

Polyampholyte Hydrogels with pH-Dependent Swelling for Controlled Catch and Release of Model Dyes

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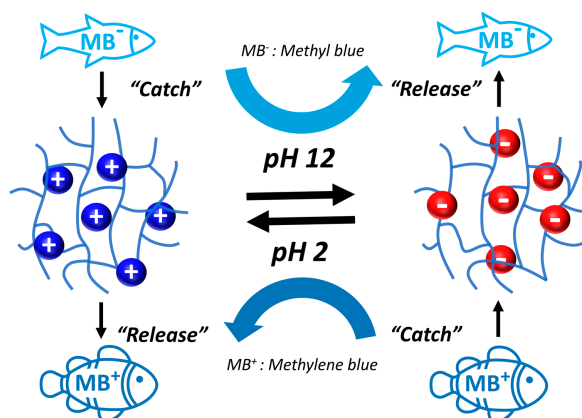
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Abstract Polyampholyte hydrogels with tunable charge are synthesized by a facile two-step approach including the free-radical crosslinking copolymerization of *tert*-butoxycarbonylaminomethylacrylate (tBAMA) with *N,N'*-methylenebisacrylamide and subsequent deprotection. Thermal, photo- and redox-initiating methods were utilized in the synthesis of crosslinked PtBAMA and the resulting polymer networks swell during deprotection in a mixture of trifluoroacetic acid/water. While the crosslinked PtBAMA forms organogels in various organic solvents such as chloroform, acetone and DMSO, polydehydroalanine (PDha) networks after deprotection form hydrogels with pH-dependent swelling and oscillatory swelling/deswelling depending on pH value and salinity. The tunable charge of the developed hydrogels was employed for a catch-and-release platform controlled by pH, in which methylene blue as a cationic model was adsorbed at pH 11 and desorbed at pH 2, whereas methyl blue as an anionic model dye was adsorbed at pH 2 and desorbed at pH 11.

Key words: polyampholyte hydrogels, charge tuning, pH-responsive hydrogels, catch-and-release

Introduction

Polymer gels are three-dimensional networks composed of a linear polymer chain crosslinked by chemical bonds or physical interactions that attract great interest due to their unique properties and potential applications in various fields from energy harvesting and additive manufacturing

to tissue engineering and drug delivery.² Hereby, examples of both hydrogels and organogels have been reported, where hydrogels are typically formed from hydrophilic polymers with a high affinity for water and can absorb and retain large amounts of water.³ Contrarily, organogels are formed from hydrophobic polymers, which have a low affinity for water and instead interact with organic solvents to form a gel-like structure.⁴ Due to their excellent water-holding capability, hydrogels are mostly used as superabsorbent materials for baby diapers and hygiene articles such as femcare and incontinence,⁵ and as water retention granules for agriculture.⁶ Their biocompatibility and ability to mimic biological environments render them interesting materials for biomedical applications such as cell regeneration and repair; moreover, the mechanical strength, elasticity, and degradation rate can be adjusted according to the targeted tissues and organs.⁷ Organogels, on the other hand, are widely utilized in applications where organic media are needed for instance in cosmetics⁸ or oral and topical drug delivery.⁹ Due to their selectivity towards the organic phase in water, organogel adsorbents have also been a promising solution for the removal of hard-to-degrade organic pollutants in wastewater.¹⁰ Swelling refers to the change in the volume of a gel as it absorbs a compatible fluid (water or organic solvent) which relies on the crosslinking density, solvent nature, and polymer-solvent interaction.¹¹ Besides, the swelling behavior of hydrogels can also be affected by some environmental factors such as the presence of certain ions, pH, and temperature.¹² For instance, the degree of ionization of the polymer network can be altered upon changes in pH-value, resulting in a change in swelling behavior.¹³ Therefore, controlling the polymer chemistry and the synthesis conditions allows us to tailor the properties of crosslinked gels. Chemically crosslinked gels are relatively durable under large de-

formation and their mechanical strength is correlated with the degree of swelling, which can be enhanced by incorporating filler materials¹⁴ and other monomers that can form their own network interpenetrating with polymer gels.¹⁵

The nature of the polymer and the desired properties of the resultant gels are decisive to choose the synthesis method of hydrogels and organogels. One typical approach for hydrogel synthesis is the chemical or physical crosslinking of hydrophilic pre-formed polymers.¹⁶ For example, natural polymers such as cellulose, chitosan, and alginate can be crosslinked by ionic or covalent binding.¹⁷ Also, synthetic amphiphilic block copolymers such as poly(ethylene glycol)-*block*-poly(ϵ -caprolactone)-*block*-poly(ethylene glycol) (PEG-PCL-PEG) in solution can form a gel by temperature change.¹⁸ A similar principle is applied in the synthesis of organogels in which a solution of the hydrophobic polymer such as polystyrene in hexane or toluene can be heated and slowly cooled leading to gel formation.¹⁹ Alternatively, adding low-molecular-weight organic gelators such as fatty acids, steroids, and anthryl derivatives or polymeric organic gelators such as poly(ethylene), poly(methacrylic acid-co-methyl methacrylate), and polyurethane promotes gelation upon cooling.²⁰ Besides all these, the free-radical crosslinking copolymerization of hydrophilic or hydrophobic monomers with bifunctional monomers used as a crosslinker is still commonly performed for gel formation due to a number of advantages such as versatility across different monomers and initiators, in combination with scalability for industrial applications.²¹ Typical examples are combinations of acrylic acid with *N,N'*-methylenebisacrylamide (MBAA) for hydrogels,²² or styrene with divinylbenzene in case of organogels.²³ Initiating systems are crucial for performing the synthesis of gels and determining whether the polymerization can be initiated by heating or light irradiation. For instance, poly(vinyl alcohol) macromers modified with pendant acrylamide groups can be photopolymerized using Irgacure 2959 as a photoinitiator towards hydrogels.²⁴ Alternatively, 2,4,6-trimethylbenzoyl-diphenylphosphine oxide (TPO) is an appealing water-soluble photoinitiator for polymerization of acrylic monomer and PEG-diacrylate crosslinker.²⁵ As thermal initiators in the synthesis of gels, azo compounds such as 2,2'-azobis(isobutyronitrile) (AIBN)²⁶ and organic peroxides such as benzoyl peroxide²⁷ are mostly preferred. Using redox initiators allows performing the synthesis of gels under milder conditions such as at room temperature or slightly elevated temperatures.²⁸ Moreover, redox-initiating systems such as ammonium persulfate (APS)/*N,N,N',N'*-tetramethyl ethylenediamine (TEMED) are often used in aqueous systems, rendering this approach suitable for the synthesis of hydrogels that are designed for biomedical applications.²⁹ However, the potential toxicity of initiators and the lack of control over the network architecture should be taken into consideration.³⁰ Some crosslinked polymers obtained by this method include poly(2-hydroxyethyl meth-

