A Journal of the Gesellschaft Deutscher Chemiker

Angewandte International Edition Chemie

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## Accepted Article

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**To be cited as:** *Angew. Chem. Int. Ed.* 10.1002/anie.201708857
*Angew. Chem.* 10.1002/ange.201708857

**Link to VoR:** http://dx.doi.org/10.1002/anie.201708857
http://dx.doi.org/10.1002/ange.201708857

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10.1002/anie.201708857

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# Tuneable Transient Thermogels Mediated by a pH- and Redox-Regulated Supramolecular Polymerization

Daniel Spitzer,[a] Leona Lucas Rodrigues,[a] David Straßburger,[a] Markus Mezger,[b] Pol Besenius*[a]

**Abstract:** We present a multi-stimuli responsive transient supramolecular polymerization of ß-sheet encoded dendritic peptide monomers in water. The glutamic acid and methionine containing amphiphiles undergo a glucose oxidase-catalyzed, glucose-fueled transient hydrogelation in response to an interplay of pH- and oxidation-stimuli, promoted by the production of reactive oxygen species (ROS). By adjusting the enzyme and glucose concentration we tune the assembly and the disassembly rates of the supramolecular polymers, which dictate the stiffness and transient stability of the hydrogels. The incorporation of triethylene glycol chains introduces thermoresponsive properties to the materials. We further show that repair enzymes are able to reverse the oxidative damage in the methionine-based thioether side chains. Since ROS play an important role in signal transduction cascades, our strategy offers great potential for applications of these dynamic biomaterials in redox microenvironments.

A key feature of living systems is their ability to adapt transient non-equilibrium states and thereby regulate structural and functional states with exceptional spatio-temporal control. The materials, polymer science and systems chemistry communities have pursued a variety of avenues to mimic such complex higher-order assemblies using synthetic man-made building blocks.[1] The successful integration of feedback-driven or multiple coupled equilibria into supramolecular self-assembly processes has led to non-equilibrium kinetically controlled processes and dissipative self-assembled materials.[2] The large majority of these systems relies on a catalyzed reaction that induces a change in the hydrophobic/hydrophilic balance of the supramolecular building blocks. For example, George and co-workers have shown that an enzyme-catalyzed and nucleoside triphosphate-fueled system is able to show a transient change in the helicity of supramolecular polymers.[3] The Hermans laboratory has disclosed a strategy to keep a fueled supramolecular polymerization in a non-equilibrium state, when operated in a reactor that continuously removes waste products of the enzyme catalyzed process.[4] Using short hydrophobic oligopeptide hydrogelators, Ulijn,[5] Walther,[6] and Miravet[7] have reported enzyme catalyzed transient hydrogel assemblies with a tuneable time domain. The connection of the molecular stimuli to a kinetically controlled reaction thus leads to programmable and autonomous transitions in adaptive soft materials. The glucose oxidase (GOx) catalyzed oxidation of β-D-glucose to gluconolactone and concomitant reduction of molecular oxygen to hydrogen peroxide is a powerful tool to address responsive materials that operate in both a pH and redox microenvironment.[8] The hydrolysis of lactone derivatives on their own has been used to trigger pH-responsive multi-component assemblies.[9] In redox-responsive molecular and polymeric materials the incorporation of thioether functional groups has been a promising approach, since the oxidation to the sulfoxide species generates a large increase in hydrophilicity.[10] This shift induces water solubility and a triggered disassembly of the supramolecular structures. Here, we propose to use the GOx catalyzed and glucose fueled release of protons coupled with the production of $H_2O_2$, in order to simultaneously generate two different chemical stimuli. In the ß–sheet encoded glutamic acid and methionine containing amphiphiles (Figure 1), these trigger molecular changes on two different time scales and the resulting kinetic differentiation induces transient states with tuneable lifetimes in an autonomous supramolecular polymerization set-up, where we also investigate the impact on the formation of a stimuli-responsive gel.[11]

