed complete disappearance of the corresponding isocyanato absorption band at 2260 cm⁻¹. This



Scheme 1 Photolabile crosslinking molecules CL-1A, CL-2A, CL-3A and CL-4B: (a) classification; (b) UV spectra; and (c) synthesized structures of the crosslinkers.

being an indicator for complete conversion of the isocyanate, the solvent was then removed under reduced pressure and the residue was purified by column chromatography over silica using CHCl₃/MeOH (10 : 1) as eluent. The obtained slightly yellow colored oil slowly solidified in the refrigerator and was found to consist of pure CL-4B (1.32 g, 2.2 mmol, 63%). Elemental analysis calc. for C₂₇H₃₇N₃O₁₂: C, 54.45; H, 6.26; N, 7.06, found C, 54.73; H, 6.59; N, 6.70%. ¹H NMR (CDCl₃): δ = 7.56 (s, 1H), 6.98 (s, 1H), 6.37 (q, 1H, *J* = 6.3 Hz), 6.10 (d, 2H, *J* = 7.7 Hz), 5.59 (m, 2H), 5.06 (s, 1H), 4.96 (t, 1H), 4.13 (m, 8H), 3.93 (s, 1H), 3.48 (m, 4H), 1.93 (d, 6H, *J* = 4.6 Hz), 1.81 (m, 4H), 1.81 (m, 1H), 1.59 (d, 3H, *J* = 6.3 Hz). ¹³C NMR (CDCl₃): δ = 167.29, 156.47, 155.20, 153.97, 147.20, 139.69, 135.96, 133.81, 126.05, 108.92, 69.10, 68.85, 64.48, 63.70, 63.65, 56.30, 40.18, 25.62, 25.46, 22.17, 18.27. MS (FD) *m/z* 595.5 (M⁺).

Photodegradation studies of crosslinkers in solution via ¹H NMR and mass spectroscopy

A 3.0×10^{-3} mol L⁻¹ solution of each sample in THF was placed in a quartz cuvette and irradiated for 10 h with 17 mW cm⁻² at wavelength of $\lambda = 315-390$ nm using a mercury short arc lamp combined with the described filters. The reaction mixture was evaporated to dryness under reduced pressure and divided into two fractions. One fraction was dissolved in CDCl₃ and investigated by ¹H NMR spectroscopy, the other fraction was investigated by field desorption mass spectrometry.

Kinetic HPLC measurements

Crosslinker solutions in THF were prepared and irradiated analogously to those used for the ¹H NMR spectroscopic

measurements. Samples were taken at fixed time intervals and directly measured by HPLC using a solvent gradient of THF/ water.

Preparation of crosslinked photodegradable PMMA gel particles by miniemulsion polymerization

Crosslinked PMMA microgels (MGs) were synthesized by free radical polymerization in miniemulsion. The dispersed phase was prepared by mixing MMA (1.00 g, 10.00 mmol), hexadecane (41 mg, 0.18 mmol), 2,2'-azobis(2-methyl-butyronitrile) (V-59) (20 mg, 0.10 mmol) and 2.5 mol% of the respective crosslinker. Afterwards, the mixture was added to the continuous phase consisting of a solution of the non-ionic surfactant Lutensol AT-50 (66 mg) in 10 mL of water. The miniemulsion was formed by first stirring the mixture at 1750 rpm for 1.5 h and then homogenizing the obtained preemulsion by ultrasonication for 2 min at 90% intensity (Branson sonifier W450 Digital, 0.5" tip) at 0 °C. Polymerizations were then carried out overnight in an oil bath set at 70 °C. The used amounts of crosslinkers of the different reactions are summarized in Table 1.

After the polymerization, any coagulates were removed by filtration and the resulting dispersions were centrifuged at 14 000 rpm for 25 min to collect the particles. The supernatant was removed and replaced by demineralised water. Redispersion was carried out using a vortex. In order to remove excess surfactant, the dispersions were further washed three times with demineralised water, following the procedure described above. Finally, the dispersions were centrifuged at 5000 rpm for 5 min and the supernatant was collected and centrifuged again for 5 min at the same speed. The supernatant

Sample	Crosslinker			Particle size	
	Туре	<i>m</i> /mg	mol%	$d_{\rm h}/{\rm nm}^a$	σ (%)
MG-0	DEGDMA	60.0	2.5	141	17
MG-X	DVB	33.0	2.5	140	13
MG-1A	CL-1A	124.0	2.5	149	21
MG-2A	CL-2A	123.0	2.5	204	19
MG-3A	CL-3A	152.0	2.5	157	18
MG-4B	CL-4B	149.0	2.5	174	19

of this procedure represents the final dispersion of the MGs in water and was examined with regard to the particle size distributions by means of dynamic light scattering (DLS) and scanning electron microscopy (SEM). Freeze-drying of the so purified dispersions removed unreacted monomer and yielded the crosslinked PMMA gel particles as white powders. The freeze-dried particles were swollen for 3 d at 0.5% (w/v) in THF at room temperature. Three additional washing steps by centrifugation at 14 000 rpm for 60 min and redispersion in THF were performed to remove the sol content which consists of all the soluble polymers and non-crosslinked particles. For every type of MG the supernatants of the washing steps were combined and evaporated yielding the sol content. The particle dispersion in THF was also evaporated and represents the gel content. By gravimetrical analysis, the sol/gel content was determined and gives a description of the crosslinking efficiency. Finally, the dried particles were redispersed either in THF or chloroform by swelling at a concentration of 0.5% (w/v) overnight at room temperature. Particle size distributions were determined by DLS in THF or chloroform as described above. SEM analysis was conducted to determine the morphology of the particles.

Photodegradation studies of crosslinked photodegradable PMMA gel particles in chloroform

Samples of 0.125% (w/v) MG in a good solvent for PMMA were placed in a quartz cuvette and irradiated with the respective UV light source. At predetermined times, a sample was collected and turbidity measurements were conducted by using a NICOMP zetasizer. The volume of the irradiated sample was retained by returning the withdrawn sample to the cuvette after every measurement. Relative scattering intensity at 90° was obtained by calculating the ratio of the scattering intensity of the irradiated sample to the one of the non-irradiated sample. Particle size distributions of the irradiated particle dispersions were obtained by DLS in the respective solvent. Furthermore, SEM images were taken to investigate the morphology of the irradiated particles.

