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Formation of Uniform Multi-Stimuli-Responsive and Multiblock Hydrogels from Dialdehyde Cellulose

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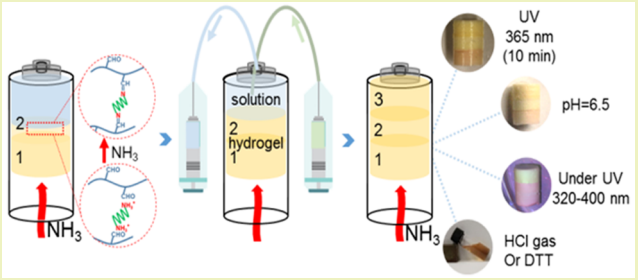
Supporting Information

ABSTRACT: Multi-stimuli-responsive and structured hydrogels represent promising materials with a broad application spectrum, such as drug delivery, sensors, and bionic machinery. However, the preparation of hydrogels starting from highly reactive compounds still needs an efficient approach for homogeneous distribution of each component within hydrogels. In addition, a method for *in situ* preparation of multiblock hydrogels is still lacking. Herein, we report the formation of uniform, multi-stimuli-responsive, and multiblock hydrogels via a novel, simple, but very efficient method by aerating ammonia gas into the solution of dialdehyde cellulose (DAC) with cross-linkers containing diamine groups. Obtained hydrogels exhibited uniform microscopic and chemical structure. Due to abundant aldehyde groups on DAC chains, diverse diamines can be used for the preparation of distinct stimuli-responsive hydrogels. For instance, 1,6-hexanediamine dihydrochloride and cystamine dihydrochloride formed hydrogels responsive to pH values as well as redox conditions. Moreover, the process of aerating ammonia gas (NH_3 gas) is controllable, which allows the *in situ* formation of multiblock hydrogels. By using cystamine dihydrochloride, aminoethyl rhodamine spiroamide, and fluorescein isothiocyanate as reaction counterparts, 3-block hydrogels were prepared, and each block was specifically responsive to factors such as pH variation, redox condition, and/or UV illumination.



KEYWORDS: *Hydrogel, Multiblock, Responsive, Cellulose, NH_3 gas*

INTRODUCTION

With the establishment of the first synthetic hydrogels by Wichterle and Lim in 1954,[1] diverse hydrogels have been developed to be applied in many fields, such as medicine,[2] agriculture,[3] and other industry branches.[4] Because the required functionalities can be realized by the careful predesign and precise control of the chemical components, various functional hydrogels have been prepared and used in the frontier research.[5,6] In the past two decades, the development of hydrogels and their applications are strongly represented by the studies on stimuli-responsive hydrogels. Stimuli-responsive hydrogels can adapt to surrounding environments, as well as change their physical and chemical properties to suit the requirement, such as pH,[7] redox,[8] temperature,[9] light,[10] and electric and magnetic fields.[11] Dong and co-workers used hydrogels based on poly(*N*-isopropylacrylamide), acrylic acid, and 2-(dimethylamino)ethyl methacrylate to design a liquid lens system that allows for autonomous focusing. Such hydrogel lens system could mimic human eyes and easily focus on different distances.[12] Takashima et al. prepared a photo-responsive supramolecular actuator reminiscent of natural muscle with cyclodextrin and azobenzene compounds via host−guest interaction.[13] Miyata et al. used the reversible binding between an antibody and an antigen in a semi-interpenetrating hydrogel network for biomedical applications.[14]

These stimuli-responsive hydrogels were used in various fields that needed delicate control. The demand for the more precise adjustment of the function or structure of hydrogels increased rapidly during the past few years. A uniform chemical structure with the homogeneous distribution of functional groups within the hydrogel should increase the efficiency during the application due to the fulfillment of most functionality. At the same time, adjustable microscopic hydrogel structure, such as hydrogels with multilayers, will provide more feasibilities to include more functions in sequence.[15]

