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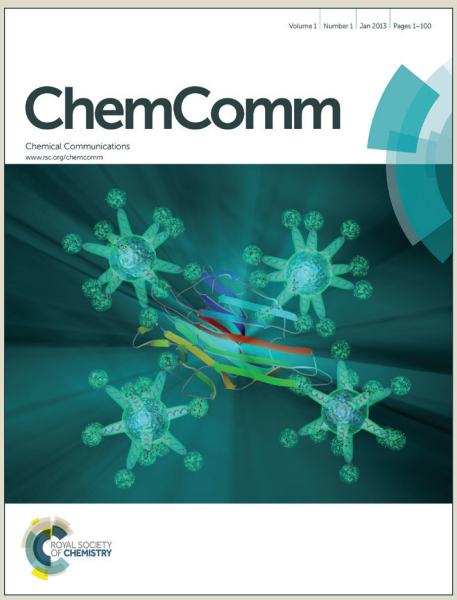

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ARTICLE TYPE

Rational Design of Peptide-based Hydrogel Responsive to H_2S

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The development of hydrogels that are responsive to external stimuli in a well-controlled manner is important for numerous biomedical applications. Herein we reported the first example of a hydrogel responsive to hydrogen sulphide (H_2S). H_2S is an important gasotransmitter whose deregulation has been associated with a number of pathological conditions. Our hydrogel design is based on the functionalization of an ultrashort hydrogelating peptide sequence with an azidobenzyl moiety, which was reported to react with H_2S selectively under physiological conditions. The resulting peptide was able to produce hydrogels at a concentration as low as 0.1% wt. It could then be fully degraded in the presence of excess H_2S. We envision that the novel hydrogel developed in this study may provide useful tools for biomedical research.

Developing new materials that undergo detectable change in response to biologically-relevant stimuli is a key challenge in the biomedical field.[1] One promising approach is to use the self-assembly of small building blocks to rationally design such "smart" materials.[2] Peptides that self-assemble into fibers to form hydrogels are of particular interest because they are normally biocompatible, biodegradable and non-immunogenic materials.[3] Peptide-based hydrogels, which are mostly made of water molecules (typically 99% or above) being held together by physical or chemical network of molecular fibers, have proven useful for a wide range of biomedical applications.[4] Their excellent deformability and their ability to efficiently encapsulate hydrophilic molecules make them ideal carriers for controlled drug delivery.[5] Their 3D structures, on the other hand, offer promising opportunities as cell structure scaffold or in tissue engineering applications.[6] As a result, there are numerous examples of peptide-based hydrogels that respond to simple physical stimuli such as pH, temperature, ionic strength, light ions and enzymes.[7] In comparison, aqueous hydrogels that respond to small molecules, in particular biologically relevant molecules, have proven more difficult to rational design and have so far yielded very few examples.[8] The reason could be due to the difficulty in accessing functional molecules that can selectively react with stimuli in complex biological environments.

Recently, ultrashort peptide hydrogelators have attracted strong interest due to their ease of preparation. Typically rich in phenylalanine, these short sequences often contain an aromatic moiety at their *N*-terminus such as Fmoc, pyrene or naphthalene, that favors fiber-like self-assembly of the peptides via a combination of hydrophobic and π-π stacking interactions.[9] Compared to longer fiber-forming peptides based on *α*-helix, *β*-sheet or again *β*-hairpin conformations, ultrashort peptide gelators are more versatile due to the possibility of introducing a wide range of responsive and functional aromatic molecules into the building block.[10] Based on this concept, a number of stimuli-responsive hydrogels have been elegantly designed.[11] For example, Hamachi *et al.* developed hydrogels that responds to hydrogen peroxide (H_2O_2) by introducing boronoaryl-methoxycarbonyl moiety as the *N*-terminus capping group.[12] Yang *et al.* developed a selenium containing peptide hydrogel which can reversibly switch between solution and gel under redox stimuli.[13]

In this study, we developed a novel hydrogel that is responsive to hydrogen sulphide (H_2S) by incorporating an azidobenzyl-carbamate group at the *N*-terminus of a typical ultrashort hydrogelator sequence. Hydrogen sulphide is a gaseous molecule that has recently been recognized as the third gasotransmitter after nitric oxide (NO) and carbon monoxide (CO).[14] It has been shown to be involved in various important physiological processes such as vasodilatation, anti-inflammation and regulation of cell growth.[15] It plays an important role as protector in the cardiovascular system and as antioxidant against oxidative stress.[16] In addition, abnormal levels of H_2S have been associated with a number of pathological diseases including Alzheimer's disease, Down syndrome, diabetes, hypertension and liver cirrhosis.[17] Currently a number of H_2S responsive materials have been developed. These materials are mainly designed for detecting H_2S, and their physical properties such as optical activity, conductivity, amperometry or oscillation frequency will undergo change when exposed to H_2S.[18] Nevertheless, to our best knowledge, no material has been found to undergo phase change when treated with H_2S. We envision that such H_2S responsive material will find useful biomedical applications such as controlled drug delivery or preparation of dynamic scaffolds for tissue engineering.