Results and discussion

Two different types (type A and type B) of novel photodegradable PMMA gel particles were synthesized by free radical copolymerization of MMA with four newly synthesized

photolabile crosslinkers in miniemulsion. The synthesized crosslinker structures were designed to exhibit two different degradation behaviors, thus influencing the swelling properties of the resulting PMMA gel particles upon irradiation in a good solvent. Type B microgels irradiated with UV-A light of $\lambda >$ 315 nm were found to consist of highly swollen partially degraded gel networks, whereas the structure of type A microgels remained intact under the same conditions. In addition, distinct photolysis rates of the different crosslinker types enable the independent time-controlled degradation of type B microgels using broadband UV light containing wavelengths of $\lambda < 315$ nm. A short irradiation time t_1 leads hereby selectively to the complete degradation of type B particles. Eventually, longer irradiation times $t_2 > t_1$ lead then to a complete particle degradation of type A microgels as well. In summary, either complete or partial particle degradation for both types of microgels could selectively be achieved by variation of the used UV light wavelengths and irradiation times (Fig. 1). Degradation behaviours were investigated by means of degradation rates, changes in the degree of swelling and particle morphologies.

Synthesis and characterization of photolabile crosslinkers

In order to investigate the desired influence of the photolabile chromophore on the photoreaction of the resulting crosslinkers, two categories of molecules differing in their absorption spectra were synthesized and characterized regarding their photolysis. Scheme 1 shows the classification of the different crosslinking molecules, their absorption spectra and the synthesized structures of CL-1A, CL-2A, CL-3A and CL-4B.

CL-1A was synthesized by carbonyldiimidazole (CDI) activated coupling of 2 equivalents of hydroxyethylmethacrylate (HEMA) with 2NPDM using catalytic amounts of sodium ethanolate. The synthesis of CL-2A was achieved by a one step reaction of 2-isocyanatoethyl methacrylate with 2NPDM. For the synthesis of CL-3A, mono-2-(methacryloyloxy)ethyl succinate was first converted to the acyl chloride by the reaction with oxalyl chloride. The product was then allowed to react further with 2NPDM to the corresponding ester. CL-4B was synthesized according to the procedure for the synthesis of CL-2A whereas in this case, DBTDL was used to catalyze the reaction of the secondary hydroxyl group with the isocyanate.

Type A crosslinkers CL-1A, CL-2A and CL-3A are based on (2-nitro-1,4-phenylene)dimethanol (2NPDM) group, the whereas type B crosslinker CL-4B contains 4-(4-(1-hydroxyethyl)-2-methoxy-5-nitrophenoxy)butan-1-ol (HEMNPBO) as the photoreactive moiety. In the latter case, the introduction of a α -methyl group onto the benzylic carbon of the *o*-nitrobenzyl core is known to increase the rate of photolysis significantly.³¹ This effect can be explained by considering the abstraction of a benzylic proton by the photoactivated nitro group as the rate limiting step in the photolysis of the o-nitrobenzyl group, whereby the additional methyl group increases the acidity of this proton. Furthermore, the introduction of alkoxy substituents into the o-nitrobenzylic core results in a modified electronic structure of the chromophore which is known to result in a considerably increased UV absorption for $\lambda > 315$ nm compared to the 2NPDM moiety.38



Fig. 1 Schematic representation of swelling and degradation behaviour of type A and type B photodegradable PMMA microgels upon UV irradiation with different wavelengths and for different irradiation times t_1 and t_2 .

For the photolysis of the crosslinkers, the only requirement to the irradiation wavelength is to overlap with the absorption band of the photolabile chromophore. However, to degrade the crosslinkers and the resulting PMMA gel particles in a controlled manner under mild conditions, Norrish-type side reactions, which primarily take place for irradiations with wavelengths of λ < 300 nm, should be avoided.^{46,47} UV-vis spectroscopy of the crosslinkers CL-1A-CL-3A shows in every case an absorption maximum at 260 nm accompanied by tailing up to 370 nm. In comparison, the spectrum of CL-4B shows the anticipated additional absorption maximum at 342 nm (see Scheme 1). Here, the alkoxy substituents on the benzylic core exhibit a + M effect and therefore decrease the energy gap of the π - π * transition, resulting in a bathochromic shift of the absorption maximum (see Scheme 1). Thus, the crosslinker CL-4B shows a dramatically increased absorption in the targeted photolysis wavelength region of $\lambda > 315$ nm.

Photolysis of the cleavable crosslinkers in solution

Even though either type of crosslinker consists of a central *o*nitrobenzylic group, the variation of the molecular attachment of the radically polymerizable methacrylate groups onto the photolabile chromophore results in different photoproducts with specific functional groups (Scheme 2). The photoreaction is based on a radical mechanism including the intramolecular benzylic hydrogen abstraction by a nitro group oxygen followed by a rearrangement and bond cleavage. Type A crosslinkers based on 2NPDM all generate a nitrosobenzaldehyde derivative together with either an alcohol for the carbonate derivative of CL-1A, an amine for the carbamate derivative of CL-2A or a carboxylic acid for the ester derivative of CL-3A. Crosslinker CL-4B, however, degrades into an amine and a ne, which is known to be less reactive towards possible imine formation with the free amino group. Regarding the incorporation of those compounds into swollen PMMA gel particles, a partial degradation of the gel does not only result in a more highly swollen state but also in the formation of previously protected functional groups covalently bound to the polymeric network, thus enabling further chemical modification.

The photodegradation behavior of the crosslinkers was first investigated by analyzing the products of the photoreaction upon irradiating crosslinker solutions in THF ($3.0 \times 10^{-3} \text{ mol } \text{L}^{-1}$) for 8 h with UV light ($\lambda = 315$ –390 nm, 17 mW cm⁻²). ¹H NMR analysis of the crude reaction mixture showed a reduction of the peaks assigned to the benzylic proton(s) next to the respective carbonate, carbamate or ester group for every crosslinker. Hence, successful degradation was confirmed.