Polymeric hydrogels demonstrate particular advantages due to their wider range of monomers containing diverse functionalities.[2,16] However, the preparation of hydrogels with successively introduced functionalities can be difficult. For this purpose, the gelation process should be controllable, and a sufficient amount of reactive groups should be present within the hydrogels, i.e., along the polymer chains. In addition, the reaction for the introduction of new groups during the

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postmodification should not affect the hydrogel network. Moreover, concerns arise due to the cost of raw materials derived from fossil resources and low biodegradability over the last years.[17,18]

Cellulose, the most common natural polymer on earth, is considered as an inexhaustible raw material for the increasing demand for sustainable and biodegradable products.[19] Due to the good biocompatibility and rich derivatives of cellulose,[20−25] more cellulose-based hydrogels were used recently for drug delivery,[26] antimicrobial wound dressing,[27] and other functional materials with tunable physical and chemical properties.[28,29] Naseri et al. used 50 wt % cellulose nanocrystals to reinforce the sodium alginate and gelatin double cross-linked interpenetrating hydrogels which could be used as a substitute for cartilage.[30] Duan et al. fabricated bilayer hydrogels using chitosan and cellulose/CMC showing shape-changing properties in response to pH-triggered swelling/deswelling.[31] Such hydrogels could be applied in diverse fields, such as biomedicine and biomimetic machines. Thus, with sustainable and excellent biocompatible cellulose-based materials, hydrogels with various functions can be prepared. However, dialdehyde cellulose (DAC) with reactive aldehyde groups along cellulose backbone has not been used for this purpose.

In this work, we present the preparation of smart, multi-stimuli-responsive hydrogels with a successively controllable multiblock structure based on dialdehyde cellulose (DAC) and diamines. DAC was synthesized after the oxidization of microcrystalline cellulose with sodium metaperiodate ($NaIO_4$). The hydrogels were formed constantly and at the same time controllably during the introduction of NH_3 gas into the solution of DAC and diamines. Using 1,6-hexanediamine dihydrochloride (HMDA·2HCl) and cystamine dihydrochloride (AED·2HCl) as reaction counterparts for DAC in water, we prepared novel uniform hydrogels that were responsive to pH and redox conditions. By consequently adjusting the compositions of hydrogels with diverse di-/amine compounds, we could prepare stimuli-responsive hydrogels with microscopic multiblock structure. As an example, 3-block hydrogels were prepared with different functions within each block.

MATERIALS AND METHODS

Materials. Microcrystalline cellulose (MCC), HMDA·2HCl, dithiothreitol (DTT), hydroxylamine hydrochloride, rhodamine, and fluorescein isothiocyanate isomer (FITC) were received from Sigma-Aldrich. $NaIO_4$, ethylene glycol, aqueous hydrochloric acid (HCl, 37% w/w), sodium hydroxide (NaOH), aqueous ammonium hydroxide (28% w/w), and AED·2HCl were purchased from VWR. All chemicals were of analytical grade or higher. Deionized water (conductivity: 0.05 μs/cm) was used throughout the experiments. Aminoethyl rhodamine (AERhB, Figure S3 and S4) was prepared using the method as shown in Supporting Information.[31]

Periodate Oxidation of Cellulose. MCC (1 g) and $NaIO_4$ (1.65 g) were mixed in 50 mL of water at room temperature, which showed a pH value of ∼3.8. Then, the reaction bottle was wrapped with several layers of aluminum foil to keep the system in dark. The periodate oxidation was performed at room temperature under stirring at a speed of 250 rpm for 3 days. At the end of the reaction, the pH value was measured as around 3.1. Ethylene glycol was added to this mixture to quench the residual $NaIO_4$.[32,33] After that, the oxidized cellulose was thoroughly purified via dialysis in water using the dialysis membrane from Thermo Fisher Scientific with a molecular-weight cutoff of 3500 Da. After the dialysis, the DAC suspension was gently stirred at 80 °C in an oil bath for 4 h, before the sample was centrifuged at 14 000 rpm (Thermo scientific Multifuge X3 FR, F15−6·100y) for 30 min to remove residual solid. Then, the supernatant was collected and stored at 4 °C.