Herein we present the first effort to create a peptide-based hydrogel that degrades into a soluble peptide upon specific reaction with H_2S. As shown in Figure 1, H_2S is expected to reduce the aryl-azide group to an amine moiety. The unstable p-aminobenzyl moiety can undergo self-immolation through 1,6-elimination, which will lead to the complete dissociation of the *N*-terminus aromatic group from the peptide sequence. This reaction is commonly used for the creation of H_2S fluorescent probes and has proven to be highly specific to H_2S even in the presence of other biological reductants. [19]

A total of five azidobenzyl containing peptides, i.e. AzBz-FFG (**1**), AzBz-FFF (**2**), AzBz-FFL (**3**), AzBz-FFE (**4**) and AzBz-FFR (**5**) were prepared in this study (Figure 1A). Various amino acids were selected as the C-terminus residue to test the effect of neutral (1), hydrophobic (2), aromatic (3), acidic (4) and basic (5)

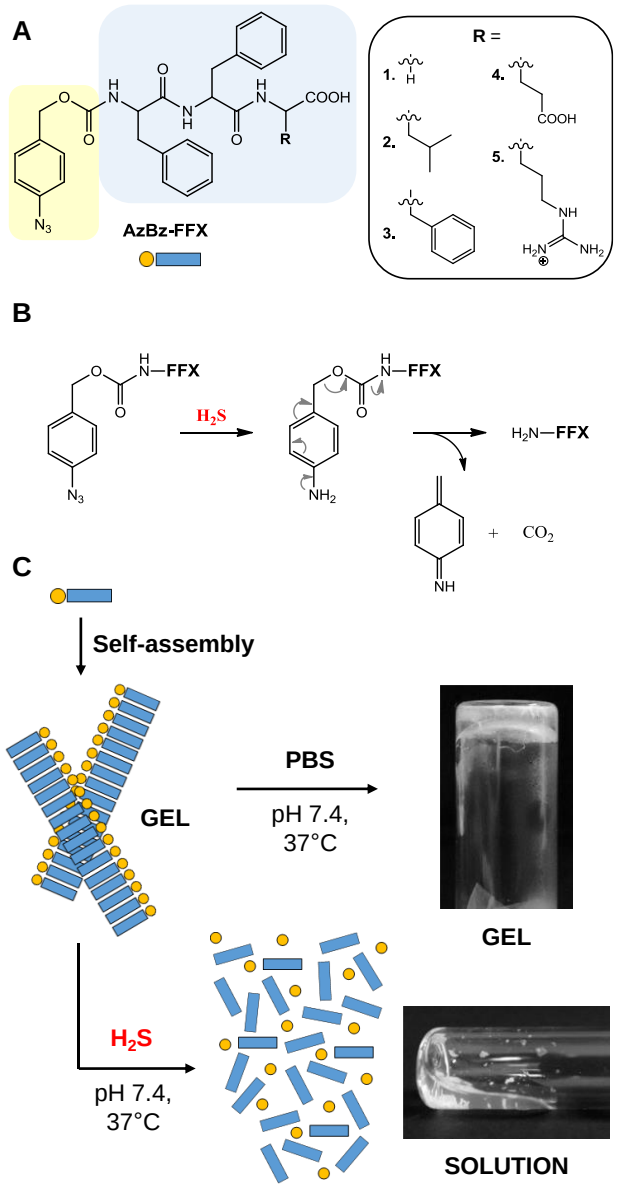

Fig. 1 (A) Structure of azidobenzyl containing peptides **1**-**5**. (B) Mechanism of peptide degradation in the presence of H_2S. (C) Schematic representation of the peptide self-assembly and responsivity towards H_2S. The pictures were taken using a freshly made hydrogel sample (200 μL) containing 0.5% wt of peptide **1** in pure water + 5% DMSO and incubated with either 40 μL of H_2S (1.22 M, 27 eq.) in PBS (pH = 7.4) (bottom) or an equivalent volume of PBS (pH = 7.4) as control (top right) at 37 ℃ for 2 hours.

groups on hydrogel formation. The tripeptide fragments were first synthesized following Fmoc-based solid phase strategy. At the same time, 4-azidobenzyl 4-nitrophenyl carbonate was synthesized via a two-steps synthesis from commercially available 4-aminobenzyl alcohol. Subsequently, 4-azidobenzyl 4-nitrophenyl carbonate was coupled to the peptides to yield azidobenzyl containing peptides **1**-**5**. The five peptides were then purified by High Pressure Liquid Chromatography (HPLC) and characterized by ESI-MS spectrometry.