Furthermore, time-dependent UV-vis measurements of the crosslinker solutions in THF were conducted (see ESI[‡]). Irradiation of either type A or type B crosslinkers with UV light of wavelengths $\lambda = 315$ –390 nm resulted in every case in a red shift of the absorption maxima. Even though these light-induced changes of the spectra point towards successful photoreactions, the spectra of the crosslinkers CL-1A–CL-3A did not show well defined isosbestic points, thus indicating the simultaneous formation of side products in addition to the reaction shown in Scheme 2. Especially in the case of CL-1A and CL-3A, the



Scheme 2 Photoreactions of the degradable crosslinkers.

secondary evolution of an additional absorption band at $\lambda > 350$ nm can be observed for irradiation times of more than 20 min (ESI, Fig. S1a[‡]), hence suggesting subsequent follow-up reactions of the primary photoproducts to the generation of o,o'-dicarboxyazobenzenes which are known to be formed by dimerization of the primary nitroso groups at longer irradiation times.^{37,38} Type B crosslinker CL-4B shows defined isosbestic points over the complete irradiation time scale (Fig. S1d[‡]). Nevertheless, the large red shift of the absorption band to $\lambda_{max} = 385$ nm and its high extinction coefficient hinder the accurate determination of the formation of possible side products absorbing light in the same spectral region. Molecular structures of the proposed secondary dimeric photoproducts are shown in Scheme S1 in the ESI[‡].

In a next step, FD-MS measurements of the irradiated samples for the ¹H-NMR investigations were performed to investigate the formed photoproducts. All crosslinkers still showed the decreased characteristic molecule peak M⁺ of the starting compounds. In addition, the appearance of the M⁺ peaks corresponding to the formed nitrosobenzaldehyde photoproducts for type A crosslinkers and the respective compound for CL4 was observed and therefore proved successful cleavage. The subsequent generation of dicarboxyazobenzenes upon irradiation was confirmed by the appearance of the respective M⁺ peak at 642 m/ z for CL-1A-D and the deprotonated $[M - 2]^+$ peak at 754 m/z for CL-3A-D. In the other cases, the M^+ peak at 656 m/z for CL-2A-D and the $[M - 1]^+$ peak at 827 m/z for CL-4B-D could be assigned to the respective azoxy compounds which are known to be generated from azobenzenes.48,49 Carboxy or alkoxy radicals necessary for this reaction are assumed to be produced in small quantities by Norrish type side reactions of the crosslinkers upon irradiation of the non-degassed solution. The molecular structures of the dimeric azo and azoxy compounds can be seen in Scheme S1 in the ESI[‡].

A quantitative time-dependent degradation analysis of the crosslinkers by UV absorption measurements was hindered by the formation of side products absorbing in the same spectral region. In this context, HPLC represents a powerful tool to examine the composition of the reaction mixtures at various times. Therefore, the kinetics of the photolysis of the photolabile molecules were then investigated by monitoring the rate of disappearance of the starting compounds during irradiation. The presence of one defined peak in the elugrams of the non-irradiated samples additionally confirmed excellent purity of the synthesized structures. The kinetic plots of -ln [CL]/[CL]₀ versus time all show excellent linearity, indicating the expected first order kinetic with respect to the chromophore concentration (see Fig. 2b). Fig. 2 presents an example of the time dependent HPLC elution curves of the photoreaction of CL-4B and the kinetic plots for the calculation of the rate constants for all crosslinkers. The obtained half-life times and rate constants are listed in Table 2.

All newly synthesized crosslinkers were found to degrade completely upon irradiation with UV light of wavelengths $\lambda =$ 315–390 nm. Elugrams of crosslinkers CL-1A–CL-3A showed the generation of multiple side products (Fig. S2‡), confirming the results obtained from UV-vis and FD-MS measurements. In contrast to the UV-vis measurements, CL-4B shows not only the formation of one main photoproduct, but also the dimeric azoxy

side product verified by FD-MS can be detected as small peak in the elugram at \sim 4.4 min elution time (Fig. 2a). As expected, CL-4B shows a dramatically increased rate constant, in comparison to the type A crosslinkers. The enhanced absorption in the used photolysis wavelength region is accompanied by an increase of the acidity of the benzylic proton by the additional α -methyl group. Hence, CL-4B reacts around 5 times faster than CL-2A and 6.4 times faster than CL-1A and CL-3A. Taking into account absorption of the products in the same spectral region as the wavelengths used for the cleavage of the crosslinkers, the photoreaction is significantly slowed down. The less reactive molecules CL-1A-CL-3A are therefore more influenced by this effect than CL-4B and the difference of the photolysis rates is increased. This promising effect could enable a time-controlled and independent degradation of a specific type of particles using a definite wavelength of UV light. In addition, the divinyl groups present in either type of synthesized crosslinker enable the preparation of a broad variety of polymeric microgels by (co)polymerization with different radical polymerizable monomers. In a first attempt, PMMA was chosen as well-known chemically inert polymer to examine the degradation behaviour of the microgels.

Preparation and characterization of crosslinked photodegradable PMMA gel particles by miniemulsion polymerization

With regard to a potential application as delivery systems, the miniemulsion polymerization approach represents a big advantage compared to emulsion polymerizations. Suppression of diffusion of compounds between droplets characterizes each droplet as a nanoreactor. Therefore, copolymerization with the respective crosslinking molecules or incorporation of active hydrophobic substances can easily be achieved during the polymerization. As no diffusion takes place, the composition of the latex particles resembles the composition of the monomer phase. Hence, all functionalities incorporated are equally distributed in each particle. In order to obtain photodegradable PMMA microgels (MG), MMA was copolymerized with the crosslinkers CL-1A-CL-3A and CL-4B in miniemulsion. In addition, MG-0 microgels crosslinked with diethylene glycol dimethacrylate (DEGDMA) and MG-X microgels crosslinked with divinylbenzene (DVB) were synthesized as reference particles for the degradation experiments. In order to assure comparability of swelling and degradation behavior, 2.5 mol% of crosslinker was used in every case. After several washing steps, the numberweighted particle size distributions of the non-swollen particles in water were determined by DLS measurements. The obtained mean hydrodynamic diameters are shown in Fig. 5. All miniemulsion copolymerizations resulted in stable dispersions of nonswollen MGs in water with hydrodynamic diameters in the size range of 140 to 200 nm. The mean hydrodynamic diameters of particles synthesized with crosslinkers CL-2A and CL-4B were 204 nm (standard deviation \pm 39 nm) and 174 \pm 33 nm, whereas the crosslinkers DEGDMA, DVB, CL-1A and CL-3A yielded smaller particles of 141 ± 24 nm, 140 ± 19 nm, 149 ± 31 nm and 157 \pm 29 nm, respectively. In all cases, representative SEM images showed spherical particles in the same size range (Fig. 3). Regarding the polydispersity of the microgels, it becomes obvious that the particle size is broadly distributed, which might



Fig. 2 Photolysis of degradable crosslinkers: (a) time dependent HPLC elution curves of the photoreaction of CL-4B in THF and (b) kinetic plots for the calculation of the rate constants of the photoreaction of CL-1A (\bullet), CL-2A (\blacksquare), CL-3A (\diamond), and CL-4B (\blacktriangle).