Determination of Aldehyde Content by Titration. Before the titration, the pH value of the aqueous DAC solution was adjusted to 3.5 using aqueous HCl solution of 1 mol/L. Then, 10 mL of hydroxylamine hydrochloride solution (5% w/w) was added into the mixture. The pH of the solution was kept at 3.5 by adding NaOH solution (0.05 mol/L) until no decrease of pH was observed. The aldehyde groups content was calculated by the consumption of the aqueous NaOH solution according to[32]

$$\mathrm{DO} = \frac{C_{\mathrm{NaOH}} V_{\mathrm{NaOH}}}{m/162} \quad (1)$$

,where DO is the degree of oxidation of the samples, C_{NaOH} is the concentration of the aqueous NaOH solution, V_{NaOH} is the volume of the used NaOH solution, m is the mass of DAC, and 162 is the molecular weight of repeating unit in cellulose.

Preparation of Hydrogels Using HMDA·2HCl and AED·2HCl. Before the gelation, the solution of HMDA·2HCl (0.5 mL, 1 mol/L) or AED·2HCl (0.5 mL, 1 mol/L) was mixed with DAC solution (2 mL, 52 mg/mL) at room temperature directly. Then, NH_3 gas that was obtained by heating the solution of aqueous ammonium hydroxide at 80 °C in an oil bath was introduced to the solution. A thin hydrogel layer on the top of the solution was first formed at the interface of liquid and gas phase. With the introduction of more NH_3 gas, the hydrogel layer became thicker and thicker, until the whole solution became a white hydrogel.

Disassembly and Reassembly of Hydrogels. Hydrogels were treated by introducing HCl gas which was obtained by heating the solution of aqueous HCl at 80 °C in an oil bath into the closed container for 30 min. During the process, the top part of the hydrogels began to become liquid. With the introduction of more HCl gas, the junction area of solid and solution phase moved slowly to the bottom, while the hydrogel simultaneously turned into a solution. Finally, the whole hydrogel was converted into the solution. For the reformation of hydrogels, the solutions were treated by aerating NH_3 gas, and the hydrogels formed successively until the whole solution turned into hydrogels. In the case of using AED·2HCl as cross-linker within hydrogels, the disassembly of hydrogels was also carried out by adding an aqueous solution of reducing agent DTT (0.4 mL, 1 mol/L) to the hydrogels. As-obtained solutions could be reversibly transformed into hydrogels by adding aqueous $NaIO_4$ solution (0.7 mL, 1 mol/L).

Fabrication of Multiblock Hydrogels. Before the preparation of multiblock hydrogels, a mixture was prepared by adding 1 mL of aqueous AED·2HCl solution (1 mol/L) to 8 mL of aqueous DAC solution (52 mg/mL), which is referred to as MS0. Then, 0.24 g (0.5 mmol) of AERhB was dissolved in 2 mL of MS0, resulting in solution MS1. At the same time, another solution MS2 was prepared by dissolving 0.097 g (0.25 mmol) of FITC in another 2 mL of MS0. For the formation of multiblock hydrogels, 1.5 mL of MS1 was added into a hollow tube. One end of the tube was covered with a plug. By aerating NH_3 gas into the solution for a certain time, ∼0.5 mL of solution became a hydrogel. The introduction of NH_3 gas was immediately stopped, and the tube was reversed. The remaining solution was taken out, and 1 mL of MS0 was injected into the tube. Then, NH_3 gas was aerated into the solution, until another ∼0.5 mL of solution was converted into hydrogel. Thereafter, the remaining solution of MS0 was replaced by MS2, and ∼0.5 mL of MS2 turned hydrogel during the aeration of NH_3 gas. After that, the multiblock hydrogel was taken out from the container and placed into water. The water was regularly changed until no change of the conductivity occurred.

Light Microscopy. The morphology images were recorded on ZEISS Axioplan 2 imaging microscope with a Nikon DS-Fi2 camera. The dried hydrogels were prepared by immersing hydrogels into the liquid nitrogen directly and subsequent freeze-drying.