acrylate),³¹ poly(acrylic acid),³² or poly(acrylamide) as hydrophilic polymers, and poly(methyl methacrylate)³³ and poly(octadecyl acrylate)³⁴ as hydrophobic examples. Interestingly, amino acid-based acrylic monomers protected by *tert*-butyloxycarbonyl (Boc) groups can be transformed into organogels, and subsequently to hydrogels by deprotection.³⁵ Hydrogels can be formed by not only homopolymers but also by different types of copolymers such as block, graft, alternating, and random.³⁶ This allows designing novel tailor-made hydrogels, for example, adding hydrophobic monomers into the hydrogel composition results in an amphiphilic polymer co-network that has an enhanced toughness as a result of interactions between the hydrophobic segments.³⁷ Hydrogels may have smart functions such as phase transition or stiffness change, swelling/deswelling, and release of a cargo molecule controlled by external stimuli such as pH, temperature, light, magnetic field, or biological triggers including enzymes, glucose, or antigens.³⁸ When polyelectrolytes constitute the hydrogel, the corresponding net charge is one way to classify these materials.³⁹ In case of weak polyelectrolytes, the net charge depends on the surrounding pH value and examples for such functional units include carboxylates, phosphates, and sulfonates as anions or primary and secondary amines as cations.⁴⁰ The charged nature of these hydrogels is not only an essential factor in physical properties but also promotes electrostatic interactions, which opens a venue for a wide range of applications such as tissue engineering, delivery devices, actuators, and electronics.⁴¹

Polydehydroalanine is a polyampholyte featuring both carboxylic acids and amines in each repeating unit and thereby provides pH-dependent charge, as polyanion at high pH, polyzwitterion at neutral pH, and polycation at low pH.⁴² PDha has an isoelectronic point at around pH 5,⁴² and despite being hydrophilic in general, solubility is best at basic pH (> pH 10) due to columbic attractions between the oppositely charged species at lower pH values.⁴³ We have recently shown that PDha can be used as a coating for magnetic nanoparticles, providing a platform for the reversible adsorption of charged dyes or macromolecules.⁴⁴ Due to its captodative nature, the direct polymerization of dehydroalanine is not possible so alternative approaches including deprotection strategies are needed, e.g., 2-acetamidoacrylic acid can be polymerized by free-radical polymerization (FRP) and subjected to concentrated HCl to cleave the amide groups.⁴⁵

Recently, our group reported the synthesis of PDha through FRP of precursor monomers, including *tert*-butoxycarbonylaminoethylacrylate (*t*BAMA), benzyl 2-*tert*-butoxycarbonylaminoacrylate (*t*BABA), and methyl 2-benzyloxycarbonylaminoacrylate (BOMA) by utilizing their selectively removable protective groups.^{42,46} *t*BAMA holds promise as a parent polymer of PDha because of its suitability for radical polymerization. We have outlined the con-

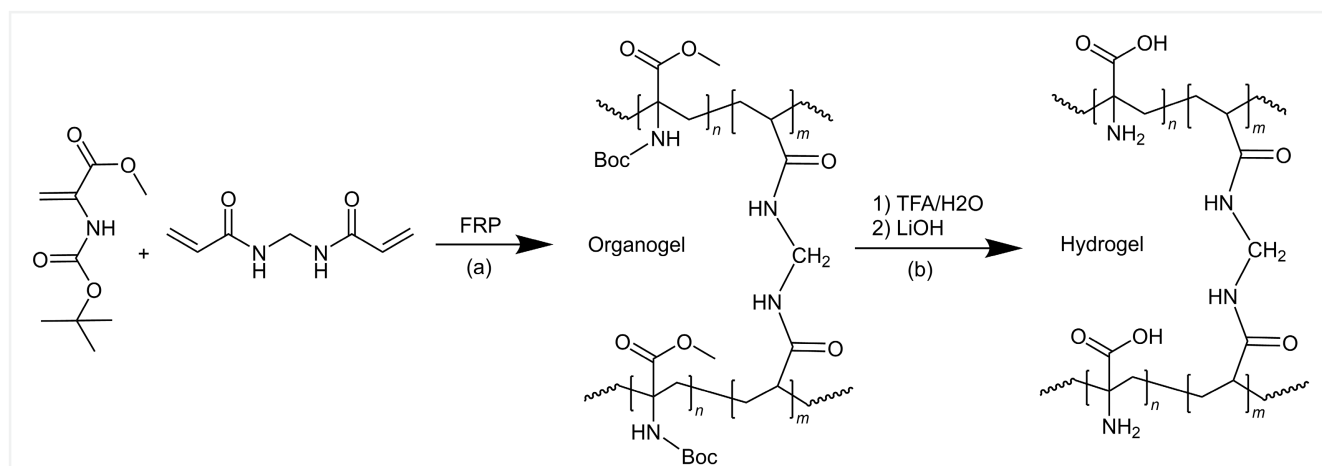
trolled radical polymerization of *t*BAMA including atom transfer radical polymerization⁴⁷ and nitroxide-mediated polymerization.⁴² We have also utilized well-defined *Pt*BAMA as a starting material to create polyampholyte hydrogels comprising PDha and poly(ethylene glycol) (PEG).⁴⁸

In this work, we describe free-radical crosslinking copolymerization of *t*BAMA with MBAA and study three different initiating systems including AIBN as a thermal initiator, TPO as a photoinitiator, and APS/TEMED as a redox initiator to identify suitable conditions for the formation of a gel. The presence of hydrophobic protective groups enabled the crosslinked *Pt*BAMA to form organogels with more apolar solvents. We investigate the mild and effective deprotection of $-NH_2$ and $-COOH$ using TFA/water mixtures to obtain PDha hydrogels. Finally, we demonstrate pH-sensitive swell-

ing of hydrogels and their potential as a catch-and-release platform using positively charged methylene blue (MB^+) and negatively charged methyl blue (MB^-) dyes.

