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# **Polyzwitterions as a Versatile Building Block of Tough Hydrogels: From Polyelectrolyte Complex Gels to Double-Network Gels**

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## ABSTRACT

The high water content of hydrogels makes them important as synthetic biomaterials, and tuning the mechanical properties of hydrogels to match those of natural tissues without changing chemistry is usually difficult. In this study, we have developed a series of hydrogels with varied stiffness, strength and toughness based on a combination of poly(2-acrylamido-2-methylpropane sulfonic acid) (PAMPS), a strong acidic polyelectrolyte, and poly-N-(carboxymethyl)-N,N-dimethyl-2-(methacryloyloxy) ethanaminium) (PCDME), a polyzwitterion with weak acidic moiety. We demonstrate that modifying the true molar ratio,  $R$ , of PCDME to PAMPS results in four unique categories of hydrogels with different swelling ratio and Young's modulus. When  $R < 1$ , a negatively charged polyelectrolyte gel (PE) is formed; when  $1 < R < 3$ , a tough and viscoelastic polyelectrolyte complex gel (PEC) is formed; when  $3 < R < 6.5$ , a conventional, elastic interpenetrating network gel (IPN) is formed; and when  $R > 6.5$  a tough and stiff double-network gel (DN) is formed. Both the PEC and DN gels exhibit high toughness and fracture stress, up to 1.8 MPa and 1.5 MPa, respectively. Importantly, the PEC gels exhibit strong recovery properties along with high toughness, distinguishing them from DN gels. Without requiring a change in chemistry, we can tune the mechanical response of hydrogels over a wide spectrum, making this a useful system of soft and hydrated biomaterials.

## 1. INTRODUCTION

Hydrogels, consisting of polymer networks swollen in water, have long been pursued as material building blocks for biomedical applications.<sup>1-4</sup> A significant problem in modern biomedical applications is infection or inflammation in the region where synthetic and natural tissues interface, which is initiated by protein adsorption.<sup>5-7</sup> Incorporating functionalities that possess protein anti-fouling or anti-bacterial properties will improve the viability of these applications. Polyzwitterions are a specific type of ion-containing polymer that possess both cationic and anionic groups in their polymeric repeating unit.<sup>8</sup> Typically the cationic group is a quaternary ammonium, and the anionic groups are sulfonate (sulfobetaine)<sup>9</sup>, carboxylate (carboxylbetaine)<sup>10</sup> or phosphonate (phosphobetaine).<sup>11</sup> Due to their unique chemistry, these materials exhibit strong protein anti-fouling properties, making them excellent candidates for biomedical applications.<sup>12-15</sup> A significant amount of literature, including many reviews have focused on their synthesis, and the basis for their significant anti-fouling abilities.<sup>8,16-18</sup> Briefly, the ionic nature of zwitterions allows for high concentrations of water to be bound to the functional groups, preventing fouling of the surface. Due to the beneficial properties of zwitterions, researchers have attempted to prepare biomaterials such as particles,<sup>19</sup> and hydrogels<sup>20,21</sup> based on these chemistries.

Previously we prepared poly-N-(carboxymethyl)-N,N-dimethyl-2-(methacryloyloxy) ethanaminium) (PCDME) hydrogels with different formulations.<sup>22</sup> From the relationship of the swelling degree and Young's modulus it was confirmed that PCDME single network hydrogels are charge-neutral in neutral aqueous media. However, due to the simple structures that lack dissipation mechanisms and high swelling ratios, the prepared

PCDME hydrogels were mechanically weak, and improvements are required for their practical use.

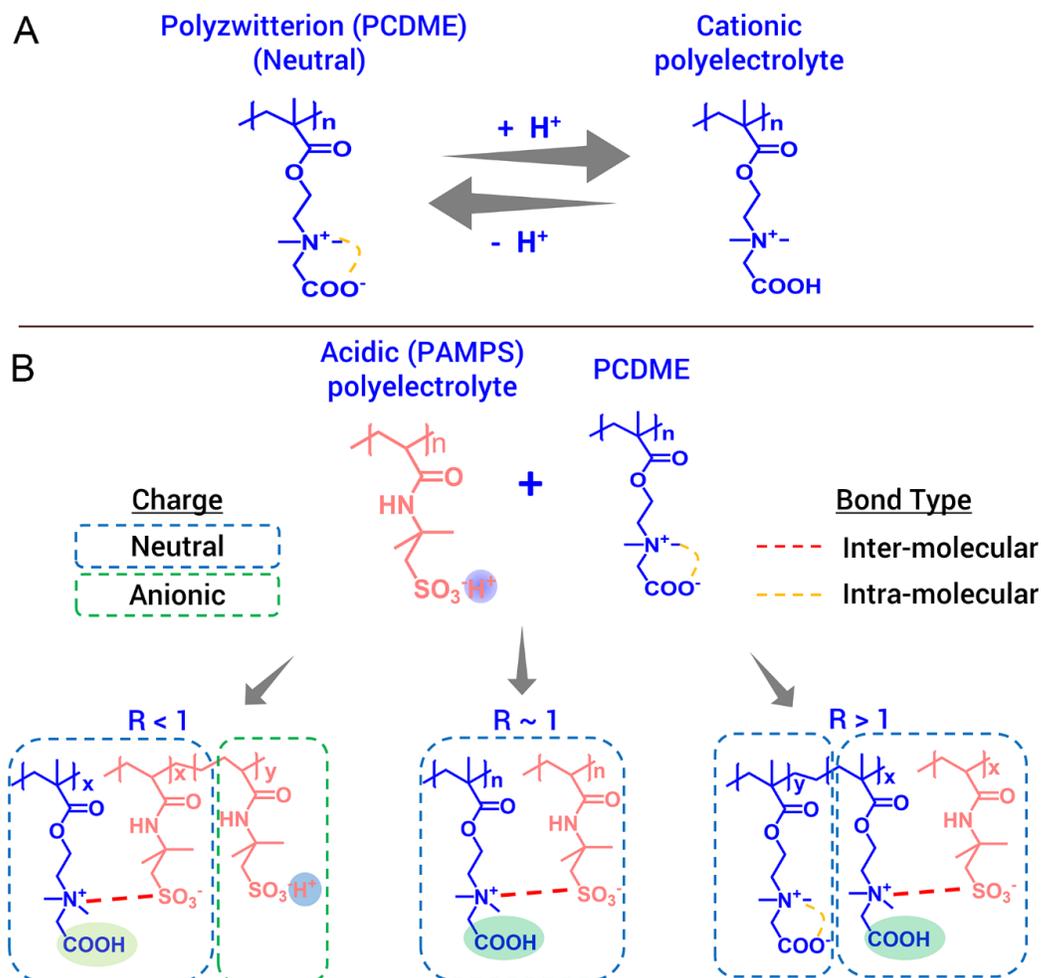
Recently, various toughening methods for hydrogels have been introduced.<sup>23–27</sup> Among them, the double network (DN) strategy has attracted much attention as an effective toughening method. A DN hydrogel consists of two interpenetrating networks with contrasting structures: the first network is rigid and brittle relative to the second network, and the second network is “stronger” than the first network. Usually, a polyelectrolyte is adopted as the first network, and a neutral polymer is employed as the second network. By a two-step fabrication process, the first network that swells significantly in the second network precursor solution is a minor component, consisting of only ~10% of the total mass of the DN gel. A DN gel is extremely tough because upon stretching, the first network fractures preferentially, dissipating energy, while the second network maintains the global integrity. When we employed PCDME as the second network to fabricate tough double-network (DN) hydrogels with poly(2-acrylamido-2-methylpropane sulfonic acid) (PAMPS), the PAMPS/PCDME DN hydrogels exhibited tunable mechanical properties with Young’s modulus of up to 0.9 MPa, fracture stress of 1.4 MPa, fracture strain of 6, and work of extension of 2.9 MJ m<sup>-3</sup>, comparable to traditional DN gels.<sup>22</sup> However, once damaged, DN gels have negligible self-recovery due to the irreversible, permanent fracture of the first network chemical bonds, which is a limitation for some applications.