We have previously reported a range of dendritic $C_3$-symmetric peptide amphiphiles that respond to pH and ionic strength and self-assemble into one dimensional (1D) nanorod-like supramolecular polymers in water.[12] We have focused on the use of alternating sequences of hydrophobic and hydrophilic

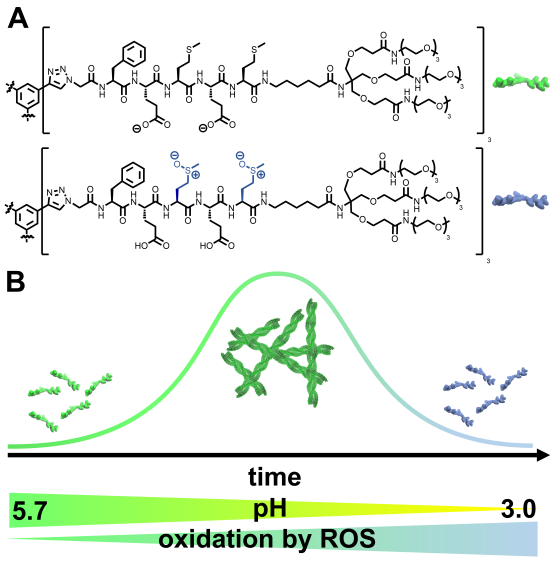


**Figure 1.** A) Molecular structures of the ß–sheet encoded dendritic peptide amphiphile **I** and its oxidized form **II**; B) Schematic representation of the pH-driven supramolecular polymerization and the oxidation-triggered disassembly.

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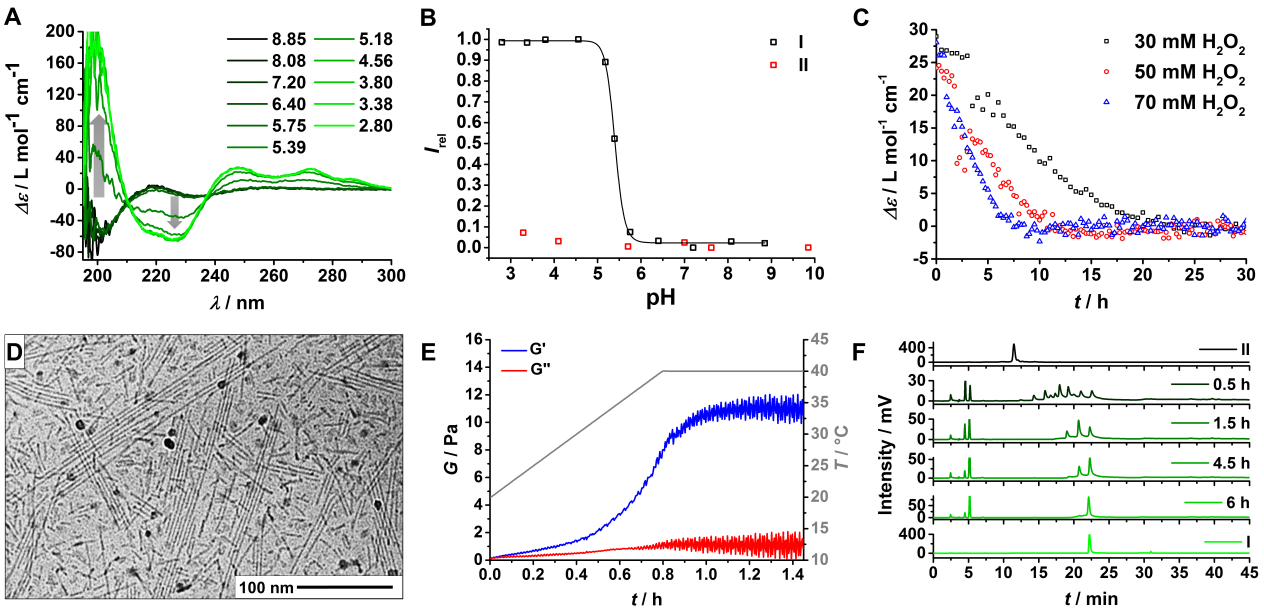