Results and Discussion

Herein, we develop an alternative strategy for polyampholyte hydrogels based on PDha via FRP of *t*BAMA and subsequent deprotection (Scheme 1). The choice of initiating system would significantly influence the formation of a gel. Our objective is to identify the most suitable initiating systems by evaluating various parameters such as solvent, crosslinker ratio, initiator ratio, and duration. The monomer *t*BAMA used in all experiments was synthesized in a two-



Scheme 1 Synthesis of *Pt*BAMA organogels by free-radical polymerization of *t*BAMA in the presence of MBAA as a crosslinker (a) and synthesis of the hydrogel by deprotection of crosslinked *Pt*BAMA with two consecutive reactions in TFA/H₂O and LiOH (b).

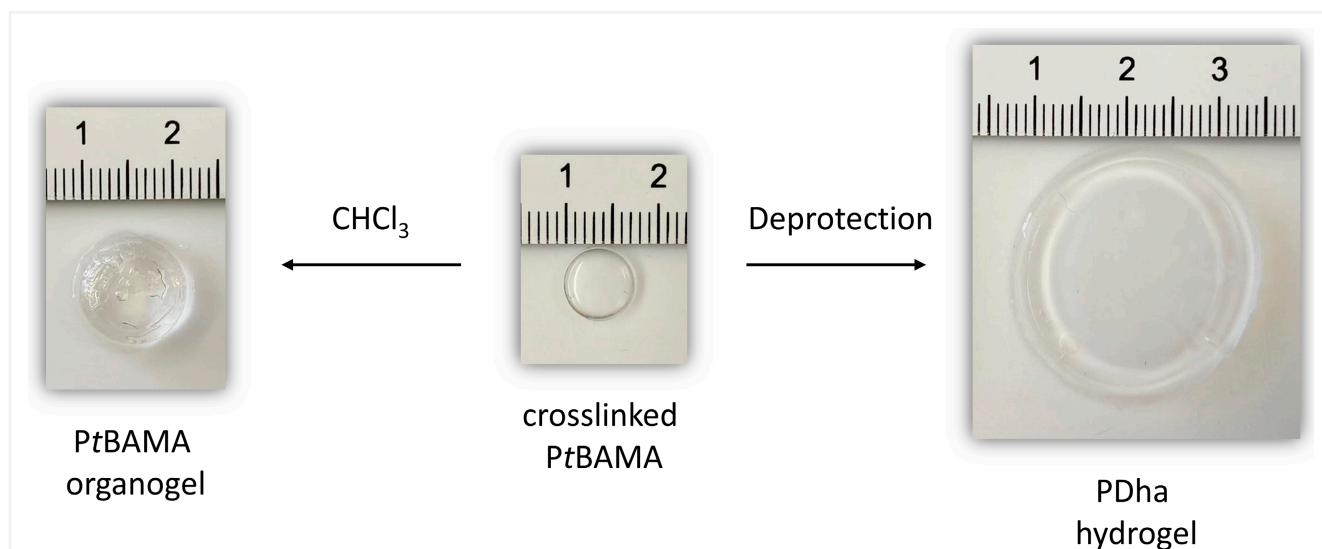


Figure 1 *Pt*BAMA organogel formed after $CHCl_3$ addition to crosslinked *Pt*BAMA and PDha hydrogel formed after deprotection reaction.

step procedure starting from serine (see Figure S1 for ^1H NMR).⁴² FRP was carried out in the presence of MBAA as a crosslinker using photo-, thermal and redox-initiating systems. This synthetic approach differs from previous attempts for PDha-based hydrogels not only with the crosslinking method used but also with achieving hydrogels mainly consisting of PDha. Hydrogels in prior studies contain predominantly PEG (up to 90%) in addition to PDha as polyampholytic stickers.⁴⁸ Cleavage of protecting groups on the crosslinked PtBAMA was possible using stepwise aqueous acid and base solutions, simultaneously leading to a conversion from an organogel to a hydrogel. Successful deprotection was followed by changes in swelling behavior of the gel, where the swelling first started at the edges of the material during deprotection, and finally leading to a fully swollen PDha hydrogel (Figure 1). After complete conversion, the developed PDha hydrogels exhibited pH-dependent swelling behavior in water and could be utilized for the reversible adsorption of oppositely charged small molecules, which is of interest in the field of water purification. In addition, we compared the herein presented synthetic approach to the chemical crosslinking of PDha in terms of pH-dependent swelling and adsorption abilities of resultant hydrogels.

Synthesis of PtBAMA Organogels

Photocrosslinking Polymerization of tBAMA Using TPO as an Initiator

Using the UV photoinitiator TPO and in the presence of the crosslinker MBAA, tBAMA was successfully polymerized. UV curing was carried out at different exposure times, while some of the samples were additionally treated by post-thermal-curing. Different solvents and bulk polymerization were employed in optimization, as well as varying crosslinker (CL%) and initiator ratios (I%) were used.

UV curing in MeOH, DMSO, and acetone successfully produced crosslinked PtBAMA resulting in a transparent solid, which turned into an organogel when exposed to CHCl_3 (2 mL) for 24 hours, while curing in dioxane was not successful. The solvent-to-monomer ratio was fixed at 1 : 1 (w/w) and the successful parameters are listed in Table 1. Photocrosslinking of PtBAMA in acetone and DMSO was achieved using 1% (w/w) of initiator at the CL% ranging between 0.25 and 7% (w/w). For curing in MeOH, the initiator ratio was reduced to provide optimal conditions for efficient crosslinking. Both dioxane and bulk polymerization did not result in the formation of crosslinked material. Independent of the amount of CL (0.25%, 2.5%, 5% w/w), initiator (1% w/w), and curing methods (Table S1), polymerization in dioxane led to non-crosslinked, branched, or partially crosslinked PtBAMA, which was dissolved in CHCl_3 . This resulting polymer had M_n of $70,000 \text{ g} \cdot \text{mol}^{-1}$ with a dispersity index of 3.4

Table 1 Synthetic parameters for successful crosslinking of tBAMA.