Fluorescence Microscopy. Fluorescence imaging was performed on a Nikon Eclipse E6000 imaging microscope. The excitation wavelength was 400 nm, and the emission wavelength was 505−540

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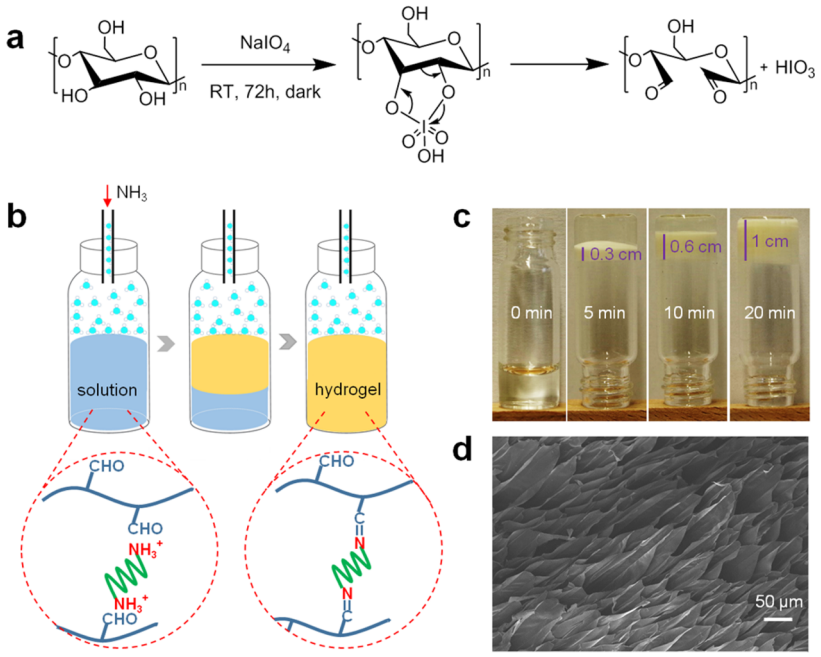

Figure 1. Schematic representation for (a) the periodate oxidation of cellulose and (b) the preparation of hydrogels by aerating NH_3 gas into aqueous solution of DAC/diamine and the mechanism for the formation of hydrogel; (c) representative optical images of starting solution of DAC/diamine as well as hydrogels; and (d) representative SEM image of a freeze-dried hydrogels formed after aerating NH_3 gas into aqueous solution of DAC and 1,6-hexanediamine dihydrochloride for 20 min.

nm. The signals were collected by Nikon DS-Fi1c camera in a dark room.

TGA. Thermogravimetric analysis using a thermobalance from NETZSCH (TG209F1 iris) was operated under nitrogen flow. Samples (5−10 mg) in the crucible were generally used for the measurement. The temperature range for the measurement was 20−700 °C, and the heating rate was 20 °C/min.

RESULTS AND DISCUSSION

DAC was synthesized after the periodate oxidation of cellulose. The linkage between the C2 and C3 of the anhydroglucose units of cellulose is cleaved during the periodate oxidation. Then, the secondary hydroxyl groups at these positions are transformed into two aldehyde groups (Figure 1a).[32,34] The product after the periodate oxidation was purified via dialysis, and a transparent solution was obtained by heating at 80 °C for 4 h. The FTIR spectrum of DAC confirmed the introduction of carbonyl groups by showing two new characteristic peaks at 1730 and 880 cm^{-1} ascribed to stretching vibration of carbonyl groups and vibration of hemiacetal linkages, respectively (Figure S1).[32] The degree of oxidation (DO) of DAC used for hydrogels was determined to be 1.57 ± 0.03 according to titration, meaning a content of aldehyde groups of 9.69 ± 0.19 mmol/g in DAC. This value is very close to the result from elemental analysis, which is often used for the determination of DO of DAC (Supporting Information).