In order to fabricate tough gels that exhibit self-recovery, many research groups have focused on incorporating weak but reversible sacrificial bonds, usually based on ionic or hydrogen bonds.<sup>27–29</sup> When stress is released after deformation, the elastic restoring force of

the polymer chains allows for reformation of the weak bonds, allowing for self-recovery of strain and subsequently toughness.<sup>30</sup> A polyelectrolyte complex (PEC) is formed from an equimolar mixture of cationic and anionic heterogeneous polyelectrolytes.<sup>31,32</sup> A PEC forms through interchain interactions between two separate chains that each carry only one specific charge. PEC hydrogels are tough hydrogels with many useful characteristics for biomedical applications.<sup>33–37</sup>

As a zwitterionic monomer, CDME contains both a negatively charged  $-\text{COO}^-$  group and a positively charged  $-\text{R}_3\text{N}^+$  group. The  $-\text{COO}^-$  group is a weak acid that exhibits pH dependent protonation, while the  $-\text{R}_3\text{N}^+$  group is pH independent. Therefore, PCDME can switch from a neutral polymer at high pH to a positively charged polymer at low pH (**Scheme 1A**). In our previous study, we saw that when large quantities of PCDME were combined with PAMPS, PCDME acts as a neutral component, despite the presence of PAMPS, a strong acid. In this case the gel was neutral because of the high value of the PCDME / PAMPS ratio,  $R$ , meaning PAMPS existed in only minute quantities. We imagine that by tuning the true molar ratio of PCDME and PAMPS, we can formulate a wide range of different gels (**Scheme 1B**). When  $R > 1$ , PCDME is neutral, resulting in the formation of swollen, interpenetrating network and double-network gels. When  $R \sim 1$ , the cationic PCDME and anionic PAMPS are in equal concentrations, and a PEC forms. When  $R < 1$ , the concentration of PCDME is too low to interact with the entire PAMPS network, resulting in the gel acting as an anionic polyelectrolyte. Through this approach, we can drastically modify the conformation and mechanical properties of the gels, without changing the precursor chemistry.

Based on this theory, we fabricate a series of hydrogels from a combination of PAMPS and PCDME with varied molar ratio of the two components. Utilizing elemental analysis, the true molar ratio of PCDME and PAMPS was determined. For the network structures containing different molar ratios of PCDME and PAMPS, four regions were



**Scheme 1. Schematic illustrations of the interactions that enable the fabrication of a variety of different gels from the same chemistry.** (A) In acidic conditions, PCDME becomes a positively charged polyelectrolyte. (B) In combination with PAMPS at different molar ratios, different types of interactions can form. When  $R < 1$ , PAMPS exists in a higher quantity than PCDME, and therefore the gel will possess anionic character. When  $R \sim 1$ , the two networks exist equally, and form inter-molecular ionic interactions. When  $R > 1$ , a neutral polymer is formed where the neat PCDME network makes up an increasingly large percentage of the total bulk gel.

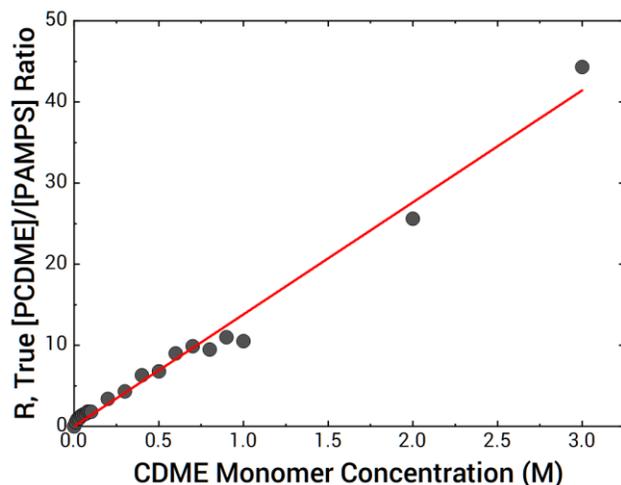
observed, in which the gels show different swelling and mechanical responses. These four regions represent different classes of hydrogels: polyelectrolyte (PE) gels, polyelectrolyte complex (PEC) gels, conventional, elastic interpenetrating network (IPN) gels, and double-network (DN) gels. In this work, we have focused on the latter three classes that possess properties that may make them useful for biomedical applications. Characterization of the materials was achieved through measuring swelling, modulus, toughness, and self-recovery. We discuss how the properties of each class differ and compare their functions as they relate towards applications. Ultimately, we show that with just one monomer combination (zwitterionic PCDME and acidic PAMPS), it is possible to develop a wide variety of hydrogels, each with their own unique blend of mechanical properties. These results will help enable to fabrication of new, biomedical materials with improved mechanical properties.