Initiator	Solvent	CL% (w/w)	I% (w/w)	Time	Temperature
TPO	Acetone	7.7	1	3 h*	RT
		2	1	1 h*	RT
		7	1	3 h	RT
	DMSO	5	1	3 h	RT
		2	1	1 h*	RT
		0.5	1	3 h	RT
		2	1	1 h*	RT
	MeOH	0.5	0.1	3 h	RT
		0.25	0.2	3 h	RT
		0.1	0.5	3 h	70 °C
AIBN	DMSO	0.5	0.5	3 h	70 °C
		1	0.5	3 h	70 °C
		2	0.5	3 h	70 °C
		0.5	0.5	12 h	37 °C
APS/TEMED	DMSO	2	0.5	12 h	37 °C

*Additional thermal treatment is applied for 12 hours.

according to size exclusion chromatography (SEC) analysis (Figure S2). Such a broad molecular weight distribution is not uncommon in FRP.

Among the listed successful conditions, we noted that 3 hours of UV irradiation was necessary to yield crosslinked polymers. Crosslinking by 1 hour of irradiation was unsuccessful unless post-thermal-curing is applied, which is often used to increase the strength of gels in photocrosslinkable resins.⁴⁹ While the polymerization occurs during this short-term irradiation, crosslinking continues during thermal treatment at 90 °C in the following 12 hours, finally resulting in polymer organogel in CHCl_3 . Besides the high conversion in relatively short times as one clear advantage of photocrosslinking using TPO, the photocrosslinking of tBAMA can be used for a quick organogel film formation, which reduces local evaporation of solvents and thus can ensure smooth film formation.

Thermal Crosslinking Polymerization of tBAMA Using AIBN as an Initiator

Crosslinked PtBAMA was also synthesized using AIBN as a thermal initiator and MBAA as a crosslinker. All the reactions were conducted in DMSO at a fixed solvent-to-monomer ratio of 1 : 1 (w/w) using a 0.5% (w/w) initiator ratio (I%), while the crosslinker ratio (CL%) was varied for optimization at 0.1, 0.5, 1 and 2% (w/w) (Table 1). As a general procedure, the crosslinker and initiator were separately dissolved in DMSO and were then added to the monomer tBAMA in a 4-mL transparent glass vial. Successful crosslinking after 3 hours at 70 °C was confirmed by swelling in CHCl_3 . However, we noticed that the resulting gels were prone to disintegration upon prolonged exposure to solvent. Those smaller gel pieces were not dissolved in the solvent,

which hints towards crosslinking, but nevertheless, we could conclude that gels were less stable if compared to the photopolymerization.

Redox-Triggered Crosslinking Polymerization of *t*BAMA Using APS/TEMED

APS as an initiator and TEMED as a catalyst are often employed in FRP at room temperature as a redox initiating system.⁵⁰ We attempted to perform crosslinking polymerization of *t*BAMA at 37 °C for 12 hours in DMSO at a fixed solvent-to-monomer ratio of 1 : 1 (w/w) using a 0.5% (w/w) initiator ratio (I%), and crosslinker ratios (CL%) of 0.5 and 2% (w/w) (Table 1). Under both conditions, we observed successful gel formation once the resulting material was exposed to CHCl_3 .

Swelling of Crosslinked PtBAMA in Organic Solvents

The swelling of polymeric networks is crucial for their potential use as adsorbents, with swelling kinetics being a key factor.⁵¹ Given that the choice of organic solvents can significantly impact how much an organogel swells, leading to different levels of expansion, we conducted an investigation into the swelling kinetics in various solvents. These solvents have different properties, including polarity, dielectric constant (ϵ), and density. The solvents we examined included chloroform (CHCl_3 , $\epsilon = 4.8$, $d = 1.49$), dichloromethane (CH_2Cl_2 , $\epsilon = 9.1$, $d = 1.33$), acetone ($\epsilon = 20.7$, $d = 0.784$), methanol ($\epsilon = 33$, $d = 0.792$), and dimethyl sulfoxide (DMSO, $\epsilon = 46.7$, $d = 1.1$), as well as water ($\epsilon = 80.1$, $d = 1$) (Figure 2). Swelling ratios (SRs) were calculated by the weight difference at regular time intervals at room temperature for crosslinked PtBAMA (0.1 I% and 0.5 CL%), which were prepared in small portions of dried gels, immersed in 20 mL solvent.

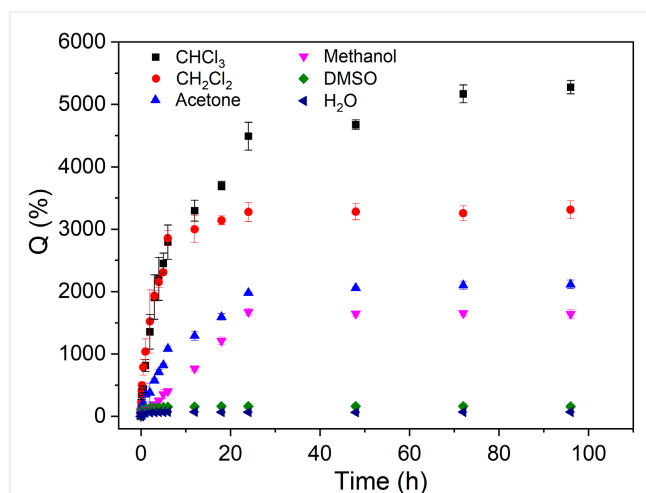


Figure 2 Solvent uptake kinetics of crosslinked PtBAMA (0.1 I%, 0.5 CL%); Swelling ratio (Q% w/w) vs. time.

We aimed at identifying the compatibility of solvents with the PtBAMA network using different organic solvents with dielectric constant ranging from 4 to 20 and high polarity with dielectric constant which is above 20, plus water as the solvent with highest polarity. We herein excluded non-polar solvents with dielectric constant below 4 like hexane as we assumed poor interaction with the PtBAMA network.⁴²

These polymer networks displayed different degrees of swelling in medium polarity solvents while the SR decreased in highly polar solvents (Table 2). We observed in general that the SR gradually increased over time, reaching a plateau after 18 hours in DMSO, 24 hours in CH_2Cl_2 , acetone, and methanol, and 72 hours in CHCl_3 . Hereby, the highest SR was 5274% in CHCl_3 , while the lowest was 157% in DMSO, recorded after 96 hours. It was also observed that the rates of absorption in CHCl_3 and CH_2Cl_2 were equal during the first 10 hours, but eventually CHCl_3 achieved a higher overall SR. When we recalculated the SR by dividing weight-based SR by the solvent density, we interestingly found a higher volume-based SR in acetone than CH_2Cl_2 despite an increased dielectric constant. In addition, the final size of the gels was similar in both cases (Figure S3). This variance in SRs could stem from lower polarity of CH_2Cl_2 if compared to acetone although it has higher ϵ .