Hydrogels were further prepared after the reaction between DAC and a cross-linker containing diamine groups, such as HMDA·2HCl or AED·2HCl. Due to the presence of HCl, a base is needed to neutralize the ammonium salts of diamines. Herein, we used a novel method by aerating NH_3 gas into the DAC solution, which allows the process of forming hydrogels to be more controllable due to the successive propagation of the hydrogel block (Figure 1b,c). With the formation of primary amine groups, Schiff base groups are formed instantly (Figure S1), i.e., imine groups between aldehyde groups of DAC and diamine groups, as shown by using HMDA·2HCl for the cross-linking (Figure 1b). The solutions gradually became hydrogels along with the formation of more Schiff base groups.

During the aeration of ammonia gas, a thin hydrogel layer was first formed at the interface of liquid and gas phase. This hydrogel layer stayed on the top of the solution, while it is porous and still accessible for NH_3 gas and hydroxide to penetrate (Figure 1c). With the introduction of more NH_3 gas, the hydrogel layer became thicker and thicker, until the whole solution became a hydrogel. Thus, the thickness of formed stable hydrogels can be easily adjusted, e.g., between 0 and 10 mm by treating the solution with NH_3 gas for 5, 10, or 20 min (Figure 1c).

In addition, the resulting hydrogels exhibited uniform microscopic and chemical structure. Common methods for preparing hydrogels include (1) direct mixing of the components leading to gels, (2) premixing the components homogeneously and then changing one condition (pH value, temperature, etc.), or (3) using initiator to cross-link the components forming gels.[9,35] In particular, for the highly reactive compounds, the latter methods are more appropriate for the formation of uniform hydrogels. As DAC contains numerous aldehyde groups, it has to be mixed with diamines homogeneously in advance before a base is added. For example, we used hydrochloride salts of diamines to avoid the Schiff base reaction at the first contact so that we could dissolve DAC and any other diamines of any molar ratios. Otherwise, if a diamine (not in its salt form) is directly used for the dissolution, then a nonuniform distribution of the components within hydrogels will occur, due to the fast reaction between aldehyde and amine groups (Figure S2).

Adding a base solution, such as an aqueous NaOH solution, is a general method for postadjustment of pH values of solutions. However, due to the high amount of hydroxyl groups within the NaOH solution and thus the fast reaction between

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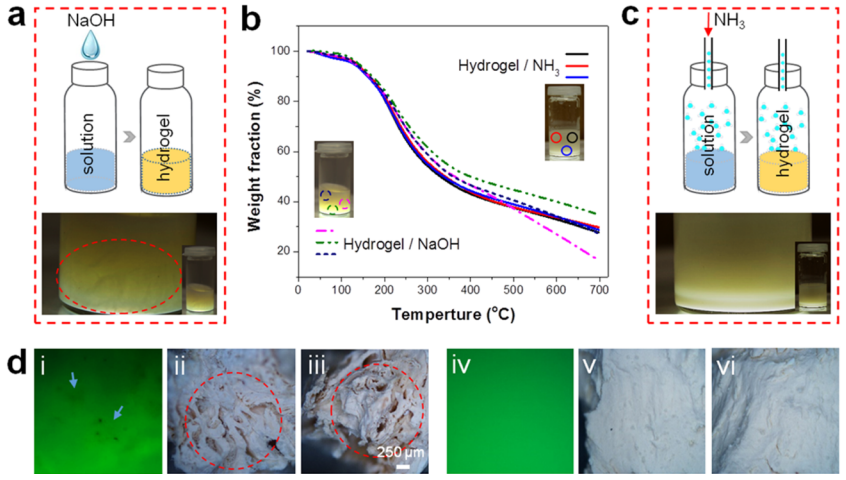

Figure 2. Characterization of hydrogels. (a) Hydrogels formed by adding aqueous NaOH solution into solution of DAC/HMDA·2HCl and optical images of hydrogels. (b) TG curves of two different kinds of hydrogels. (c) Hydrogels formed by aerating NH_3 gas into solution of DAC/HMDA·2HCl and optical images of hydrogels, (d) i: fluorescence microscopic image of hydrogel/NaOH, ii and iii: optical images of freeze-dried hydrogels/NaOH, iv: fluorescence microscopic image of hydrogel/NH_3, v and vi: optical images of freeze-dried hydrogels/NH_3.