**Figure 2.** A) pH dependent CD spectra for **I** (60 µM in 10 mM phosphate buffer); B) Normalized CD data for 60 µM solutions of **I** and **II** in 10 mM phosphate buffer at λ = 220 nm. Dimensionless degree of aggregation is set to 1 for the fully polymerized state and to 0 for the monomeric state; C) Probing the oxidation of **I** to **II** (60 µM, 40 °C) over time in the presence of varying amounts of $H_2O_2$, by monitoring the intensity of the CD-band at λ = 265 nm; D) Cryo-TEM of **I** (2.5 mg·mL$^{-1}$ at pH 3.0, 10 mM TRIS); E) Rheological temperature dependent time sweeps of **I** (7 mg·mL$^{-1}$ in $H_2O$ pH 3.00, containing 50 mM glucose, with a constant frequency of 1 Hz). F) Analytical RP-HPLC chromatograms showing the enzymatic reduction of **II** to **I**, accompanied with a hydrophobic shift in retention time followed at λ = 210 nm over time. Reduction conditions: 60 µM **II**, 15 mM DTT, 8 µg·mL$^{-1}$ MSRA, 8 µg·mL$^{-1}$ MSRB2, 20 mM TRIS-buffer, pH 7.4, 40°C.

amino acids and shown that they are strong ß-sheet directing supramolecular units.[12] Here, we report the use of a pentapeptide sequence FEMEM where the pH-switchable glutamic acid (E) and the redox-responsive methionine (M) amino acids result in multi-stimuli responsive properties. Using a convergent synthetic approach, we coupled an azido glycine terminal pentapeptide, bearing a hexyl spacer and triethylene glycol functionalized Newkome-type dendron,[13] to 1,3,5-triethynylbenzene using Cu(I)-catalyzed azide-alkyne cycloaddition chemistry.[14] After acid deprotection, the $C_3$-symmetric amphiphilic monomer **I** (Figure 1) was obtained in four synthetic steps. The detailed synthetic procedures and material characterization are provided in the supplementary information.

We first investigated the pH-dependent self-assembly process of **I** in 10 mM aqueous phosphate buffer by circular dichroism (CD) spectroscopy (Figure 2A). At neutral pH = 7.2, only weak CD bands at λ = 202 nm and λ = 218 nm are observed, suggesting the presence of molecularly dissolved species, which is further supported by negative stain transmission electron microscopy (TEM) images (Figure S4). Repulsive Coulomb interactions of the deprotonated glutamic acid side chains in the pentapeptide sequence hamper the ß–sheet directed formation of supramolecular nanorods. Upon decreasing the pH, positive CD bands appear at λ = 200 nm, 248 nm, 273 nm and one negative band at λ = 225 nm. When monitoring the intensity of the strong negative CD band, a sharp transition at pH 5.4 is observed, which is indicative of the formation of ordered supramolecular polymers. In agreement with our previously reported investigations, the strong thermodynamic driving force for self-assembly leads to a pronounced shift of the apparent p$K_a$ values of the glutamic acid side chains.[15] The formation of ordered 1D supramolecular polymers, with a thickness of 5.7 nm and average length of 130 nm, was shown by *cryo*TEM and TEM images in acidic pH (Figure 2D and Figure S4). To determine the intermolecular dimensions of the aggregates, we performed X-ray scattering. A strong scattering peak was observed at 13.3 nm$^{-1}$, corresponding to a real space distance of $d$ = 0.47 nm (Figure S13). This peak was assigned to the intermonomer distance and is in agreement with our previously published molecular dynamics simulations, which suggested values of 0.45 nm.[12a]