Table 2 Equilibrium swelling ratio (SR or Q) of PtBAMA organogels after immersion for 96 hours in different solvents.

Solvent	ϵ	Polarity	SR% (w/w)	SR% (v/w)
CHCl_3	4.81	4.1	5274	3540
CH_2Cl_2	9.1	3.1	3309	2488
Acetone	20.7	5.1	2114	2695
Methanol	32.7	5.1	1640	2071
DMSO	46.7	7.2	157	143
H_2O	80.1	10.2	70	70

The rate of solvent uptake gradually decreased from CHCl_3 to methanol as the ϵ of the respective solvent increased, however, a decrease in SR was not as dramatic as a decrease in dielectric constant, leading to the conclusion that crosslinked PtBAMA can form organogels in a wide range of organic solvents. We also noted that water was quite incompatible with the material at this stage, resulting in collapse, showing very low SR of about 70%. This can be explained by the nature of PtBAMA which has bulky and hydrophobic protecting groups such as Boc for amine and methyl ester for carboxylic acid. Overall, PtBAMA can form organogels in organic solvents with ϵ ranging from 4.81 to 32.7 and be utilized in both encapsulation of hydrophobic molecules and some environmental applications such as adsorbing organic wastes.⁵² With this motivation in hand, we attempted to use the crosslinked PtBAMA for crude oil ad-

sorption, resulting in 400% SR after 96 hours in spite of high viscosity as seen in Figure S3.

Since the crosslinked PtBAMA forms organogels and can be synthesized using conventional initiators by means of UV irradiation, heating and redox reaction, we believe that it holds a potential to widespread use in organogel applications such as drug delivery media for topical and oral pharmaceuticals.⁵³

Synthesis of PDha Hydrogels

As PDha represents a polyampholyte with high charge density, we were also interested in mainly PDha-based hydrogels. In previous work, we described the deprotection of the Boc protective group using TFA at 50 °C or the hydrolysis of the methyl ester in PtBAMA homopolymers at 100 °C using LiOH-H₂O. Additionally, treatment with TFA at room temperature can simultaneously remove both the Boc group and the methyl ester.⁵⁴ We therefore varied the conditions used in the deprotection step towards more mild conditions. The crosslinked PtBAMA were successfully converted to PDha hydrogels by hydrolysis of both protecting groups in a two-step process. We hydrolyzed crosslinked PtBAMA (0.5% CL, 1% I) using TFA solutions, leading to the formation of poly (dehydroalanine-co- aminomethylacrylate) P(Dha-co-AMA) hydrogel. Here, the Boc groups are cleaved resulting in -NH₂ groups and also the methyl ester is hydrolyzed to a certain extent. Subsequently, the resultant hydrogel is treated by a basic LiOH solution for complete deprotection of the methyl ester resulting in -COOH groups.

Figure 3 shows the ¹³C CP/MAS NMR spectra of the cross-linked PtBAMA and the dried gels obtained via the successful conditions as in 50% w/w TFA aqueous solution for 6 h and 0.1 M LiOH solution for 2 h. The signals of the crosslinker overlapped with the signals of PtBAMA, so they are invisible on the spectrum. We noted a complete cleavage of-Boc groups for all reaction conditions as in TFA for 3 h and 12 h, and in 50% w/w TFA aqueous solution for 6 h as seen in Figure S4. The signals at 29 and 155 ppm assigned to the methyl carbons and the carbonyl carbon of-Boc group, respectively, only appeared in the reference sample and vanished by TFA treatment. We also observed that the methoxy groups were cleaved to a large extent, giving successful deprotection of 92% for 6 h in 50 wt.% TFA aqueous solution, 85% for 3 h and 92% for 12 h in neat TFA. As it represents milder conditions, 50 wt.% TFA aqueous solution was selected for the rest of our studies. After the reaction, the swollen gel was washed six times with diethyl ether to remove TFA as well as byproducts. It was later kept under air for 1 day and under a high vacuum the following day to get fully dried.

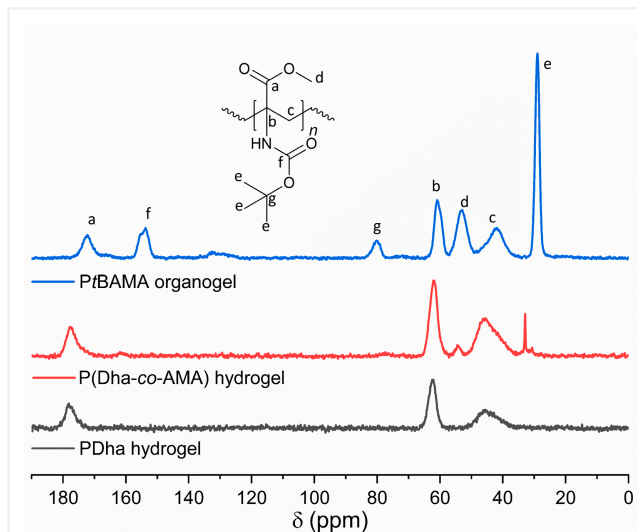


Figure 3 ¹³C CP/MAS NMR of dried PtBAMA organogel (0.5% CL, 1% I) (upper), dried P(Dha-co-AMA) hydrogel obtained after deprotection in 50% w/w TFA aqueous solution for 6 h (middle), and dried PDha hydrogel resulting from deprotection of P(Dha-co-AMA) hydrogel in 0.1 M LiOH for 2 h (lower).