## 2. RESULTS

To fabricate tough hydrogels, we utilize the two-step sequential polymerization method described previously.<sup>25,33,38</sup> Briefly, first, the PAMPS gel is synthesized from aqueous solution containing 1 M AMPS monomer and crosslinker. This “first network” is then immersed in excess quantities of the CDME monomer solution of various concentration. The first network greatly swells in the CDME solution due to their polyelectrolyte nature and high osmotic pressure. After swelling, CDME is subsequently polymerized in the presence of the diluted first network. By changing the concentration of PCDME/PAMPS in the fabricated gel, we aim to create different types of gels with varying physical properties, as demonstrated in **Scheme 1B**. After the polymerization of PCDME, the gels were immersed in pure water to reach equilibrium. Details are given in the experimental section.

The PAMPS/PCDME gels were fabricated with a varying concentration of CDME, from 0 M (neat PAMPS gel) to 3 M. The true molar ratio,  $R$ , of PCDME to PAMPS in the fabricated hydrogels was experimentally determined by elemental analysis, in accordance with previous literature.<sup>22</sup> Briefly, the elemental composition of each monomer was calculated. Sulfur is only present in the PAMPS network, acting to distinguish the two networks. Details are shown in the Supporting Information (section 1). A total of 19 formulations, spanning over two orders of magnitude in  $R$ , were fabricated. The relationship between the CDME monomer concentration and the resulting true molar ratio,  $R$ , is shown in **Figure 1**. Due to significant swelling of PAMPS gel in the CDME monomer solution, the true ratio greatly exceeds the in-feed molar ratios.

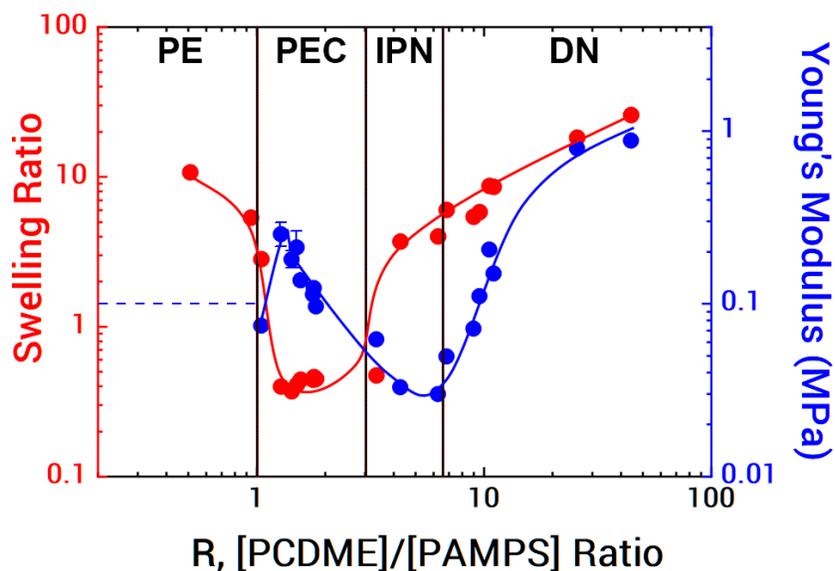
For each sample, the equilibrium swelling ratio was measured by the volume ratio of the PCDME/PAMPS sample at equilibrium to the as-prepared PAMPS single network gel.



**Figure 1.** A plot of the ratio ( $R$ ) of PCDME and PAMPS versus the CDME molar concentration in second network precursor solution. For all experiments, the first network was synthesized with a thickness of 1 mm and a PAMPS concentration of 1 M. The red line is a best fit of the experimental data.

Tensile tests were performed to measure the Young's modulus (details in the experimental section).

Results of both swelling ratio and Young's modulus as a function of  $R$  can be seen in **Figure 2**. The water content of these gels exhibits a trend similar to swelling ratio and is discussed in the Supporting Information (section 2, **Figure S1**). We see that the swelling ratio is initially very large for low values of  $R$ . When  $R$  approaches 1, the swelling ratio drops significantly to below 1. When  $R$  exceeds 3, the swelling ratio again begins to increase, ultimately exceeding the values measured at low  $R$ . The trend exhibited by Young's modulus was different. Young's modulus for samples at very low  $R$  are not shown because their high brittleness makes tensile testing extremely difficult. As a guide, one value is shown for the polyelectrolyte region ( $R = 0$ ), taken from the neat PAMPS gel, which has a Young's modulus of 0.1 MPa. This is denoted as a dashed line when  $R < 1$ . For  $R$  between 1 and 3, Young's