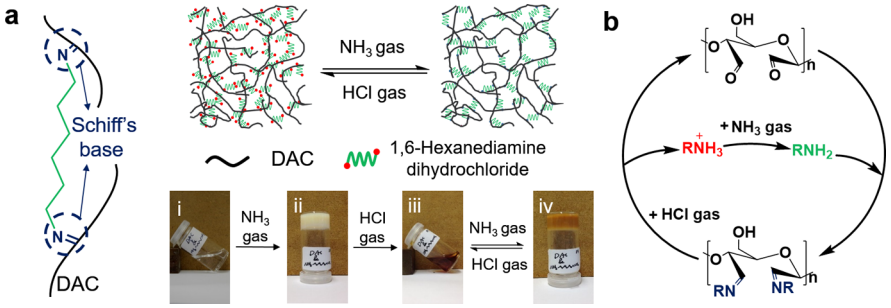

Figure 3. Stimuli-responsive hydrogels from DAC and HMDA·2HCl. (a) Schematic and optical images (i–iv) showing the switchable process between hydrogel and solution by aerating NH_3 gas and HCl gas, respectively. (b) Schematic illustration for the switching mechanism of pH-responsive hydrogels during the introduction of NH_3 and HCl gas.

aldehyde and amine groups at the moment of the contact with NaOH solution, aggregates were formed due to the rapid reaction between DAC and HMDA. These aggregates are optically visible (Figure 2a). TG measurement confirms the heterogeneous distribution of imines within hydrogels on a molecular level (Figure 2b). Different thermal degradation curves were recorded for the samples from randomly selected distinct locations within the same hydrogel, which means different chemical compositions for these areas and thus a nonuniform hydrogel. In addition, these aggregates result in lots of defects and cracks after drying, as measured for dried hydrogels via light or fluorescence microscopy (Figure 2d-i–iii). In particular, big cracked aggregates are obvious within dried hydrogels, indicating the previous nonuniform structure within hydrogels.

In comparison, our new method of aerating NH_3 gas into the solution of DAC and diamine to neutralize hydrochloride led to homogeneous hydrogels (Figure 2c). Due to the uniform distribution of NH_3 molecules and thus homogeneous contact with the whole solution surface, a layer of hydrogel could be formed rapidly after the first contact between the NH_3 gas and the aqueous solution of DAC/diamine. Thus, the aggregation of DAC chains was avoided, in contrast to the method of adding aqueous NaOH solution. The TG analysis of different areas within hydrogels displayed nearly the same degradation curves and thus confirmed the homogeneous chemical compositions on the molecular level (Figure 2b). The light microscopic and fluorescence microscopic images of dried hydrogels also showed uniform samples without significant aggregates or cracks after freeze-drying (Figure 2d-iv–vi). Thus, aerating NH_3 gas into the solution of DAC and diamines demonstrates an efficient method for preparing homogeneous hydrogels with adjustable thickness. Such hydrogels with homogeneous structure are of particular interest for diverse application, such as for catch-and-release system, hybrid materials, bionic hydrogels, and bio-/catalysis.[12,36–38]

Furthermore, these hydrogels based on Schiff base groups between DAC and diamines showed stimuli-responsive properties due to the pH-responsive character of Schiff base. The Schiff base groups can be cleaved and reformed by decreasing and increasing the pH values, respectively. Depending on the type of diamines that can contain further functional groups, further functionalities can be easily introduced, e.g., using AED·2HCl containing a disulfide linkage.

We started with the preparation of pH stimuli-responsive hydrogels using HMDA·2HCl as cross-linker for DAC (Figure 3a). Hydrogels were obtained after aerating NH_3 gas for 30 min. By introducing HCl gas for 20 min, the hydrogel was destroyed and became a solution again. During the introduction of HCl gas, the Schiff base groups were cleaved, and the diamine groups turned into ammonium salt again. At the same time, a color change of the solution from colorless to brown