Swelling Behavior of PDha Hydrogels

The SR is an important property for hydrogels. It depends on factors like how tightly the hydrogel is connected, how the material behaves under stress, its internal structure, and external factors such as pH and salt concentration.⁵⁵ In this study, hydrogels begin swelling as deprotection occurs. However, to properly assess the SR, it needs to be measured at equilibrium conditions. In this regard, solid gels formed through the deprotection of PtBAMA (0.5% CL, 0.1% I) were immersed in deionized water for 48 hours. In cases where not specified otherwise, experiments were conducted in triplicate, and the average SR was determined, resulting in an equilibrium SR of 8420 ± 883%. To explore how pH affects swelling, the gels were submerged in water with different pH levels for 76 hours. Figure 4a displays the pH-dependent SR of PDha hydrogels, resulting in the following values: 298 ± 70% at pH 3, 801 ± 189% at pH 5, 3231 ± 785% at pH 7, 3349 ± 733% at pH 9, and 3797 ± 549% at pH 11. The SR showed a modest increase up to pH 5. However, a significant and abrupt increase was observed at pH 7, likely resulting from the complete deprotonation of -COOH and the formation of a polyzwitterionic gel. As pH reached 11, a further slight increase in SR was noted, possibly due to electrostatic repulsion between the predominantly polyanionic chains between the crosslinks.⁵⁶ The capacity to maintain swelling properties over multiple cycles is a crucial attribute for hydrogels that experience volume changes due to external stimuli. Consequently, we exposed PDha hydrogels to three swelling–deswelling cycles in solutions with oscillating pH levels ranging from 12 to 2 at room temperature. The results,

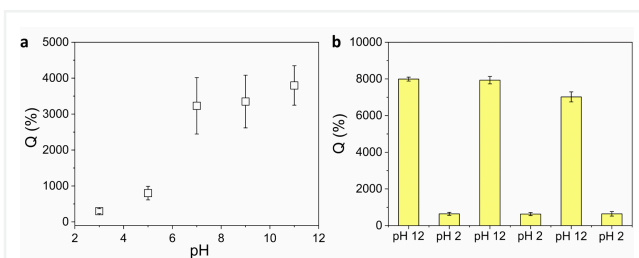


Figure 4 Swelling properties of PDha hydrogels (0.5% CL, 0.1% I); pH-dependent swelling (a) and oscillatory swelling cycles at pH 12 and 2 (b).

illustrated in Figure 4b, indicate that the hydrogels can be reversibly swollen. We therefore also carried out rheological amplitude sweep measurement to ascertain the magnitude of the linear viscoelastic (LVE) response and the storage modulus (G') within the LVE region. Results were also compared with hydrogels comprising PDha stickers as reported earlier^{48a} (Figure S5). When G' remains constant regardless of the strain amplitude, the sample can be deformed within this range without irreversible damage, being comparable to the toughness of such a sample.⁵⁷ The LVE region of the herein-developed PDha hydrogel stretches up to 2.5% strain with an average storage modulus (G') of 1700 Pa. The significant drop in G' indicates that the material exhibits brittle fracturing behavior. The behavior before the crossover point suggests that the material has a gel-like structure and behaves as a viscoelastic solid before microcracks start forming.

Dynamic Catch-and-Release of Anionic and Cationic Model Dyes

Polyampholytic hydrogels are appealing to relevant fields including wastewater treatment because they supply enhanced removal and separation of pollutants and delivery systems providing the controlled release of carried cargo molecules on target.⁵⁸ We hypothesize that the hydrogels designed in this study, characterized by a high density of dynamic charge, have the potential to demonstrate controlled adsorption and release of charged molecules by adjusting the pH levels. Those used as anionic and cationic models are extensively employed in textile, leather, and paper industries as colorants (Figure S6). By PDha hydrogels (0.5% CL, 0.1% I), cationic methylene blue (MB^+) was captured at basic pH and released at acidic pH. In contrast, anionic methyl blue (MB^-) was captured at acidic pH and released at basic pH.

In the case of cationic model, as demonstrated in Figure 5a, the pre-equilibrated hydrogel (48 hours at pH 12) was immersed in MB^+ solution ($0.025 \text{ mg} \cdot \text{mL}^{-1}$, in water at pH 12) for 48 hours and the dye adsorption was monitored by UV-Vis spectra (Figure 5b). The cationic dye molecules are supposed to be electrostatically attracted by anionic groups of PDha hydrogel at this basic pH. The MB^+ -adsorbed hydrogel was then washed with pH 12 solution and placed

in pH 2 solution. After 48 hours, we observed that the hydrogel shrank and released MB^+ molecules. Meanwhile, the variance of the absorption band of MB^+ as seen when pH is changed to 2 was probably due to the disturbance of the self-aggregated dimer formation.⁵⁹ We noted that the hydrogel remained slightly blue after desorption of MB^+ , although the overall net charge is supposedly positive under these conditions. We explain this by the fact that some MB^+ is physically entrapped inside hydrogel meshes. We suppose this phenomenon was due to the H-bonding between the carboxylic acid groups of PDha at acidic pH.⁶⁰ The remaining dyes were somewhat released after the second round of washing with acid solution (Figure 5b). Adsorption and desorption of MB^+ were quantified by UV-Vis absorbance, and the calibration curve developed earlier is used for the latter.^{44a} The adsorption capacity (w/w%) per mg of dry gel followed the decreasing regime by increasing the amount of hydrogel used, being on average 2.8% for 6 mg, 2.4% for 15 mg and 1.9% for 29 mg (Figure 5c). We noted that 98.5% of the adsorbed dyes were released only after the first washing of the hydrogel having 2.4% MB^+ with acid solution. In case of the anionic model, we similarly performed pH-controlled adsorption/desorption but this time by using MB^- and going from acidic to basic pH (Figure 6a). In a similar fashion, the pre-equilibrated hydrogel (48 hours at pH 2) was immersed in MB^- solution ($0.075 \text{ mg} \cdot \text{mL}^{-1}$, in water at pH 2) for 48 hours leading to the decrease in absorbance due to the adsorption of dye (Figure 6b). Here we believe electrostatic attraction is again the driving force of adsorption, however, this time it occurs between cationic groups