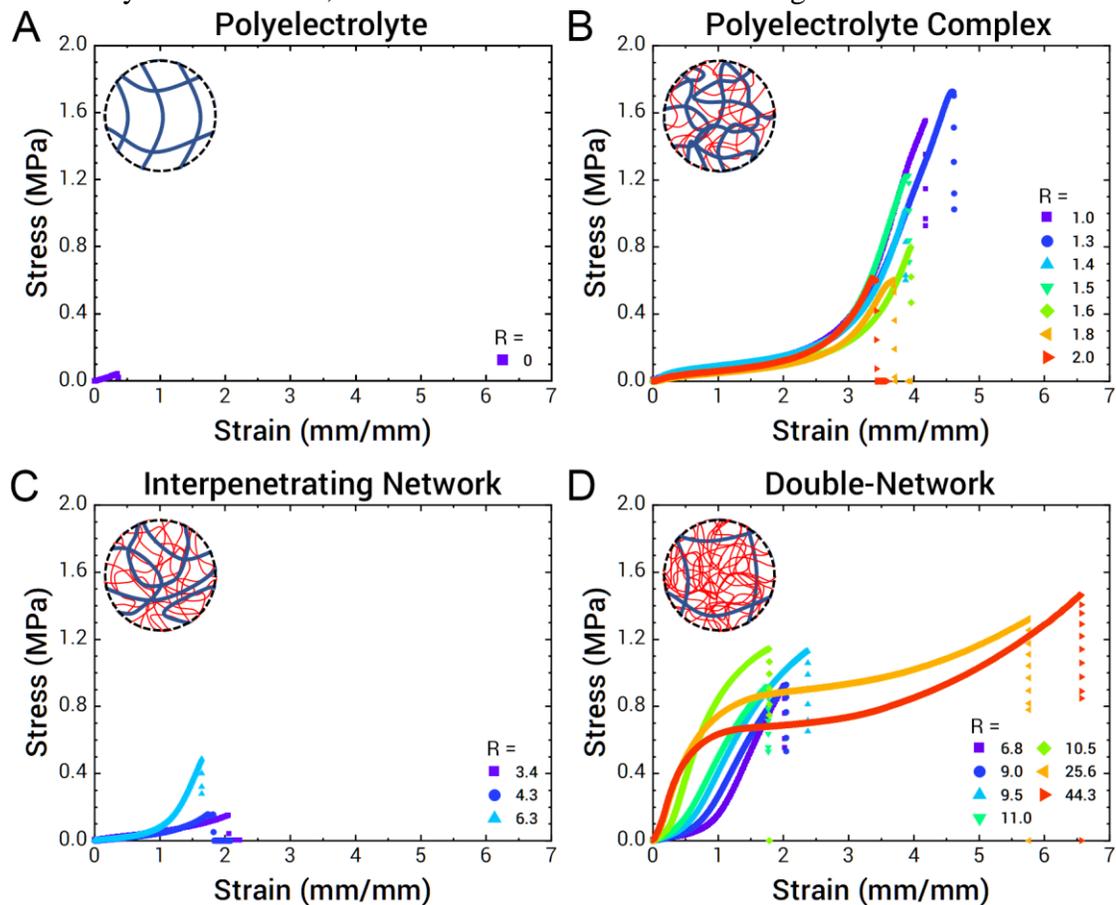
**Figure 2.** Four different gel regions can be formed by changing PCDME/PAMPS ratio,  $R$ . These different categories of gels are defined by their relative swelling ratio and Young's modulus. Red and blue lines are drawn as guides for the eye.

modulus is relatively high, exceeding 0.1 MPa. As  $R$  increases, the modulus decreases, until about  $R = 6.5$ , where it again begins to climb, ultimately reaching a Young's modulus near 1 MPa at  $R = 44.3$ . Based on these trends, we can distinguish four distinct regions that represent unique hydrogel classes formed from PCDME/PAMPS hydrogels: 1) the polyelectrolyte (PE) region,  $R < 1$ , where swelling ratio is high and modulus is low; 2) the polyelectrolyte complex (PEC) region,  $1 < R < 3$ , where swelling ratio is low and modulus is high; 3) the conventional interpenetrating network (IPN) region,  $3 < R < 6.5$ , where swelling ratio is relatively high and modulus is low; and 4) the double network (DN) region,  $R > 6.5$ , where swelling ratio is high and modulus is high.

Considering these four regions as distinct categories of gels, we aim to understand the relationship between their structural and mechanical properties. **Figure 3A** through **Figure 3D** contain the stress versus strain curves for each region, along with a schematic of the proposed network morphology (upper left insets). In these schematics, thick blue lines represent PAMPS and thin red lines represent PCDME. **Figure 3A**, corresponding to the polyelectrolyte (PE) region, contains gels with little or no PCDME content (data for  $R = 0$ , pure PAMPS gel, is shown). In this region, although the PCDME is positively charged, the concentration of PCDME is too low to fully balance the charges of the PAMPS network. As a result, the gels have net negative charges, acting as anionic polyelectrolyte gels. Due to the high osmotic pressure of the counterions of the first network, the gels are highly swollen with water. As the first network is in fully extended state, these gels are very brittle, fracturing at low stress and low strain. Due to the poor mechanical properties, the following analysis in this paper will focus on the remaining three regions.

The polyelectrolyte complex (PEC) region, shown in **Figure 3B**, contain gels where the true molar ratios of anionic PAMPS and cationic PCDME are nearly matched. The ionic interaction results in collapsed networks, containing dense PAMPS and PCDME. This region begins slightly above a value of  $R = 1$ , because the carboxyl group in PCDME is sensitive to pH. In some instances, the zwitterionic compounds may maintain their internal charge balance, requiring a higher concentration of PCDME to result in a truly charge-neutral hydrogel. Furthermore, once intermolecular interactions are saturated, additional PCDME content can be added without breaking the electrostatic weak bonds, up to  $R = 3$ . The Young's modulus of the gels in this region is relatively high due to their high network density and PEC structure. This region exhibits significantly higher fracture stress and fracture strain than the neat PAMPS gel. While the Young's modulus is still relatively low, and the gels undergo significant strain hardening around a strain of 3. For the  $R = 1.3$  formulation, a fracture stress of up to 1.8 MPa was recorded.

**Figure 3C** contains gels that exhibit a conventional, elastic IPN structure. These formulations exhibit high swelling ratio and low modulus. These gels lack a specific toughening mechanism. Due to the high second network (PCDME) content relative to the first network, higher osmotic pressure results in increased swelling ratio, and a dilution of the intermolecular electrostatic interactions seen in the PEC region. Excess PCDME maintains its internal charge balance, and the conventional IPN gel is neutral. The swelling ratio is less than seen in the polyelectrolyte region, meaning the first network chains are not in the fully extended state, and therefore the conventional IPN gels do not exhibit the double-



**Figure 3. Stress versus strain curves for the four different gel conformations:** (A) polyelectrolyte (PE) gel, (B) polyelectrolyte complex (PEC) gel, (C) conventional interpenetrating network (IPN) gel, and (D) double-network gel.