 Table 2
 Rate constants and half-life times for the photolysis reactions of the synthesized degradable crosslinkers

Crosslinker	k/s^{-1}	$\tau_{1/2}/{ m min}$
CL-1A	$0.43 imes10^{-4}$	270
CL-2A	0.56×10^{-4}	206
CL-3A	0.43×10^{-4}	271
CL-4B	2.75×10^{-4}	42

be explained by the utilization of Lutensol AT-50 as a non-ionic surfactant for stabilization of these miniemulsions. Compared to electrostatic stabilization by ionic surfactants, the sole steric effect by Lutensol AT-50 is here not as efficient. Even though particles with a more narrowly distributed particle size could be obtained by using anionic sodium dodecyl sulfate (SDS), a non-ionic surfactant was chosen to assure best possible swellability in organic solvents. In contrast to the organic soluble Lutensol AT-50, this would be hindered by the presence of non-organic soluble SDS molecules on the particle surface.

Potential applications of the photodegradable particles require stable dispersions in a good solvent for the polymer chains forming the network. Therefore, the freeze-dried microgels were allowed to swell in THF for 3 d and the sol content was removed by additional washing steps. Evaporating the solvent under reduced pressure yielded MGs as pale yellowish solids. Redispersion of the microgels could easily be achieved by swelling the dried samples in a good solvent such as THF or chloroform overnight. The obtained dispersions were sterically stabilized only by the dangling chains of the swollen outer layer of the microgels and no additional surfactant was needed. SEM showed still spherical particles after the redispersion indicating successful crosslinking in every case. Representative SEM images for the microgels after redispersion in chloroform are shown in Fig. 4.

Dynamic light scattering measurements yielded the hydrodynamic diameters of the swollen particles which showed a significant increase compared to the values obtained from dispersions in water. The degree of swelling (DGS), or the swelling ratio, was then calculated as $DGS = V_{swollen}/V_{non-swollen}$. The obtained values are shown in Fig. 5 together with the hydrodynamic



Fig. 3 Characterization of non-swollen PMMA gel particles prepared with different crosslinkers. Representative SEM images and hydrodynamic diameters obtained by dynamic light scattering.



Fig. 4 Representative SEM images of crosslinked microgels after redispersion in chloroform (and drying).

diameters of the swollen particles in THF and chloroform. Comparing the hydrodynamic diameters in the different solvents, the largest particle diameters are found for the dispersions in chloroform. Therefore, all particle degradation experiments were conducted in the highly swollen state of the microgels in chloroform.

Gravimetrical analysis of the combined supernatants of the washing steps and the remaining particle dispersions afforded the sol/gel contents, which are shown in Fig. 5b. The gel contents are in the range of 83-90% and did not vary significantly among the various microgels synthesized with different crosslinkers. The sol contents of 17-10% may be explained by possible ring formation due to backbiting reactions of the crosslinking molecules.⁵⁰

While the determination of the sol/gel content in combination with the measured degree of swelling did not permit a quantitative evaluation of the crosslinking density or an absolute conclusion regarding the inner morphology, it allowed the expedient comparison of crosslinking efficiency of the different compounds among one another and relative to DEGDMA. Therefore, equally successful crosslinking and comparable distribution of crosslinks in the different microgels were presumed for all used crosslinkers.

Photodegradation studies of the PMMA gel particles in chloroform

In general, photodegradation of the microgel particles was conducted by irradiating 0.125% (w/v) dispersions of the microgels in chloroform by UV light of different wavelengths. At a first glance, a reduction in turbidity was detected for samples containing the photolabile moieties. In contrast, a dispersion of the MG-0 reference particles showed no alteration. The reduced turbidity was attributed to a loosening of the network structure by degradation of cleavable crosslinking points, because a more swollen gel particle is characterized by a reduced contrast in the refractive indices between solvent and particle. As a result, the scattering intensity decreases, leading to an optically more transparent dispersion. A theoretic explanation for this phenomenon is based on the following equation for the turbidity $\tau = cQ_{\text{ext}}3/(2d\rho)$ as described by Lechner.⁵¹ Here, c is the mass concentration of the particles, Q_{ext} is the Mie extinction efficiency, d is the particle diameter and ρ is the particle density. The value of the parameter Q_{ext} is a function of the relative refractive index $n_{\rm p}/n_0$ ($n_{\rm p}$ being the refractive index of the particles and n_0 the one of the solvent) and decreases with decreasing



Fig. 5 Characterization of the PMMA MGs: (a) hydrodynamic diameters in (\blacksquare) water, (\bigcirc) THF, (\triangle) chloroform and (b) (\blacksquare) gel contents of the isolated MG particles and DGS in (\bigcirc) THF and (\triangle) chloroform.

value of $n_{\rm p}/n_0$. The resulting influence on turbidity was described by Al-Manasir *et al.* and used to monitor the temperature dependent swelling of PNIPAM microgels in water.⁵² With the intention to follow the particle swelling or degradation, turbidity measurements were carried out in chloroform by measuring the intensity of the scattered light at 90°. In detail, the intensity count rates of the irradiated samples $I_{\rm irr}$ were determined relative to those of the non-irradiated samples I_0 . The values for the relative turbidity $t_{\rm rel}$ obtained from the equation, $t_{\rm rel} = (I_{\rm irr}/I_0) \times 100\%$, therefore reflect the relative degree of particle degradation.

In order to confirm the correlation between decreasing turbidity and increasing particle size, the reciprocal turbidity *i.e.* the transparency was plotted together with the corresponding hydrodynamic diameters against the time, for a dispersion of MG-4B upon irradiation with UV light ($\lambda = 315$ -390 nm, $I = 17 \text{ mW cm}^{-2}$). The resulting graph in Fig. 6 shows a good agreement between the light-induced increase in particle swelling and the decrease in scattering intensity.