The self-assembling properties of these five building blocks were systematically tested by dissolving the peptide powder in DMSO and then diluting it rapidly with a high volume of water ($V_{(DMSO)}$:$V_{(water)}$ 1:19). Among the five peptides, only peptide **1**

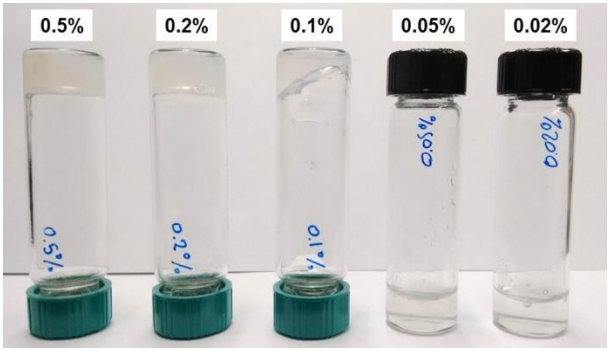

Fig. 2 Critical gelation concentration for peptide **1** in pure water + 5% DMSO. The percentages correspond to the mass concentration of **1**.

was found to form a hydrogel. Peptide **2** formed a viscous solution while peptide **3** formed a relatively clear solution with some precipitate. Peptides **4** and **5** appeared to precipitate out (Figure 1 & S8). In the case of peptide **1**, the gel formed within seconds. We reckon that maintaining a delicate balance between hydrophobic and hydrophilic group is critical for the self-assembly of the peptide into fibrous network to form the hydrogel.[20] If the balance is disturbed by increasing hydrophobicity or hydrophilicity, the self-assembly process of a peptide may be disrupted and the gel formation would be interfered. Using the rapid dilution method described above, the critical concentration of gelation for peptide **1** was determined to be approximately 0.1% wt (Figure 2). TEM imaging of a gel sample containing 0.5% wt of peptide **1** confirmed the presence of a network of entangled fibers, typically ranging from 20 to 60 nm in diameter, which is characteristic of the formation of stable hydrogels (Figure 3A).[21]Next, we studied the response of the hydrogel to the addition of hydrogen sulphide. H_2S solutions were generated via dissolution of $Na_2S.xH_2O$ and the resulting concentrations of sulphide species were determined via UV measurement at 230 nm as described in the literature.[22] We conducted a simple experiment by incubating a sample of hydrogel with 27 equivalents of H_2S in PBS (pH = 7.4) at 37 ℃ for two hours. The gel degraded to a clear solution containing white aggregates (Figure 1C). Similar white aggregates were previously observed in the literature for oxidation-sensitive hydrogels.[23] Since the free tripeptide FFG is soluble in water under these conditions, the white precipitate observed might be associated with the formation of 3-imino-6-methylene-1,4-cyclohexadiene as an insoluble by-product of the reaction. In contrast, the control sample incubated with water only remained as a gel under the same conditions (Figure 1C). It is also noted that the hydrogels derived from **1** were found to be pH sensitive and readily dissolved under basic conditions. To avoid interference from pH changes, extra care was taken to ensure that each experiment presented in this study was carried out at a controlled pH of 7.4.

We then characterized the gel degradation via H_2S using transmission electron microscopy (TEM) techniques. In order to avoid the interference from the salts, we use pure water for the experiments. As shown in Figure 3, TEM pictures of the gel degraded by H_2S showed only amorphous organic materials (Figure 3C), whereas the control sample incubated with water under the same conditions showed the same nanofiber network as the sample prior to incubation (Figure 3B). The results unambiguously proved that the collapse of the peptide hydrogel is to be attributed to H_2S rather than other factors, e.g. temperature.