Importantly, when selectively oxidizing the methionine residue of building block **I** into the sulfoxide species **II** using $H_2O_2$, we did not observe any formation of supramolecular polymers by CD or TEM, even at low pH (Figures 2B, 2C, S2 and S5). The increased hydrophilicity of the sulfoxide functional group compared to the thioether precursor is accompanied by a strong increase of the dipole moment and a downfield shift of the NMR signal of the methyl protons next to the sulfur atom from 2.1 ppm to 2.5 ppm (Figure S6).[10e, 10h] In addition, signal broadening is observed due to the formation of a mixture of six racemic sulfoxide stereocenters. It is important to note that the switch in hydrophilicity is a well-known phenomenon used for oxidation-responsive thioether containing amphiphilic systems.[10]

A straightforward way to follow the reduction of the sulfoxide (i.e. the repair process) is given by analytical reversed-phase HPLC tracing, which shows a strong shift towards higher elution times, due to the increase in hydrophobicity after reduction of the sulfoxide bearing amphiphile **II** to the thioether functional **I** (Figure 2F).[16] We used dithiothreitol (DTT) as stoichiometric reducing agent and a mixture of the enzymes methionine sulfoxide reductase A (MSRA) and B2 (MSRB2), specific for the *S*- and *R*-methionine sulfoxide diastereomers, respectively. We followed the conversion of **II** into **I**, at 40 °C over time. Between 30 min and 4.5 h the HPLC chromatogram shows the appearance of

10.1002/anie.201708857




numerous hydrophobic species, which we assign as partially reduced derivatives of **II**. After 6 h the chromatogram shows one reduced species, with the same retention time as the thioether derivative **I**. In addition, the consumption of DTT ($t_R$ = 4.8 min) into its oxidized disulfide form ($t_R$ = 5.2 min) is also shown by HPLC. It should be noted that under the standard MSRA/MSRB2 reaction conditions at pH 7.4, amphiphile **I** does not self-assemble, but instead remains in its molecularly dissolved state. Since the conditions for the pH-dependent polymerization are incompatible with MSRA/MSRB2, we employed a derivative **IV** (Figure S3 and S19), where the glutamic acids were swapped for phenylalanine groups. Its reduced form **III,** with the ß-sheet encoded amino acid sequence FMFM, does not show pH-dependent supramolecular polymerization. Remarkably the reduction of **IV** to **III**, under conditions where **III** self-assembles, proceeds on a similar time scale as for the amphiphile **I** and is complete after 6 h (Figure S9). This highlights the high robustness of the oxidation damage repair and substrate promiscuity of this class of reductases.[17]

In many of our previous investigations, we relied on dendritic tetraethylene glycol chains to enhance the water solubility of the supramolecular polymers.[12, 18] We further relied on their steric demand and high chain flexibility in order to introduce repulsive forces in the supramolecular polymerization process, which avoids the formation of infinitely long polymers, a process we usually refer to as frustrated growth. Inspired by the large body of work on thermoresponsive materials, with characteristic lower critical solution temperature (LCST) properties,[19] we introduced shorter triethylene glycol chains. These give rise to a thermally induced dehydration in a biologically relevant temperature range from 30 - 40 °C. Hence, we performed temperature-dependent rheological studies of our supramolecular polymers at acidic pH. Using tube inversion tests, we estimated the critical gelation concentration of **I** to be slightly below 0.7 wt %. We first conducted oscillatory shear rheology experiments with an angular frequency range from 0.01 - 10 rad·s$^{-1}$ at 20 °C and 40 °C, to show the frequency independence of the storage (G') and loss moduli (G'') (Figures S10-S11). We then used a constant frequency of 1 Hz to perform time sweeps at 20 °C at a concentration of 0.7 wt % of **I** at pH 3.0. The solution remained completely liquid and any indication of hydrogelation was absent at this temperature. However, upon slow heating to 40 °C the solution became viscous and the storage modulus (G') shows a sharp increase while the loss modulus (G'') remains constant, indicating the formation of thermoresponsive hydrogels (Figure 2E).