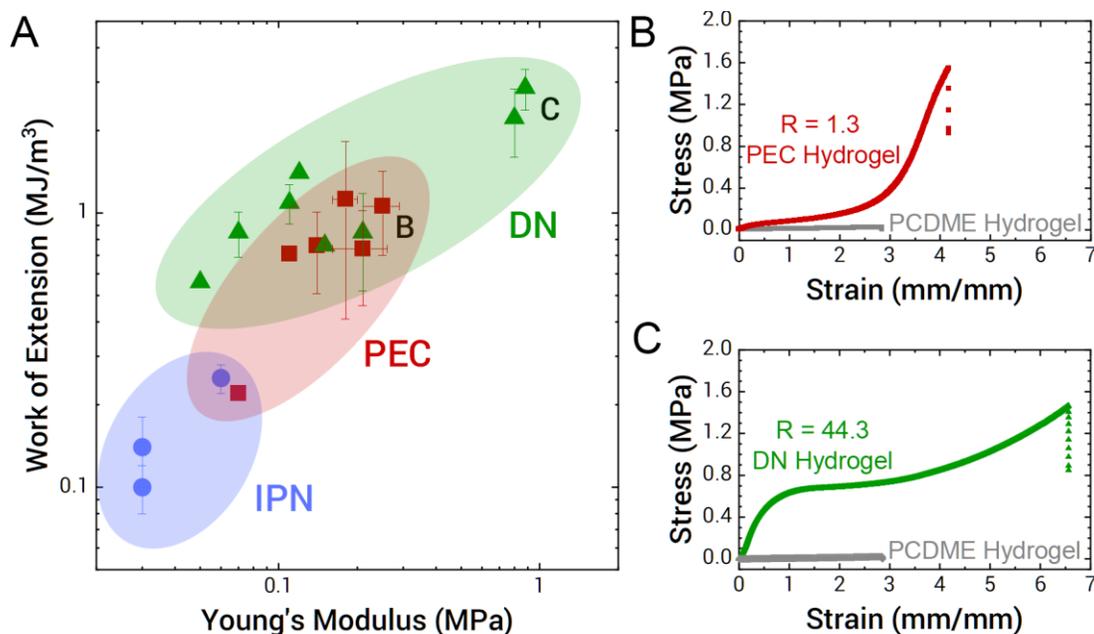
network effect. Here we see a decrease in fracture stress and fracture strain, compared to the PEC region. No crack blunting energy dissipation mechanisms exist in these gels, resulting in the decreased strain at break.

Finally, in the double network (DN) region (**Figure 3D**), significant swelling occurs due to the extremely high concentration of PCDME, extending the PAMPS first network strains near their maximum extensibility. Because the PAMPS network makes up only a small portion of the entire gel in this region, the gel is neutral. The large  $R$  in this region also ensures a stronger second network than the first network, which is required to show the DN effect.<sup>38,39</sup> The resulting double-network structure of a brittle first PAMPS network and a soft second PCDME network, leads to stiff and tough DN gels. Samples within this region at the low  $R$  range demonstrate increased stiffness due to extreme stretch of the PAMPS network strands, yet still fracture at lower strain than those in the PEC region. At very high values of  $R = 26.7$  and  $44.3$ , the sample undergoes yielding and strain hardening prior to fracture, exhibiting very high strength and toughness.

In **Figure 4A**, we plot the results from the tensile tests in the form of an Ashby plot, consisting of volume-normalized work of extension (calculated as the area under the stress versus strain curve) versus Young's modulus. By changing the ratio of PCDME/PAMPS, we are able to access nearly two orders of magnitude of both work of extension and Young's modulus. The three classifications of interest are highlighted. The IPN gels make up the lowest modulus and work of extension samples. The DN gels exhibit high work of extension over a wide range of Young's modulus. The PEC gels exist in an intermediate, overlapping region. The symbols corresponding to the highest performing PEC ( $R = 1.3$ ) and DN gels ( $R$

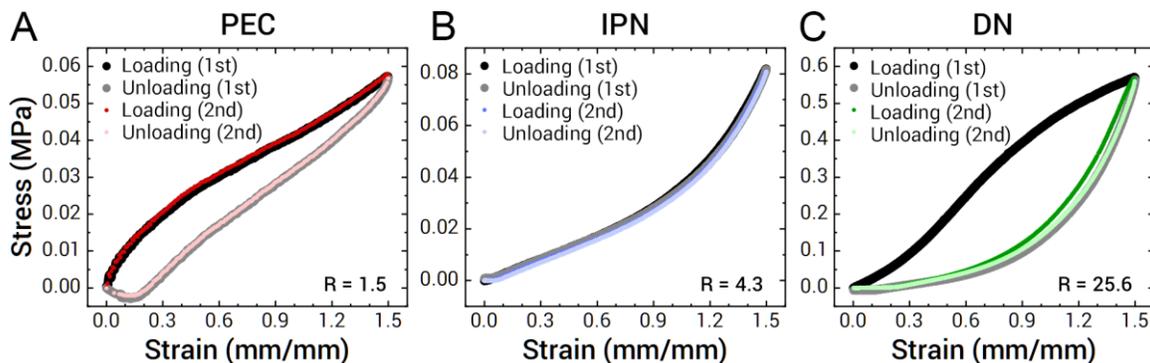
= 44.3) are denoted in the plot, and their stress versus strain responses compared to a neat PCDME gel are plotted in **Figure 4B** and **Figure 4C**, respectively. Utilizing either the PEC or DN toughening mechanism results in hydrogels with significantly improved mechanical properties compared to neat PCDME zwitterionic hydrogels, while stress-strain curves of the PEC and DN gels seem to be significantly different.