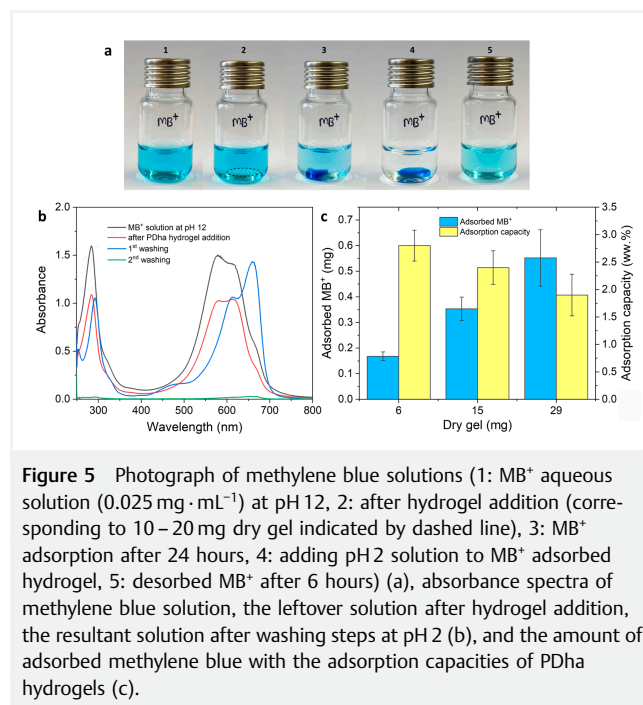
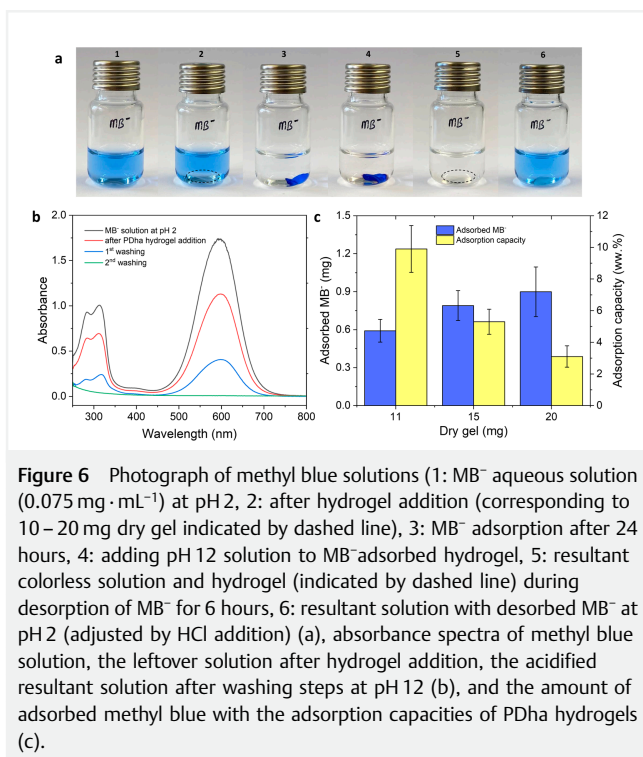


Figure 5 Photograph of methylene blue solutions (1: MB^+ aqueous solution ($0.025 \text{ mg} \cdot \text{mL}^{-1}$) at pH 12, 2: after hydrogel addition (corresponding to 10–20 mg dry gel indicated by dashed line), 3: MB^+ adsorption after 24 hours, 4: adding pH 2 solution to MB^+ adsorbed hydrogel, 5: desorbed MB^+ after 6 hours (a), absorbance spectra of methylene blue solution, the leftover solution after hydrogel addition, the resultant solution after washing steps at pH 2 (b), and the amount of adsorbed methylene blue with the adsorption capacities of PDha hydrogels (c).



of PDha hydrogels and anionic MB⁻ molecules. The adsorbed MB⁻ were then released out of hydrogel when it is subject to a basic solution (pH 12) for 48 hours, resulting from the electrostatic repulsion between anionic charges of PDha hydrogel and dyes. We also noted the resultant solution needs to be acidified to pH 2 as the dye is colorless in alkaline media. Quantification of adsorption and desorption was done according to UV absorbance of MB⁻ at pH 2 and revealed that the adsorption capacities were 9.9% for 11 mg, 5.3% for 15 mg and 3.1% for 20 mg dry gel (Figure 6c). We further found that the hydrogel with 5.4% MB⁻ released almost ca. 99% of the adsorbed MB⁻ after the first washing. From these findings, we believe that PDha hydrogels with a pH-triggered two-way catch-and-release feature might be utilized to develop a facile, selective and reversible adsorption/desorption platform. Further studies may include the reversible adsorption of other small molecules with different charge density, the investigation of the adsorption isotherms and the upscaling of catch-and-release platform for wastewater treatment.

Conclusions

Herein we described a synthetic two-step pathway for PDha hydrogels: the FRP of *t*BAMA is first realized by photo-, thermo-, or redox-initiation systems in the presence of a bifunctional crosslinker, and then the protecting groups of the re-

sulting crosslinked polymer are cleaved. Additionally, the crosslinked *Pt*BAMA prior to deprotection was able to swell in common organic solvents. After deprotection, the resulting polyampholytic PDha hydrogels show pH-responsive swelling, as demonstrated by multiple cycles and up to 8420% of the equilibrium SR in deionized water. We demonstrate the proof of concept for a two-way catch-and-release platform using these PDha-based polyampholytic hydrogels that can reversibly adsorb both positive MB⁺ and negative MB⁻ model compounds depending on the pH value. While hydrogels show an efficient desorption of both dyes, adsorption depends on gel amount, and the average adsorbed amounts of MB⁺ at pH 12 and MB⁻ at pH 2 were found to be 22 and 50 μg · g⁻¹, respectively. Reversible adsorption using larger charged compounds such as proteins or forming film with various morphologies can be the subject of upcoming studies. We envision that PDha hydrogels with pH-controlled dynamic charge features can find utility in a number of areas of environmental and biological/medical science.

Experimental Section

General Methods

All chemicals and solvents were purchased from either Sigma Aldrich, TCI, CHEMSOLUTE®, or Carbolution Chemicals and used without purification if not mentioned otherwise. *t*BAMA was synthesized according to an earlier described protocol.⁴² For detailed experimental procedures and characterization including SEC, NMR and UV/Vis spectroscopy, and rheology, please refer to the Supporting Information.