Using the described multi-stimuli responsive properties, we were eager to investigate the potential of transiently stable thermally induced hydrogels, with a tuneable lifetime mediated by the pH-triggered assembly and oxidative stress promoted disassembly of the supramolecular polymers. To this end, we used the enzyme glucose oxidase since it provides all the requirements to perform kinetic investigations of a fully autonomous supramolecular system: (1) it catalyzes the oxidation of β-D-glucose to gluconolacton which slowly hydrolyzes to gluconic acid reaching a buffering point determined by its p$K_a$ = 3.86. This pH drop in turn triggers the supramolecular polymerization of **I** by deactivating the repulsive electrostatic forces of the glutamic acid based carboxylic acid moieties, accompanied by hydrogelation at temperatures T > 30 °C. (2) While oxidizing β-D-glucose, molecular oxygen is reduced to

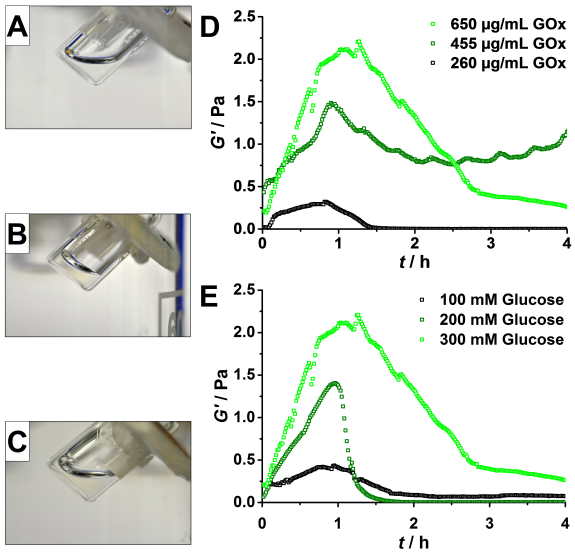


**Figure 3.** Transient hydrogelation of a solution of **I** (7 mg·mL$^{-1}$) in $H_2O$ with 300 mM glucose and 650 µg·mL$^{-1}$ GOx at 40°C: A) 30 min B) 3 h C) 8 h; D) Time sweeps at 1 Hz, 40 °C of **I** (7 mg·mL$^{-1}$) in $H_2O$ containing 300 mM glucose, 100 mM NaCl and various amounts of GOx starting at pH 5.7; E) Time sweeps at 1 Hz, 40 °C of **I** (7 mg·mL$^{-1}$) in $H_2O$ containing 650 µg·mL$^{-1}$ GOx, 100 mM NaCl and various amounts of glucose starting at pH 5.7.

hydrogen peroxide. Compared to the pH decrease, $H_2O_2$ acts on a considerably slower time scale by oxidizing methionine to the more hydrophilic methionine sulfoxide and thereby leading to a delayed disassembly of the non-equilibrium supramolecular polymer state. Thus, by adjusting the concentration of GOx and its fuel glucose at 40 °C, we aimed to tune the time-window for the transiently stable hydrogels (Figure 3), as also shown in elegant work on pH-responsive gels by the Walther group.[20] First, we investigated the influence of the GOx concentration on the transient hydrogelation while keeping a constant glucose concentration of 300 mM (Figure 3D). Starting from 260 µg·mL$^{-1}$, we observed an increase of the storage modulus within approximately 50 min to 0.3 Pa, which decreases again to the initial values after 90 min. By increasing the enzyme concentration to 650 µg·mL$^{-1}$ time sweep measurements showed a much stronger increase of the storage modulus within the first 45 min to reach a maximum value of 2.1 Pa at around 70 min, which slowly decreases over the period of 180 min. This confirms the successful formation of a transient weak hydrogel which is stable for several hours at 40 °C, as also demonstrated by tube inversion tests (Figure 3A-C). From these data we conclude that by increasing the enzyme concentration, glucose is consumed faster leading to a faster drop in pH (Figure S14), which increases the rate of hydrogelation and leads to the formation of a stronger hydrogel. Eelkema and van Esch have reported similar findings, whereby the overall rate of gelation can be enhanced using acid and nucleophilic catalysts. This leads to an increased formation of defects in the gel forming fibres, resulting in branching fibrillary structures and a strengthening of the gels.[2d,21] At the highest GOx concentration, destabilization of the hydrogel is observed after 110 min, due to $H_2O_2$ promoted oxidative damage of the monomer building blocks inducing the depolymerization of the supramolecular nanofibres, which subsequently results in a