Wavelength-controlled selective degradation of MG-4B microgels

Kinetic turbidity measurements of the microgel dispersions were conducted to examine the influence of the different crosslinker photolysis rates on the time dependent swelling behaviour of the respective gel particles.

It was expected that upon irradiation with wavelengths of $\lambda >$ 315 nm, the faster photo-reaction of CL-4B due to the significantly higher absorption in this spectral region also results in an accelerated increase of the corresponding gel particle size compared to the size change of particles synthesized with CL-1A–CL-3A.

Irradiation experiments conducted with UV light of wavelengths 315–390 nm and an intensity of 17 mW cm⁻² confirmed this assumption as can be seen in Fig. 7a. In the case of microgel particles containing photolabile crosslinking points, the decrease in turbidity upon irradiation was found to follow an exponential decay to a constant level. In contrast, non-degradable MG-0 particles did not show any change of turbidity. As expected, MG-4B microgels are much more sensitive to light irradiation than MG-1A–MG-3A particles.

in chloroform ($\lambda = 315-390$ nm and I = 17 mW cm⁻²).

It was assumed that the enhanced degradability of MG-4B microgels occurred due to the different photolytic reactivity of the crosslinkers. This should enable a selective degradation of MG-4B particles upon irradiation with UV-A light of wavelengths $\lambda > 315$ nm. Therefore, the different photolytic reactivity should in principle enable the successive decomposition of one specific type of microgel after the other in a mixed dispersion.

The turbidity of all the microgels containing either type A or type B photolabile crosslinkers decreases upon irradiation until a constant level is reached. The MG-4B microgels being the most sensitive for UV light of the spectral region over 300 nm showed a decrease to a constant level of 42%, whereas MG-2A reached 59% and MG-1A and MG-3A still exhibited a reduced turbidity to around 70%. Even much longer irradiation times of 3600 s did not result in a further decrease. It becomes obvious that even in the case of the most labile CL-4B crosslinker no complete particle degradation was achieved under the irradiation conditions used. During degradation of crosslinking points in the microgels, the photoproducts are probably still connected to a certain extent to the gel network. Therefore, the observed intermolecular formation of dimeric azobenzene or azoxybenzene moieties can take place to form new crosslinking points simultaneous to the cleavage of the photodegradable crosslinkers. The resulting "steady state" is represented by a constant maximum degree of swelling which can be seen as a plateau in the turbidity curves. In order to support this explanation and exclude polymer chain entanglement as a reason for incomplete particle degradation due to physical "crosslinks", non-crosslinked PMMA particles were prepared analogue to the microgels MG-0. The freeze-dried polymer latices dissolved readily in THF or chloroform as good solvents for PMMA and no particles could be detected either by DLS or SEM, suggesting that incomplete particle degradation is not a result of entanglements. Even though in the experiments conducted with the described wavelengths only partial degradation was observed in either case, an enlarged particle volume after irradiation represents an increase in solvent uptake, which correlates to a looser network structure in the gels. Thus, even partial degradation of the gel particles might be advantageous for delivery applications as diffusion out of the network proceeds faster.

In order to quantify the increase in swelling of the particles, DLS measurements of the particle dispersions in chloroform after different irradiation times were conducted. The degrees of swelling (DGS_{irr}) were then calculated as the volumes of irradiated particles relative to those of the non-irradiated ones in the same solvent. The DGS_{irr} of the samples after 3600 s of irradiation time is shown in Fig. 7b. As expected, the MG-4B particles synthesized with type B crosslinker CL-4B showed a dramatically increased DGS_{irr} compared to the microgels containing CL-1A-CL-3A. Only the size of the reference particles MG-0 was not influenced at all. The kinetic turbidity measurements show that using shorter irradiation times increases the selectivity of MG-4B degradation. The degradation of MG-4B microgels already reaches a constant level after 400 s of irradiation, whereas the MG-1A-MG-3A particles still exhibit a higher turbidity compared to 3600 s irradiation time. Fig. 7b shows the corresponding degrees of swelling after 400 s of irradiation time which confirm an enhanced selectivity of MG-4B degradation.



hydrodynamic diameters upon the irradiation of a dispersion of MG-4B



Fig. 7 Irradiation experiments of the PMMA MGs with $\lambda = 315-390$ nm and I = 17 mW cm⁻²: (a) time dependent turbidity measurements and (b) DGS_{irr} determined by DLS measurements after (\blacktriangle) 400 s of irradiation and (\bullet) 3600 s of irradiation.

The particle morphology of the irradiated samples was studied by SEM. Representative images of the MGs still showed the presence of spherical particles. However, the defined spherical morphology disintegrated to a certain extent and the particles are flattened on the surface. Here, the partial degradation of the crosslinking points led to a much softer gel material, which results in flattened particles, as can be seen exemplary for MG-4B in comparison to the non influenced reference particles of MG-0 in Fig. 8.

Irradiation of the respective microgel dispersions with UV light of wavelengths in the spectral region above 350 nm should increase the difference in the swelling behavior of the type A and type B gel particles dependent on the irradiation time. Type B crosslinking molecules exhibit an absorption band with a maximum at 360 nm, whereas type A molecules show minor absorption in this spectral region. For this purpose, dispersions of the microgels in chloroform were irradiated with a UV-LED emitting at a discrete wavelength of 365 nm with an intensity of 60 mW cm⁻². Fig. 9a shows the corresponding time-dependent turbidity measurements. The degrees of swelling after 200 s of irradiation are presented in Fig. 9b. In comparison to the irradiation experiments conducted with $\lambda = 315-390$ nm UV light and the resulting DGS_{irr} (Fig. 6), it can be seen that the selective sensitivity of MG-4B microgels to irradiation can be drastically increased by tuning the spectral region of the used UV light.

Furthermore, it is noteworthy that the time scale of degradation was significantly shortened compared to the use of 17 mW cm⁻² UV light of wavelengths $\lambda = 315-390$ nm. As expected, a higher light intensity causes an increase in the degradation rate



Fig. 8 SEM images of PMMA microgels after UV irradiation for 400 s ($\lambda = 315-390$ nm and I = 17 mW cm⁻²) in chloroform: (a) MG-0 out of CHCl₃ and (b) MG-4B out of CHCl₃.

of crosslinking points, which results in a faster swelling behavior of the microgels. This allows the control of particle degradation kinetics by adjustment of UV light intensity as an external trigger. In addition, an increase in light intensity does not result in a higher degree of swelling, thus confirming the presence of an equilibrium between crosslinker cleavage and new formation as described earlier.