General Procedure for Free-Radical Crosslinking of *t*BAMA

*Pt*BAMA was synthesized by radical polymerization in the presence of MBAA as a crosslinker using TPO, AIBN, and APS as initiators in the bulk and various solvents including 1,4-dioxane, chloroform, acetone, methanol, and DMSO. Different crosslinker (CL% w/w) and initiator (I% w/w) ratios were used during polymerization, which were defined as follows:

$$\text{CL\%} = \frac{\text{crosslinker (g)}}{\text{crosslinker (g)} + \text{monomer (g)}} \times 100\% \quad (1)$$

$$\text{I\%} = \frac{\text{Initiator (g)}}{\text{Initiator} + \text{monomer} + \text{crosslinker}} \times 100\% \quad (2)$$

Photocrosslinking

*t*BAMA (300 mg), MBAA (6 mg, CL 2% w/w), and TPO (3 mg, 1% w/w) were dissolved in 0.3 mL MeOH in a 4-mL glass vial protected by an aluminium foil. After stirring the mixture for 15 min, the reaction vial was degassed with argon for

10 min, placed in the UV cube (250 W) for polymerization. After 1 hour, the reaction was aborted by removing the vessel from the UV cube. The resultant gel was further treated at 90 °C for 12 hours and then placed in 3 mL CHCl₃ to yield a swollen organogel.

Thermal Crosslinking

tBAMA (300 mg), MBAA (1.5 mg, CL 0.5% w/w), and AIBN (1.5 mg, 0.5% w/w) were dissolved in 0.3 mL DMSO in a 4-mL glass vial. The reaction mixture was stirred for 15 min and degassed with argon for 10 min. After that, the reaction vial was placed in an oil bath at 70 °C for polymerization. The reaction was stopped after 3 hours, and the resultant gel was subject to 3 mL CHCl₃ to yield a swollen organogel.

Redox-Triggered Crosslinking

tBAMA (300 mg), MBAA (1.5 mg, CL 0.5% w/w), (NH₄)₂S₂O₈ (1.5 mg, 0.5% w/w) and TEMED (0.3 mg, 0.1% w/w) were dissolved in 0.3 mL DMSO in a 4-mL glass vial. After degassing the reaction mixture with argon for 10 min and stirring for 15 min, the vial was placed in an oil bath at 37 °C. The reaction was aborted after 12 hours and placed in 3 mL CHCl₃ to yield a swollen organogel.

Deprotection of the Crosslinked PtBAMA to Yield PDha Hydrogel

30 mg of crosslinked PtBAMA were soaked in 5 mL of 50% w/w aqueous TFA solution for 6 hours. The resultant swollen gel was washed with diethyl ether six times, during which time the gel collapsed. The modified gel was then dried in the air for 24 hours, followed by drying under high vacuum. After that, the dried gel was immersed in a 0.1 M aqueous LiOH solution for 2 hours. The resultant deprotected hydrogel was washed six times with diethyl ether and dried in air for 24 hours, followed by drying under high vacuum, to be used in NMR analyses and swelling studies.

Solubility Test After Crosslinking

The solubility test was done for rapid testing to qualify the resultant materials after crosslinking. The obtained materials were subjected to CHCl₃ to test whether they could swell to form an organogel.

Swelling of the Crosslinked PtBAMA in Organic Solvents

Solvent uptake kinetics of crosslinked PtBAMA gels were studied gravimetrically at room temperature. Freshly prepared dry gels (50–100 mg) were immersed in the respective solvents such as CHCl₃, CH₂Cl₂, acetone, MeOH, DMSO and H₂O. A measured amount of dry gel (W_d) was added into the solvent, and then gels were taken out in a specific interval of time, blotted the surface quickly, and weighed (W_s). The SR value was determined at least from three samples and mean and standard deviation were calculated. W_d and W_s are the mass of the dried and swollen crosslinked poly-

mer samples, respectively. The equilibrium SR was calculated using equation as follows:

$$SR\% = \frac{W_s - W_d}{W_d} \times 100\% \quad (3)$$

Swelling of Hydrogels in Water

Freshly prepared dried hydrogels (10–20 mg) were immersed in the respective solvents such as CHCl₃ and water. A measured amount of dry gel (W_d) was soaked in the solvent for 96 hours. After that, hydrogels were taken out, blotted the surface quickly, and weighed (W_s), to minimize errors due to the surface solvent. The SR was determined at least from three samples, and mean and standard deviation were also calculated. The equilibrium SR values of PDha hydrogels were calculated using the given SR% equation. For the pH-dependent SR calculation, dry gels were placed in water at pH ranging from 2 to 12 for 48 hours. For the oscillatory swelling, a dry gel was first placed in water at pH 12 for 24 hours and hydrogels were weighed, and subsequently this hydrogel was placed in water at pH 2 for 24 hours and weighed again. This cycle was then repeated with the same hydrogel two times.

Dynamic Catch-and-Release of Anionic and Cationic Model Dyes

Methylene blue (MB⁺) was used as the cationic model compound. Dry gels (10–20 mg) were placed in pH 12 water for 48 hours for equilibrium and immersed in aqueous MB⁺ solution (0.025 mg · mL⁻¹) at pH 12 for 48 hours. After that, gels were taken out and the UV-Vis absorbance of the resultant solution was recorded. The adsorbed MB⁺ amount was calculated according to molar extinction constant at 579 nm. These swollen MB⁺-absorbed gels were then placed in water at pH 2 for desorption. After 48 hours, gels were taken out and the UV-Vis absorbance of the resultant solution was recorded. The released MB⁺ amount was calculated using an earlier-developed calibration curve.^{44a} The desorption was repeated one more time with a fresh portion of pH 2 water.

Methyl blue (MB⁻) was used as the anionic model compound. Dry gels (10–20 mg) were placed in pH 2 water for 48 hours to reach equilibrium and immersed in aqueous MB⁻ solution (0.075 mg · mL⁻¹) at pH 2 for 48 hours. After that, gels were taken out and the UV-Vis absorbance of the resultant solution was recorded. The adsorbed MB⁻ amount was calculated according to the molar extinction constant at 596 nm. These swollen MB⁻-absorbed gels were then placed in water at pH 12 for desorption. After 48 hours, gels were taken out and the pH of resultant solution was adjusted to pH 2 using concentrated HCl. The UV-Vis absorbance of this solution was recorded as for the adsorption study of MB⁻ and the desorbed MB⁻ amount was calculated. All calculations were made in triplicate for both compounds.

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Supporting Information

Supporting information for this article is available online at <https://doi.org/10.1055/a-2228-4757>.

Conflict of Interest

The authors declare no conflict of interest.

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