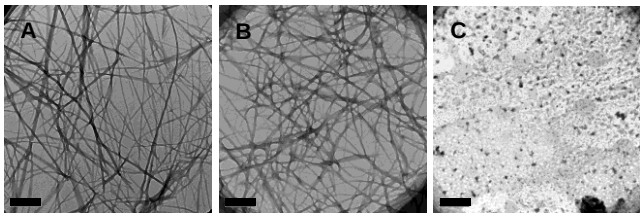

Fig. 3 TEM images of a 100 µL gel smaple of peptide 1 (0.5% wt) in pure water + 5% DMSO (A) before and (B) after overnight incubation at 37 ℃ in the presence of 25 µL pure water or (C) overnight incubation at 37 ℃ in the presence of 25 µL of H_2S (0.82 M, 56eq.) in pure water (scale bar = 0.5 nm).

In order to further characterize the "gel to solution" phase change, degradation of peptide **1** by hydrogen sulphide in solution was quantified using HPLC. The degradation behavior of peptide **1** by various equivalents of H_2S was studied first (Figure 4A). It was found that 9 equivalents of H_2S were sufficient to degrade the vast majority of peptide **1** when incubated at 37 ℃ after 16 h.As expected, the reaction proceeded less efficiently at 25 ℃ and 33 equivalents of H_2S were the needed to reach a similar result. Subsequently a time-lapse experiment was carried out to estimate the kinetic of the reaction between peptide **1** and H_2S. The results showed that peptide **1** in solution could be completely degraded after approximatively one hour when incubated with 46 equivalents of H_2S at 37 ℃ (Figure S7). HPLC spectra of a solution of peptide **1** before and after incubation with H_2S can be found in the Supporting Information (Figure S8). Results indicated that the major product after H_2S treatment was the tripeptide FFG.

Finally the responsivity of hydrogels towards various amounts of H_2S was quantified using a method similar to reported literature.[12] Briefly, small domes of hydrogel were spotted onto a glass slide, and 5 µL drops containing the appropriate concentration of analytes were deposited onto the gels (Figure 4B). Addition of 40 equivalents of H_2S resulted in the complete collapse of the hydrogel sample within 1 hour of incubation at 37 ℃, while it took twice this time for 15 equivalents of H_2S to fully degrade a similar gel sample. Further incubation did not lead to further degradation of the other gels. Interestingly, when the same experiment was carried out at 25 ℃, only minor degradation of the gel incubated with 40 equivalents of H_2S was observed, while the other gels remained intact (Figure S9). These results are in accordance with the results obtained in solution phase, showing that the degradation of peptide **1** is less efficient at 25 ℃. Difference in the concentration of H_2S required to degrade peptide **1** was observed between solution and gel phase. This can be justified by the more difficult diffusion of H_2S molecules in the hydrogel phase.

Because the action mechanism of H_2S is based on reducing the azidobenzyl group into the corresponding amine, we wanted to demonstrate the selectivity of our gel versus another biologically reductant. Glutathione (GSH) was chosen because it is well-known as the major reducing species produced by the cells. As seen in Figure 4, the stability of peptide **1** remained unaffected by the addition of GSH in both solution and hydrogel phase, demonstrating good selectivity of our peptide building block towards H_2S.

The concentration of H_2S in living biosystems ranges from nano to millimolar across various physiological and pathological states.[24] The sensitivity of hydrogels in our study is considered to be not high at the moment. Firstly, we reckon that the sensitivity