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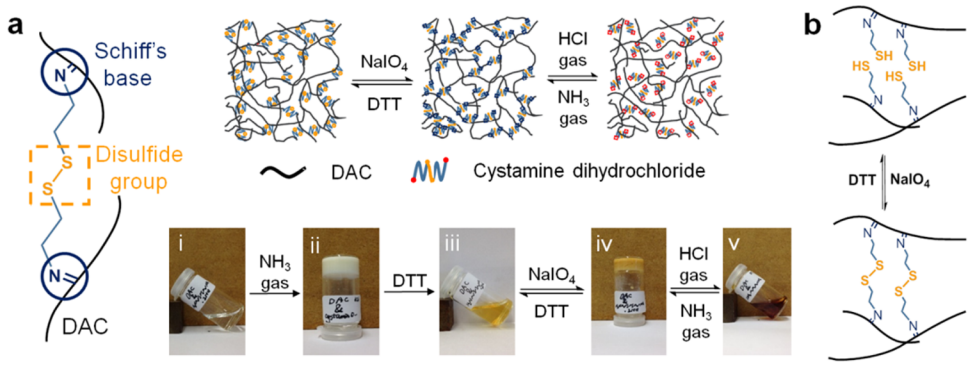

Figure 4. Stimuli-responsive hydrogels from DAC and AED·2HCl. (a) Schematic and optical images (i–v) showing the formation and dissociation of pH and redox-responsive hydrogels; (b) schematic illustration for the cleavage/formation of disulfide linkages using DTT/$NaIO_4$.

was visible. This color change should be due to the formation of small molecular byproducts via the Maillard reaction.[39] The aeration of NH_3 gas into solution led to the hydrogels again, which is due to the transformation of the ammonium salt of diamine and subsequent rapid reaction with aldehyde groups of DAC (Figure 3b). Thus, pH-responsive hydrogels could be prepared by introducing NH_3 gas and could be reversibly switched to solution by alternatively introducing HCl gas (Figure 3a). The principal mechanism is the reversible formation and cleavage of Schiff base groups and ammonium salts, depending on the presence of acid or base (Figure 3b).

By using another diamine-containing further functionality, more functions can be easily introduced into the pH-responsive hydrogels. We used further AED·2HCl that contains a disulfide group for multi-stimuli-responsive hydrogels. By aerating NH_3 gas into the solution of DAC and AED·2HCl, a hydrogel is formed instantly after several minutes (Figure 4a). Due to the presence of disulfide group, the hydrogel network could be dissociated into solution via the reduction of disulfide groups using DTT as reducing agent. By adding oxidizing agents, such as $NaIO_4$, the hydrogel was reformed again. Thus, the hydrogel was responsive to the redox condition. Due to the presence of Schiff base groups within the hydrogel, it is also pH-responsive as demonstrated above for the hydrogels containing HMDA as cross-linker (Figure 4a,b).

On the basis of advantages of our method including controllable gelation process and the presence of numerous reactive aldehyde groups of DAC, multi-stimuli-responsive hydrogels with microscopic multiblock structure can be efficiently prepared. In addition, specific functions can be preprogrammed into each single block of multiblock hydrogels, e.g., distinct stimuli-responsiveness or fluorescence (Figure 5). The procedure for the preparation of multiblock hydrogels is illustrated in Figure 5a.

In this study, hydrogels with 3 blocks with a height of ~5 mm for each block were prepared as example. Starting with the solution of DAC, AED·2HCl, and aminoethyl rhodamine (AERhB, referred to as MS1), block 1 was obtained via aerating NH_3 gas. Then, solution MS1 was replaced by the solution of DAC and AED·2HCl (referred to as MS0). Aerating NH_3 gas into the tube led to the formation of block 2. By replacing MS0 with another solution of DAC, AED·2HCl, and FITC (referred to as MS2) and subsequently aerating NH_3 gas, block 3 within the hydrogel was obtained. Thus, 3-block hydrogels with diverse functions within each block were prepared.