Kinetically controlled selective degradation of MG-4B and complete degradation of microgels

Since a significant increase in swelling was already achieved upon irradiation with UV-A light in a reasonable time scale under mild conditions ($\lambda = 315-390$ nm, I = 17 mW cm⁻² and $\lambda = 365$ nm, $I = 60 \text{ mW cm}^{-2}$), further investigations with high intensity UV light of a broader spectral region were carried out to determine the possibility of complete particle degradation. For that purpose, dispersions of the microgels in CHCl₃ were irradiated with UV light of wavelengths $\lambda = 200-600$ nm and an intensity of 95 mW cm⁻². The time-dependent relative turbidity is shown in Fig. 10a. In contrast to the irradiation experiments with UV-A light, using broadband UV light leads to turbidity diminishments down to 1-2% for the samples containing the photolabile crosslinking points, implying complete particle degradation. This observation confirms the assumed presence of newly formed crosslinkers as dimeric side products of the irradiation. Whereas irradiation with wavelengths of $\lambda > 300$ nm does not influence those crosslinking points, the use of broadband UV light of $\lambda =$ 200-600 nm is known to cleave azobenzene or azoxybenzene groups. Azoxybenzenes48 as detected for CL-2A and CL-4B yield phenyl nitroxides by direct photolysis. Photodegradation of azobenzenes^{48,49} (CL-1A-D and CL-3A-D; see ESI, Scheme S1[‡]) depends on the presence of radicals which are assumed to be generated in situ by Norrish type reactions upon irradiation.

Concerning the turbidity of the MG-0 reference particles, it becomes obvious that microgels with no photodegradable crosslinker were also partially disintegrated. This could be assigned to Norrish type side reactions, which are known to take place for wavelengths below 300 nm.^{46,47} In addition, the curve obtained for the MG-0 particles does not follow an exponential



Fig. 9 Irradiation experiments of the PMMA MGs with $\lambda = 365$ nm and I = 60 mW cm⁻²: (a) time dependent turbidity measurements and (b) DGS_{irr} determined by DLS measurements after 200 s of irradiation.

decay. In this case, a degradation mechanism based on Norrish type reactions is assumed, since the simultaneous occurrence of several non-defined photoreactions leads to a different degradation profile compared to the photolabile microgels. It is further assumed that partial particle disintegration of the MG-0 particles crosslinked with DEGDMA occurs mainly due to photolytic Norrish type I cleavage reactions of the ester bonds present in this molecule, rather than due to Norrish type II PMMA main chain degradation reactions. The latter are known to dominate at shorter wavelengths (157 nm)⁴⁷ than the ones used in the described experiment (>200 nm). Microgels prepared with a crosslinker, not containing any labile ester bonds connecting two polymer chains, should therefore exhibit an enhanced

photostability. In order to prove this assumption and to increase the advantage of photodegradable microgels, PMMA particles MG-X crosslinked with divinylbenzene (DVB) were synthesized analogue to the MG-0 particles. For irradiation of microgels MG-X in chloroform with UV-light of wavelengths of 200– 600 nm, only a negligible decrease of turbidity was detected for irradiation times up to 1200 s. As a result only minor degradation of those particles was assumed and further proved by DLS and SEM measurements. SEM analysis showed still spherical particles and no loss of structural integrity was observed. The control particles therefore represent a photostable system, which exhibits only negligible amounts of Norrish type II PMMA main chain degradation.



Fig. 10 Irradiation experiments of the PMMA MGs with $\lambda = 200-600$ nm and I = 95 mW cm⁻²: (a) time-dependent turbidity measurements; (b) DGS_{irr} determined by DLS measurements after 90 s of irradiation; (c) DGS_{irr} determined by DLS measurements after 225 s of irradiation; and (d) DGS_{irr} determined by DLS measurements after 750 s of irradiation.

With regard to a selective and independent degradation of MG-4B particles, the kinetic turbidity measurements reveal the additional possibility of an irradiation time controlled method. Compared to the wavelength selective approach, in this case a fixed UV light source can be used to achieve the selectivity.

After 90 s of irradiation MG-4B microgels exhibit already a decay of their turbidity down to 33%. In contrast, the turbidity of the microgel MG-2A only decreased down to 77% and those of the microgels MG-1A and MG-3A even just to 91-94%. Determination of the DGS_{irr} after 90 s of irradiation confirms the selective swelling of MG-4B particles which show a significantly increased particle volume compared to the microgels MG-1A-MG-3A. The respective DGS_{irr} is presented in Fig. 10b. The selectivity of the irradiation time-controlled swelling of MG-4B microgels is characterized by the deviation between the DGS_{irr} of MG-4B and those of the type A microgels MG-1A-MG-3A. The observed differences are comparable to those obtained from the wavelength-controlled method, hence indicating equal selectivity. In comparison, no significant decrease in turbidity or increase in particle size (represented by the DGS_{irr} in Fig. 10b) was detected for the reference particles of MG-X and even for the MG-0 microgels, which are based on DEGDMA as crosslinker, thus rendering those particles stable under the irradiation conditions used.

Further irradiation experiments were conducted to investigate the selective complete degradation of MG-4B microgels. In this case, an irradiation time of 225 s yielded a turbidity of $\sim 0\%$ which was assumed to correlate with complete particle disintegration. As a matter of fact, no spherical structures but a polymer film were observed by SEM analysis of the irradiated MG-4B microgels (see Fig. 11b). In contrast, DLS measurements of the MG-1A-MH-3A gel latices treated in the same way revealed only partial degradation, characterized by an increase in particle size. The resulting degrees of swelling after irradiation are shown in Fig. 10c. Even though MG-1A-MG-3A particles are also partially degraded, their relatively small volume changes clearly demonstrate the possible selective complete degradation of type B MG-4B microgels. Regarding the MG-0 and MG-X microgels, no significant particle degradation was observed. In both cases, turbidity measurements did not show any considerable decrease as well as DLS measurements did not reveal any changes in the DGS_{irr}. Therefore, the reference microgels are stable under the used conditions to completely degrade MG-4B particles.