The PCDME/PAMPS gels toughened by the DN mechanism exhibit high strength and work of extension by using the fully swollen PAMPS network as a sacrificial network, fracturing covalent bonds to dissipate energy. One shortcoming of this method is that it limits the cycle-ability of these materials. Generally, after one loading cycle, upon reloading the work of extension decreases significantly, since the covalent sacrificial bonds of the first



**Figure 4. A comparison of PEC, IPN, and DN gel mechanical properties.** (A) An Ashby plot, comparing the work of extension to the Young's modulus. Work of extension and Young's modulus can be modulated over two orders of magnitude by changing  $R$ . (B) and (C) represent the stress versus strain response of representative PEC and DN hydrogels, compared to neat PCDME polyelectrolyte gels.

network strands that were near their extension limit have already broken. In contrast, PEC hydrogels having non-covalent sacrificial bonds based on weak but reformable ionic interactions. To test the reversible effect of the non-covalent sacrificial bonds, cycle tests were performed. A strain,  $\varepsilon = 1.5$  was applied, followed by unloading. After a waiting period, the sample was again loaded by applying  $\varepsilon = 1.5$ , followed by a second unloading. The results for the PEC ( $R = 1.5$ ), IPN ( $R = 4.3$ ) and DN ( $R = 25.6$ ) gels, with a five-hour waiting time can be seen in **Figure 5A**, **Figure 5B**, and **Figure 5C**, respectively. Each gel exhibits a unique response. For the PEC gel, the first cycle demonstrates hysteresis: the fracture of the weak ionic sacrificial bonds results in energy dissipation. After the waiting period, the second cycle overlaps with that of the first cycle, again dissipating energy, suggesting full recovery of the dissociated ionic bonds during waiting. The PEC gels also show large fracture strain (large stretching capacity) due to their dense network structure. The IPN gel exhibits an elastic response. During the first cycle, the unloading curve overlaps the loading curve, demonstrating no energy is dissipated. After the waiting time, again the extension and retraction curves overlap with the initial curve. Finally, the DN gel exhibits significant



**Figure 5. Cyclic tensile tests were performed to measure hysteresis and recovery ability.** Tests were performed with a strain of 1.5 for (A) PEC, (B) IPN, and (C) DN gels. The waiting time between the 1<sup>st</sup> and 2<sup>nd</sup> cycle was 5 hours.

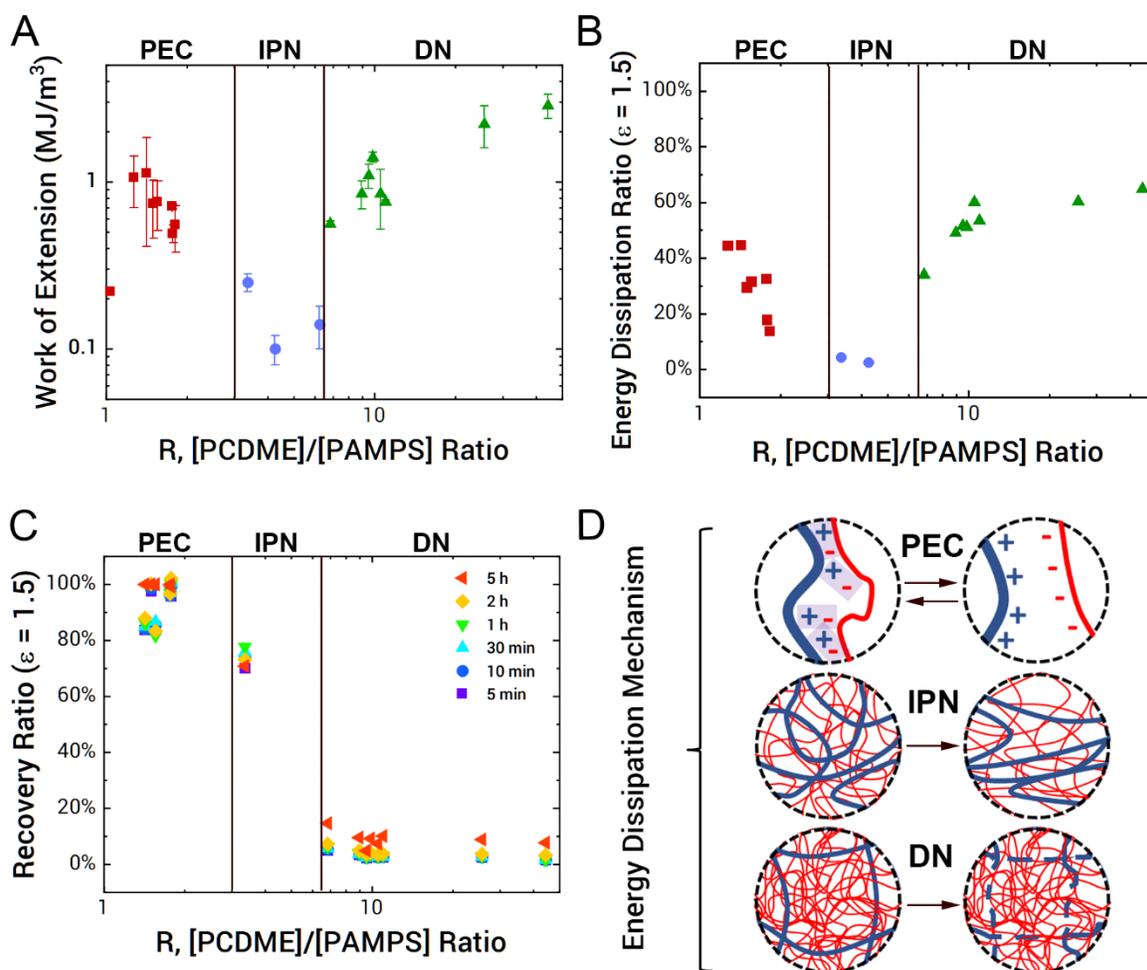
hysteresis in the first cycle, similar to the PEC gel. However, even after a five-hour waiting time, both the loading and unloading curve of the second cycle overlap with the unloading curve of the first cycle. Little energy dissipation is visible in this second cycle, demonstrating the irreversibility of dissipation in DN gels.

By combining the results of the tensile tests and cyclic tests, we can draw conclusions on the overall mechanical properties of gels produced by varying the ratio of PCDME and PAMPS in the network structure. **Figure 6A** shows the work of extension to fracture as a function of  $R$ , as calculated from tensile tests. We see that sacrificial bonds, whether weak ionic interactions or strong covalent bonds, result in gels that are very tough. Conventional IPN gels, lacking specific sacrificial bonding mechanisms, are much less tough. The incorporation of sacrificial bonds ultimately increases the work of extension to fracture by over one order of magnitude.