In block 1, AERhB was immobilized, which provides this block with tunable color change due to its responsiveness

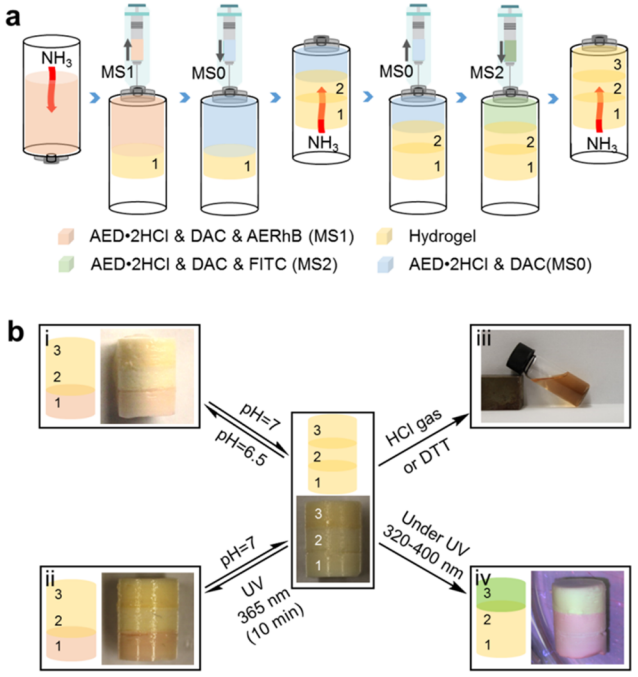

Figure 5. Preparation of multiblock stimuli-responsive hydrogels. (a) Schematic representation for the preparation of the multiblock hydrogels. (b) Representative optical images and schematic representations (i–iv) of multi-stimuli-responsive properties of a multiblock hydrogel.

against UV-illumination and pH value. By placing the hydrogel in PBS solution with a pH value of 6.5 for 2 min or illuminating the hydrogel with UV light of 365 nm for 10 min, the color of block 1 became magenta (Figure 5b-i,ii), while the other blocks did not show significant color change. The magenta color could be switched back to yellow by treating the hydrogel using PBS solution with a pH value of 7. Block 2 contains Schiff base groups between DAC and AED·2HCl, as well as the disulfide groups. This block is responsive to pH values as well as redox condition. Moreover, because the whole hydrogel contains these bonds, the whole hydrogel can be disassembled using HCl gas or reducing agent DTT (Figure 5b-iii). In block 3, FITC was fixed in the matrix, which enables this block to be fluorescent, as shown by the image taken under the UV light (Figure 5b-iv).

Thus, this method allows us to introduce various functions and stimuli-responsive properties into multiblock hydrogels. The aminoethyl rhodamine and fluorescein isothiocyanate

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isomer could be replaced by other functional reagents, which allows the introduction of other functionalities into the hydrogel. Moreover, the microscopic structure of hydrogels can be simply adjusted by generating blocks of diverse numbers and block lengths within the same hydrogels. The advantages of multiblock hydrogels provide us more possibilities to design functional materials to fulfill more complicated requirements, ranging from tissue engineering to pharmaceutical applications.[15,16,18,40]

CONCLUSIONS

We show for the first time the preparation of multiblock and multi-stimuli-responsive hydrogels with uniform chemical structures using a controllable and efficient method by aerating NH_3 gas into the solution of DAC and di-/amines. The hydrogels formed by DAC together with HMDA·2HCl, and AED·2HCl could be tuned between solution and hydrogel status, if certain stimuli such as changing pH (HCl and NH_3 gas) or redox condition (DTT and $NaIO_4$) were applied. Furthermore, multiblock hydrogels could be prepared, and each block could contain its particular functions by adjusting the location of desired functionality. Thus, the exact location of diverse functions could be generated either throughout the whole hydrogels or within a certain block. In the present study, the disulfide linkages and the Schiff base groups from the reaction between AED and aldehyde groups were generated within the whole multiblock hydrogels, while each block contained another different function, such as fluorescence and alternative optical color. Thus, we demonstrated in this work the preparation of uniform multifunctional and multiblock hydrogels via a novel efficient method, which enables a broad spectrum of further promising stimuli-responsive functional materials.

ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acssuschemeng.7b00646.

Characterization of DAC; synthesis and characterization of rhodamine methacrylamide (PDF)

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Notes

The authors declare no competing financial interest.

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