In order to examine the light-induced degradation of microgels containing crosslinkers of type A subsequent to the selective swelling or disintegration of type B MG-4B particles, DLS measurements were conducted to determine the DGS_{irr} at longer irradiation times. Here, 750 and 1200 s represent the points in



Fig. 11 Representative SEM images of PMMA MGs after irradiation in chloroform ($\lambda = 200-600$ nm and I = 95 mW cm⁻²): (a) 90 s irradiation; (b) 225 s irradiation; and (c) 750 s irradiation.

time corresponding to a decay of turbidity to almost 0%. Therefore, complete particle disintegration was assumed for those irradiation times. The resulting data from DGS_{irr} determination are shown in Fig. 10d. At an irradiation time of 750 s the microgels MG-2A were completely decomposed and no particle size could be determined by DLS. In contrast, the MG-1A and MG-3A particles showed an increasing DGS_{irr} with increasing irradiation time and still exhibited a spherical structure consisting of highly swollen gel networks (see Fig. 11c). Turbidity measurements of irradiation experiments of the nonphotolabile reference particles reveal also partial degradation for MG-0 microgels at longer irradiation times. As mentioned above, this effect, which results from Norrish type I ester cleavage side reactions of the DEGDMA crosslinker, can be avoided by using DVB as a crosslinker. As can be seen from turbidity measurements and DGS_{irr} values, the respective MG-X microgels exhibit a good stability even for longer irradiation times. Therefore, the impact of photodegradable microgels is dramatically enhanced.

Complete degradation for all microgels containing either type of photolabile crosslinkers could be observed by SEM after 1200 s of irradiation (data not shown). The DGS_{irr} of the MG-0 reference particles seems to decrease with increasing irradiation time. It was assumed that degradation reactions and crosslinking reactions based on radical recombination and transfer reactions take place simultaneously and therefore do not result in a defined degradation of the microgel particles. In addition MG-X reference particles exhibit only a minor decrease in turbidity and DGS_{irr}, therefore representing photostable microgels.

All irradiated samples were further characterized with respect to the particle morphology using SEM. After 90 s of irradiation, the presence of spherical particles could still be observed in all cases, as can be seen in Fig. 11a. Similar to the irradiation experiments with UV-A light, the flattened particles on the silica surface result from the disintegration of the defined spherical morphology of MG-4B due to the cleavage of crosslinking points. However, for longer irradiation times of 225 s no particles were detected anymore for MG-4A. Fig. 11b shows the representative images of the polymer film resulting from the complete degradation of MG-4B and exemplary for type A MGs, the flattened spherical structures of the swollen MG-2A particles. MG-0 reference microgels treated similarly are shown as an example of non-light sensitive particles. In Fig. 11c SEM images are presented which show the resulting structures after 750 s of UV irradiation. The MG-2A microgels were completely degraded, whereas MG-1A and MG-3A particles only disintegrated to a certain extent and can be identified as flattened spherical structures on the surface. Representative for type A microgels, MG-3A particles are shown in comparison to the MG-0 reference. Even though MG-0 reference particles still exhibit a defined spherical structure as well, MG-X microgels represent reference particles of increased photostability, as can be seen from SEM analysis (see ESI, Fig. S4[‡]), the turbidity measurements and the DGS_{irr} discussed above. In the case of longer irradiation times of 1200 s, all particles containing either type of photolabile crosslinker were completely decomposed (data not shown), whereas the MG-0 and MG-X reference particles still exhibited a spherical structure (see ESI, Fig. S4[‡]).

In conclusion, depending on the used UV wavelengths and intensities, either partial and selective photolysis of the crosslinking points or complete degradation of the gel particles was achieved as is schematically summarized in Fig. 1.

Conclusion

In summary, we have developed a new system for controlled light-triggered release applications based on photodegradable microgels. The concept is based on the application of two classes (type A and type B) of newly synthesized photolabile crosslinkers. The crosslinkers were designed to exhibit significant differences in the photolysis rates depending on the irradiation conditions, therefore enabling their successive and independent cleavage by adjusting the irradiation wavelengths and times. The divinyl functionality of the crosslinkers offers the possibility for the preparation of a broad range of photodegradable (micro-) gels by radical copolymerization with different vinyl functionalized monomers. Investigating photodegradable PMMA microgels as a model system for possible future materials for light-triggered release applications, it was shown that independent and successive degradation of the microgels containing type A or type B crosslinkers can be achieved by either a wavelengthcontrolled or an irradiation time-controlled approach. This specific performance in organic solvents represents a great potential for the controlled release of two different functional compounds embedded in two types of microgels out of a mixed dispersion thereof. In this context, e.g. the embedding of metallic nanoparticles as possible functional compounds would give rise to new light-triggered catalytic materials.

Acknowledgements

D.K. acknowledges the International Max Planck Research School (IMPRS) for financial support.

References

- 1 S. Nayak and L. A. Lyon, Angew. Chem., Int. Ed., 2005, 44(47), 7686–7708.
- 2 M. Karg, I. Pastoriza-Santos, J. Perez-Juste, T. Hellweg and L. M. Liz-Marzan, *Small*, 2007, **3**, 1222–1229.
- 3 J. D. Debord and L. A. Lyon, J. Phys. Chem. B, 2000, 104(27), 6327-6331.
- 4 T. Dvir, M. R. Banghart, B. P. Timko, R. Langer and D. S. Kohane, *Nano Lett.*, 2010, **10**(1), 250–254.
- 5 M. Hamidi, A. Azadi and P. Rafiei, *Adv. Drug Delivery Rev.*, 2008, **60**(15), 1638–1649.
- 6 N. A. Peppas and W. Leobandung, J. Biomater. Sci., Polym. Ed., 2004, 15(2), 125–144.
- 7 A. M. Kloxin, A. M. Kasko, C. N. Salinas and K. S. Anseth, *Science*, 2009, **324**(5923), 59–63.
- 8 Y. Zhao, Chem. Rec., 2007, 7, 286-294.
- 9 Y. Mitsukami, M. S. Donovan, A. B. Lowe and C. L. McCormick, *Macromolecules*, 2001, 34(7), 2248–2256.
- 10 M. Nuopponen, J. Ojala and H. Tenhu, Polymer, 2004, 45(11), 3643– 3650.
- 11 T. Mauser, C. Dejugnat, H. Mohwald and G. B. Sukhorukov, *Langmuir*, 2006, **22**(13), 5888–5893.
- 12 A. G. Skirtach, C. Dejugnat, D. Braun, A. S. Susha, A. L. Rogach, W. J. Parak, H. Mohwald and G. B. Sukhorukov, *Nano Lett.*, 2005, 5(7), 1371–1377.
- 13 K. Landfester, Macromol. Rapid Commun., 2001, 22(12), 896-936.
- 14 K. Landfester, Adv. Mater., 2001, 13(10), 765-768.
- 15 K. Landfester, Angew. Chem., Int. Ed., 2009, 48(25), 4488-4507.