Next, we measure a similar property, the energy dissipation ratio, from the cyclic tensile tests (**Figure 6B**). We define the energy dissipation ratio as the ratio of hysteresis energy from cycle testing to the work of extension during the loading portion of the cycle test. Similar to the trend seen in **Figure 6A**, we see that the PEC and DN gels dissipate the most energy. For the PEC gel, up to 45% of the total work of extension is dissipated, whereas for the DN gel up to 60% energy dissipation was observed. In **Figure 3**, we saw that PEC gels exhibit significant hardening above a strain of 3, and it is likely that the energy dissipation ratio would increase with increased strain. Conversely for the DN gels, the high swelling ratio causes high elongation of the first network polymer strands, meaning that even at relatively low strains, DN gels can dissipate large amounts of energy. The IPN gels show

very low energy dissipation ratios of only a few percent, due to their elastic character. The usefulness of these gels will be considered further in the subsequent discussion section.

The primary characteristic that allows us to differentiate between DN gels and gels fabricated at lower  $R$  is the recovery ratio. **Figure 6C** shows the hysteresis recovery during cycle testing, with varying waiting time. The hysteresis recovery was calculated by



**Figure 6. Comparison of toughness during tensile testing and cycle testing.** (A) Work of extension to fracture, calculated by integrating the stress versus strain curve to fracture for each tensile test. (B) Energy dissipation ratio, calculated by dividing the hysteresis energy by the work of extension at  $\epsilon = 1.5$ . (C) Recovery ratio, calculated by dividing the work of extension after a variable waiting period, by the work of extension of a virgin sample. (D) Schematics of the energy dissipation mechanisms for PEC, IPN, and DN gels.

comparing the hysteresis energy of the first cycle to the second cycle. These tests were performed with a waiting time between cycles, ranging from five minutes to five hours. Longer waiting times results in a slight increase in recovery, yet we see that for both PEC gels and IPN gels a majority of the dissipation energy is recovered after just five minutes. DN gels, on the other hand, never recover significant energy, even after long waiting times.

Based on the results of the tensile and cycle tests, we can draw conclusions on how the energy dissipation mechanisms influence the resulting mechanical responses for different classes of gels formulated from PAMPS/PCDME structures. Schematic illustrations of the dissipation mechanisms for the PEC, IPN, and DN gels in the undeformed and deformed states are shown in **Figure 6D**. For the PEC gels, the dissipation mechanism is based on the reversible inter-network ionic bonds. While bulk gelation is due to the covalent cross-linking of each polymer components, energy dissipation comes from weak ionic interactions. When deformed, these weak interactions break, dissipating energy. However, the ionic interactions can be reformed upon unloading. This results in high work of extension, and high recovery.

For the conventional IPN gels, their swelling ratio is significantly higher than that of the PEC gels, yet not large enough to cause the first network to reach an extended state. Due to dilution of the ionic interactions in the gels by swelling, the effect of ionic sacrificial bonds on the mechanical properties of the IPN gels is negligible, resulting in their elastic mechanical properties. When stretched, both first and second network deform and can recover without significant fracture or damage. Unlike DN gels, the polymer strands are not extended to the point that they can sacrificially fracture during deformation. Therefore, at relatively low strain when damage occurs in either network, complete fracture of the sample occurs. This

occurrence is in contrast to DN gels that utilize sacrificial bonds to blunt cracks, enabling high stress and strain at break.

DN gels are formed when the high concentration of PCDME results in significant swelling of the PAMPS network, causing the network strands to be highly extended. During loading, the first network strands break dissipating energy. While this results in high work of extension, it is not a reversible process. These results demonstrate that simply by modifying the ratio of PCDME to PAMPS we can formulate gels that have a wide range of mechanical response and function.

### **3. DISCUSSION**

When developing materials for biological prosthetic applications, it is important to consider both the biocompatibility of the materials as well as the mechanical properties. Utilizing polyzwitterions as a building block for biomaterials is an attractive approach due to their inherent biocompatibility. Polyampholytes, which are charge neutral and similar to PEC gels have been shown to exhibit biocompatibility.<sup>28</sup> Moreover, charged surfaces can also act as suitable substrates for cell culturing.<sup>40,41</sup> Here, we demonstrate that through utilizing only two components, PAMPS and PCDME, and changing their relative ratio and concentration, we can create four different classes of materials with varying mechanical properties. Of these four materials, three have been the focus of our work and carefully characterized. Each of these materials has their own strengths and weaknesses. The resulting physical properties are qualitatively compared in **Table 1**. We note that here we are specifically comparing mechanical properties, and the application of these hydrogels as biomaterials will require in-depth biocompatibility and cell culturing studies.

Within living organisms, different tissues play different functional roles, but universally nearly all contain water.<sup>4</sup> Due to their similarities, gels represent the best type of material for use in biological prosthetics. The tunability of the hydrogels introduced here can be useful towards obtaining materials for a wide range of applications, while containing the same core chemistry. Cartilage, for example, is strong and tough. To achieve similar mechanical properties to these bio-tissues, DN gels formulated from PCDME and PAMPS with a mix ratio of  $R > 6.5$  would provide the best properties. Specifically, this formulation provides the highest modulus, along with high toughness. Skin is an important biomaterial that is able to deform easily while maintaining toughness yet possesses high recoverability. In this case, while DN gels dissipate more energy, PEC hydrogels would likely be preferable due to their combination of toughness and recoverability. In this case, a mix ratio of  $1 < R < 3$  is preferable. Resilin, a unique protein found in insects, provides organs and tissues with highly elastic properties, with little energy loss (high resiliency).<sup>42</sup> The conventional, elastic interpenetrating network gels, with a formulation of  $3 < R < 6.5$  also demonstrate high stretchability with low energy dissipation. We provide these comparisons not to propose PAMPS/PCDME hydrogels as synthetic mimics in their current form, but to demonstrate the usefulness of two-component hydrogel systems that can achieve a wide spectrum of different mechanical responses without requiring different chemistry.