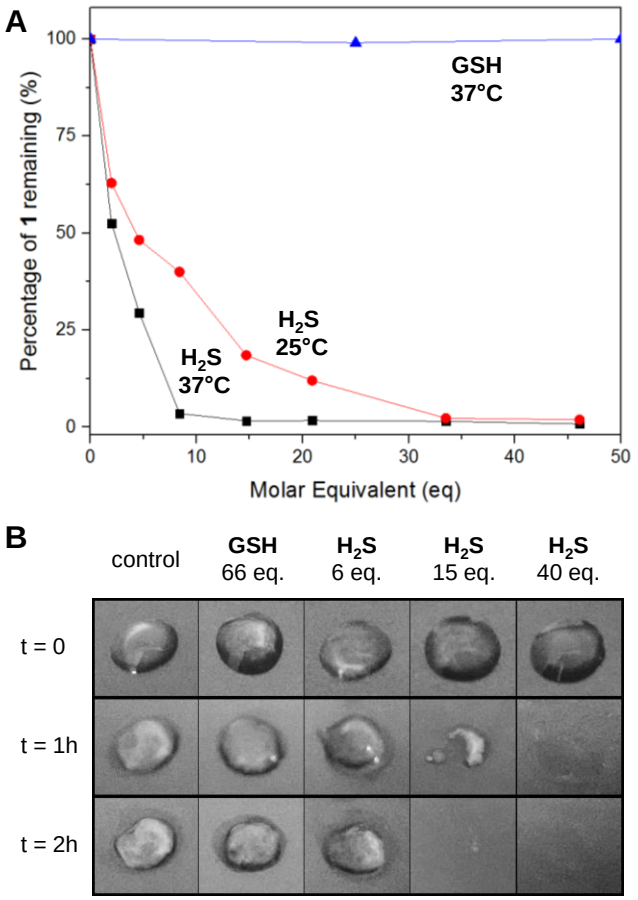

Fig. 4 (A) Degradation of a solution of peptide **1** (0.33 mM) upon addition of various equivalents of H_2S or GSH (22 µL) in PBS (1 M, pH = 7.4). Incubation was carried out for 16 hours at the indicated temperatures. Percentage of peptide **1** remaining was characterized by HPLC analysis and calculated using the area of integration of the peak corresponding to **1** at 254 nm. (B) Photographs of peptide **1** hydrogel (0.4% wt) in pure water + 5% DMSO before and after addition of various equivalents of H_2S or GSH. The experiment was carried out on 20 µL hydrogel samples spotted on a glass plate. H_2S or GSH were added in the form of a 5 µL drops of solutions (0.18 M, 0.43 M, 1.22 M and 2 M) in PBS at pH = 7.4. Incubation was carried out at 37 ℃ for the indicated amounts of time. Gels spots incubated with high levels of H_2S collapsed and were washed away during the washing step.

might be improved by longer incubation of H_2S. Secondly, the degradation reaction is not catalytic. It requires one equivalent of H_2S to degrade one equivalent of peptide. With the critical gel concentration (CGC) of peptide 1 at 0.1%, 1.8 mmol of H_2S (1 equivalent) will be required to degrade the peptide completely. To improve the sensitivity, the peptide sequence can be elongated with appropriate amino acid residues to decrease the CGC, thereby decreasing the required amount of H_2S. In addition, we reckon that the sensitivity can be improved by developing hydrogel nanoparticles which have larger surface to volume ratio. Our group is currently developing methods to fabricate hydrogel nanoparticles for H_2S-responsive delivery applications.

In summary, we have developed the first example of a H_2S-responsive hydrogel by incorporating an aryl-azido moiety into a hydrogelating peptide sequence. The hydrogel was shown to form at low concentration of the building block and to selectively collapse in the presence of excess hydrogen sulphide. Exploration of the potential biological applications for this H_2S-responsive

hydrogel is currently underway. Despite the concentration of H_2S being high at the moment, we believe that this study presents a convincing proof of concept which can, after optimization, have great implications for the development of novel "smart" materials for biomedical applications.

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Notes and references

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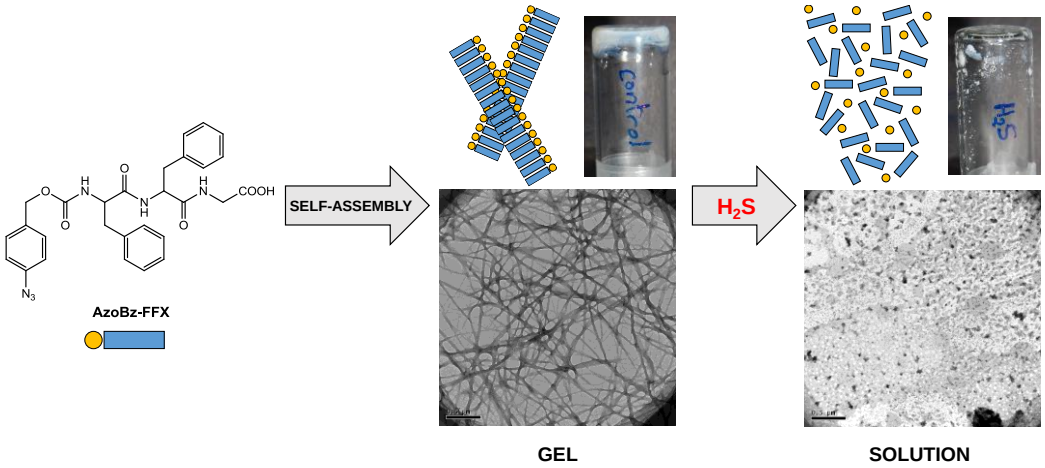

By introducing an azidobenzyl moiety into an ultrashort hydrogelating peptide, we reported on the design of a novel hydrogel that could be selectively degraded by H_2S under physiological conditions.