- 16 Y. Lu, Y. Mei, M. Drechsler and M. Ballauff, Angew. Chem., Int. Ed., 2006, 45(5), 813–816.
- 17 H. Kawaguchi and K. Fujimoto, *Bioseparation*, 1998, 7(4-5), 253-258.
- 18 A. Guiseppi-Elie, N. F. Sheppard, S. Brahim and D. Narinesingh, *Biotechnol. Bioeng.*, 2001, 75(4), 475–484.
- 19 C. C. Lin and A. T. Metters, Adv. Drug Delivery Rev., 2006, 58(12– 13), 1379–1408.
- 20 S. B. Jhaveri and K. R. Carter, *Macromolecules*, 2007, 40, 7874–7877.
 21 S. L. Goh, N. Murthy, M. C. Xu and J. M. J. Frechet, *Bioconjugate* Control of Co
- *Chem.*, 2004, **15**(3), 467–474. 22 M.-M. Russew and S. Hecht, *Adv. Mater.*, 2010, **22**(31), 3348–3360.
- 23 D. Klinger, K. Nilles and P. Theato, J. Polym. Sci., Part A: Polym. Chem., 2010, 48(4), 832–844.
- 24 S. Seiffert, W. Oppermann and K. Saalwaechter, *Polymer*, 2007, **48**(19), 5599–5611.
- 25 S. Gupta, D. Kuckling, K. Kretschmer, V. Choudhary and H. J. Adler, J. Polym. Sci., Part A: Polym. Chem., 2007, 45(4), 669– 679.
- 26 L. A. Connal, R. Vestberg, C. J. Hawker and G. G. Qiao, Adv. Funct. Mater., 2008, 18(20), 3315–3322.
- 27 G.-C. Kuang, Y. Ji, X.-R. Jia, Y. Li, E.-Q. Chen, Z.-X. Zhang and Y. Wei, *Tetrahedron*, 2009, **65**(17), 3496–3501.
- 28 D. J. Shi, M. Matsusaki, T. Kaneko and M. Akashi, *Macromolecules*, 2008, **41**(21), 8167–8172.
- 29 J. Q. Jiang, B. Qi, M. Lepage and Y. Zhao, *Macromolecules*, 2007, 40(4), 790–792.
- 30 C. P. Holmes, J. Org. Chem., 1997, 62(8), 2370-2380.
- 31 S. Buhler, I. Lagoja, H. Giegrich, K. P. Stengele and W. Pfleiderer, *Helv. Chim. Acta*, 2004, 87(3), 620–659.
- 32 N. Fomina, C. McFearin, M. Sermsakdi, O. Edigin and A. Almutairi, J. Am. Chem. Soc., 2010, 132(28), 9540–9542.
- 33 D. J. Yoo and M. M. Greenberg, J. Org. Chem., 1995, 60(11), 3358– 3364.

- 34 A. M. Piggott and P. Karuso, Tetrahedron Lett., 2005, 46(47), 8241-8244.
- 35 X. P. Bai, Z. M. Li, S. Jockusch, N. J. Turro and J. Y. Ju, Proc. Natl. Acad. Sci. U. S. A., 2003, 100(2), 409–413.
- 36 J. F. Cameron and J. M. J. Frechet, J. Am. Chem. Soc., 1991, 113(11), 4303–4313.
- 37 E. Reichmanis, B. C. Smith and R. Gooden, J. Polym. Sci., Part A: Polym. Chem., 1985, 23(1), 1–8.
- 38 H. Barzynski and D. Sanger, Angew. Makromol. Chem., 1981, 93(Feb), 131–141.
- 39 J. S. Katz, J. Doh and D. J. Irvine, Langmuir, 2006, 22(1), 353-359.
- 40 W. K. Wong, H. Schupp and W. Schnabel, *Macromolecules*, 1989, **22**(5), 2176–2181.
- 41 A. del Campo, D. Boos, H. W. Spiess and U. Jonas, Angew. Chem., Int. Ed., 2005, 44(30), 4707–4712.
- 42 C. Park, K. Lee and C. Kim, Angew. Chem., Int. Ed., 2009, 48(7), 1275–1278.
- 43 Y. Li, J. Xinru, G. Min, G. Kuang and Y. Wei, J. Polym. Sci., Part A: Polym. Chem., 2010, 48, 551–557.
- 44 E. Burakowska, S. C. Zimmerman and R. Haag, Small, 2009, 5(19), 2199–2204.
- 45 C. P. Holmes and D. G. Jones, J. Org. Chem., 1995, 60(8), 2318–2319.
- 46 D. Braun and J. Berger, Kolloid. Z. Z. Polym., 1972, 250(2), 142-147.
- 47 P. F. Conforti and B. J. Garrison, *Chem. Phys. Lett.*, 2005, **406**(4–6), 294–299.
- 48 V. Malatest and K. U. Ingold, *Tetrahedron Lett.*, 1973, 14(35), 3307– 3310.
- 49 V. Rehak, F. Novak, J. Kuncicky and I. Cepcians, *Tetrahedron Lett.*, 1970, **11**(23), 1967–1970.
- 50 J. Kopecek, J. Polym. Sci., Part A: Polym. Chem., 2009, 47(22), 5929-5946.
- 51 M. D. Lechner, J. Serb. Chem. Soc., 2005, 70(3), 361-369.
- 52 N. Al-Manasir, K. Z. Zhu, A. L. Kjoniksen, K. D. Knudsen, G. Karlsson and B. Nystrom, J. Phys. Chem. B, 2009, 113(32), 11115–11123.