**Table 1.** Qualitative comparison of the mechanical response for PEC, IPN, and DN gels.

	<b>PEC</b>	<b>IPN</b>	<b>DN</b>
Swelling ratio	<i>Low</i>	<i>High</i>	<i>High</i>
Young's modulus	<i>High</i>	<i>Low</i>	<i>High</i>
Work of extension to fracture	<i>High</i>	<i>Low</i>	<i>High</i>
Mechanical hysteresis (energy dissipation)	<i>High</i>	<i>Low</i>	<i>High</i>
Recoverability	<i>High</i>	<i>High</i>	<i>Low</i>

#### 4. CONCLUSION

The polyelectrolyte PCDME with carboxyl group exhibits a unique property that makes it exceptionally useful for hydrogels: depending on the environmental character, it can either exhibit a charge, or be charge neutral. We make use of this character by combining the PCDME in an interpenetrating structure with a strong polyelectrolyte acid, PAMPS. By only modifying the relative content of two fixed chemical networks, hydrogels can be fabricated with a wide range of useful mechanical properties. Specifically, four different classes of hydrogels, corresponding to the true PCDME/PAMPS ratio,  $R$ , have been obtained. When  $R < 1$ , a negatively charged polyelectrolyte gel is formed; when  $1 < R < 3$ , a charge-balanced polyelectrolyte complex gel is formed; when  $3 < R < 6.5$ , a conventional, neutral and elastic interpenetrating network gel is formed; and when  $R > 6.5$  a neutral double-network gel is formed. Both the PEC and DN gels exhibit high work of extension, making them useful for

applications. Importantly, the PEC gels exhibit strong recovery properties along with high toughness, distinguishing them from the double-network gels that cannot recover hysteresis after deformation. This method allows us to create biomaterials with tailored mechanical properties without changing the polymer chemistry.

## 5. EXPERIMENTAL SECTION

### 5.1 Materials

Monomers, *N*-(carboxymethyl)-*N,N*-dimethyl-2-(methacryloyloxy)ethanaminium, inner salt (CDME, Osaka Organic Chemical Co., Ltd., Japan) and 2-acrylamido-2-methylpropane - sulfonic acid (AMPS, Toa Gosei Co., Ltd., Japan) were used as received. Initiator, 2-Oxoglutaric acid (Wako Pure Chemical Industries, Ltd.) was used as received. Crosslinker, *N,N'*-Methylenebis(acrylamide) (MBAA, Wako Pure Chemical Industries, Ltd., Japan) was recrystallized from ethanol.

### 5.2 Synthesis of PAMPS/PCDME hydrogels

PAMPS/PCDME hydrogels were prepared by a two-step sequential free-radical polymerization. In the first step, poly(2-acrylamido-2-methylpropanesulfonic acid) (PAMPS) hydrogels were prepared from 1 M of AMPS, 4 mol% of cross-linker MBAA, and 0.1 mol% initiator (both relative to the AMPS monomer). A reaction cell was made from a 1 mm silicone spacer separating two glass plates, and the polymerization proceeded by UV irradiation for 8 h in an argon glove box. In the second step, the prepared PAMPS hydrogels were immersed into a large excess aqueous solution containing 0.01–3 M of CDME, 0.02 mol% of MBAA and 0.01 mol% initiator (both relative to the CDME monomer) for at least 3 days. The first network gel swelled similarly, regardless of CDME concentration. The PCDME second network was synthesized between two polyethylene terephthalate plates by UV irradiation. After this 2-step synthesis, the PAMPS/PCDME hydrogels were immersed in pure water for 1 week until reaching swelling equilibrium.

### 5.3 Elemental analysis

After freeze-drying, elemental analysis of carbon, hydrogen, nitrogen, and sulfur was conducted at the chemical analytical center of Hokkaido University, Japan, using standard techniques. The swelling degree of the gels was estimated by measuring the mass ratio of the sample in its swollen state to its dried state. The procedure for calculating the true molar ratio,  $R$ , was performed using nitrogen and sulfur, and the calculation is shown in the Supporting Information.

### 5.4 Swelling measurement

Swelling behaviors of the PAMPS/PCDME hydrogels in pure water were characterized by the volume swelling ratio  $V/V_0 = (H/H_0)^3$ , where  $H$  and  $H_0$  are the thickness of the PAMPS/PCDME hydrogels in the swollen state and the as-prepared PAMPS gel ( $H_0 = 1$  mm), respectively.

### 5.5 Tensile testing

Mechanical properties of PAMPS/PCDME hydrogels were measured by tensile testing using a tensile tester (Instron 5965, Instron Co.). For the tensile test, samples of 0.72 ~ 2.96 mm in thickness were cut into a dumbbell shape (width of 2mm, gauge length of 12mm) using a gel cutter (JIS-K6251-7). Tensile velocity was 50 mm/min. For the tensile tests, the fracture stress and the fracture strain were determined as the nominal stress and the nominal strain at the failure point, respectively. Young's modulus  $E$  was determined as the slope at the strain range of 0-0.1 mm/mm from the stress-strain curve. The work of extension to fracture was

determined from the area under the stress-strain curve of the tensile test. Measurements were performed at least three times for each sample.

### **5.6 Cycle testing**

For the cyclic tensile test, all of the experiments were carried out in a water bath to prevent samples from become dry. Sample geometry was the same as for regular tensile testing. A fixed strain of ( $\varepsilon = 1.5$ ) was applied to the sample. The sample was then unloaded at the same rate as loading, 50 mm/min. Work of extension was calculated from the loading and unloading curve. Hysteresis energy was determined as the area between the loading curve and the unloading curve. Energy dissipation is presented as a percentage of hysteresis energy divided by the work of extension during loading. The work of extension was determined as the area between the loading curve and the horizontal axis. Recovery ability was determined by stretching the sample to a strain of ( $\varepsilon = 1.5$ ) and unloading, followed by a variable waiting time. After this waiting time, the cycle test was again performed. Recover ability is presented as a percentage of the hysteresis energy of the second cycle test compared to the first cycle test.

## **6. CONFLICTS OF INTEREST STATEMENT**

There are no conflicts to declare.

## **7. ACKNOWLEDGEMENTS**

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## **8. SUPPORTING INFORMATION**

Raw data of elemental analysis and method for calculating the true molar ratio, R.  
Comparison of swelling ratio and water content.

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