decrease of the storage modulus. In comparison, at 260 μg·mL$^{-1}$ and 455 μg·mL$^{-1}$ GOx concentrations, the mechanical stability of the peptide hydrogels is significantly reduced and the oxidative damage proceeds much faster, the combination of which compresses the time-domain of the transient hydrogels. In order to confirm these observations, we performed fuel dependent kinetic rheology experiments. At a constant GOx concentration of 650 μg·mL$^{-1}$, we varied the glucose concentration from 100 mM to 300 mM (Figure 3E). In agreement with the previous experiments, increasing the glucose concentration leads to an enhancement of the catalysis rate and the formation of a stronger transient hydrogel with an extended time-domain. We were thus able to show, that by varying the enzyme and glucose concentrations, an autonomous supramolecular hydrogelation set-up is obtained with programmable lifetimes and tuneable mechanical properties.

In summary, we present glutamic acid and methionine containing dendritic peptide monomers, that are able to undergo multi-stimuli responsive ß–sheet self-assembly in water. Using a glucose oxidase catalyzed, glucose fueled interplay of pH- and oxidation-triggers transiently stable supramolecular polymers are obtained. Thermoresponsive side chains are able to induce the formation of physical hydrogels at temperatures T > 30 °C and peptide contents of 0.7 wt %. By adjusting the enzyme and glucose concentration we tune the kinetics and lifetime of the supramolecular polymers, which dictate the stiffness and time-domain of the transient hydrogels. Furthermore, we show that methionine sulfoxide reductase repair enzymes are able to reverse the oxidative damage in the thioether side chains of the monomers. Since reactive oxygen species play an important role in signal transduction cascades, our strategy offers great potential for applications of these dynamic responsive biomaterials in redox microenvironments.[22]

## Acknowledgements

We thank Willi Schmolke for help with the rheology and Prof. Sebastian Seiffert for critical reading of the manuscript.

**Keywords:** supramolecular chemistry in water • transient self-assembly • redox regulation • dynamic materials • kinetic control

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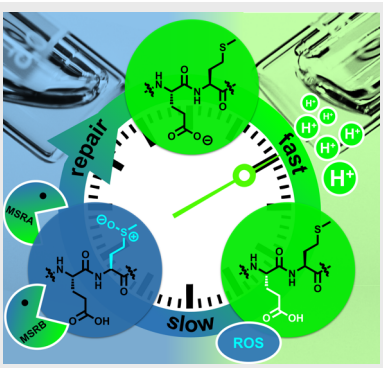
Layout 1:

## COMMUNICATION

ß–sheet encoded dendritic peptide monomers containing glutamic acids and methionines undergo a transient supramolecular polymerization, in response to an interplay of pH- and oxidation-stimuli, promoted by the production of reactive oxygen species. By adjusting the glucose oxidase enzyme und glucose fuel concentrations, the assembly rates and lifetime of the supramolecular polymers are tuned, which dictate the stiffness and transient stability of the thermoresponsive hydrogels.

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**Tuneable Transient Thermogels Mediated by a pH- and Redox-Regulated Supramolecular Polymerization**