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Synthesis and Application of Modulated Polymer Gels

Zhibing Hu,* Xiaomin Zhang, Yong Li

A class of environmentally responsive materials based on the spatial modulation of the chemical nature of gels is proposed and demonstrated here. The modulation was achieved by limiting the interpenetration of part of one gel network with another gel network. The gels so produced have an internally heterogeneous or modulated structure. Three simple applications based on the modulated gels are described here: a bigel strip, a shape memory gel, and a gel "hand." The bigel strip bends almost to a circle in response to a temperature increase or an increase in solvent concentration. The shape memory gel changes its shape from a straight line to a pentagon to a quadrangle as the temperature increases. These transitions from one shape to another are reversible. The gel "hand" in water can grasp or release an object simply by an adjustment of the temperature.

Polymer gels have attracted much interest because their volume can be changed by three orders of magnitude in response to the change of an external factor such as solvent, temperature, electric field, or light (*1–6*). The potential application of gel materials as artificial muscles was first demonstrated by Katchalsky's group in his famous collagen engine (*7*). Subsequently, the ability of gels to serve as drug-delivery devices (*8–10*), chemical valves and actuators (*11–13*), and magnetic resonance monitoring agents (*14*) has been explored. The gels used in all of these reports had macroscopically uniform structures.

Here we propose and demonstrate a class of materials based on the spatial modulation of the chemical nature of gels. The modulation is achieved by allowing only part of one gel network to interpenetrate with another gel network. The resultant gels have an internally heterogeneous or modulated structure. We present three simple applications of these modulated gels: a bigel strip, a shape memory gel, and a gel "hand." These three applications are based on changes in the volume of gels in response to external environmental changes (*15*). In particular, the temperature sensitivity of the *N*-isopropylacrylamide (NIPA) gel and the acetone concentration sensitivity of the acrylamide (PAAM) gel (*16*) are the controlling mechanisms for the three applications described here. The bigel strip bends almost to a circle in response to an increase in its temperature or to an increase in the concentration of the acetone solvent. The shape of the shape memory gel changes among straight, pentagonal, and quadrangle forms at different temperatures. A temperature adjustment causes the gel "hand" to grasp or release an object. The results reported here have significance for the manufacture of active gel devices and sensors.

We synthesized the bigel strip by first making a NIPA gel slab. Two glass slides with a ~1.0-mm gap between them were immersed in 100 ml of an aqueous solution of 690 mM NIPA, 8.6 mM methylene-*bis*-acrylamide (BIS), and 8 mM sodium acrylate. The polymerization of the solution was initiated by the addition of 240 µl of tetramethylethylenediamine and 40 mg of ammonium persulfate [for experimental details, see (*6*)]. About 20% of the water in the NIPA gel was evaporated for a better interpretation process. In the second step, a PAAM gel slab was made between two glass slides (approximately 2.0 to 3.0 mm apart) with the NIPA network (~1.2 mm thick) between them and in contact with one of the glass slides. The distance between the two glass slides was larger than the thickness of the swollen NIPA network. The acrylamide gel "ingredient" was allowed to diffuse into the NIPA network for a sufficiently long time (~1 hour) before polymerization was initiated. This ensured the formation of NIPA-PAAM interpenetrating networks. The acrylamide gel consisted of 700 mM acrylamide and 8.6 mM BIS. The end product was a gel slab 2.0 to 3.0 mm thick with a layered network structure: A PAAM network 0.8 to 1.8 mm thick and a 1.2-mm PAAM network interpenetrated by a NIPA network is shown in Fig. 1A.

It is well known (*16*) that the volume of the ionic NIPA gel (made with 8 mM sodium acrylate) shrinks drastically at temperatures higher than 37°C, whereas the volume of the PAAM gel does not. Similarly, the volume of the PAAM gel shrinks much more in acetone-water mixtures (>34% by weight) than does the NIPA gel. At room temperature (~22°C) the fully swollen bigel strip bends slightly toward the PAAM gel side. If the temperature is increased above 37°C, the NIPA gel responds by shrinking drastically, whereas the PAAM gel is insensitive to the temperature change. As a result, when the bigel strip is heated uniformly, it gradually bends into an arc (Fig. 1, B and C). However, because the PAAM gel shrinks drastically in acetone-water mixtures and the NIPA gel does not, bending in the opposite direction occurs as the bigel strip is immersed in an acetone-water mixture (Fig. 1, D and E). The transition between the straight and the arc forms is reversible. We found that the variation in the degree of bending in nine sequential straight-bending-straight cycles was less than 3%.

The amount of bending can be quantified by the bending angle, θ, defined to be the angle between the two tangents of the gel arc at the two ends. The strains induced in the gel are then equal to $s = (\theta d)/L$, where d and L are the thickness and the length of the gel, respectively. This equation is valid even for large bending (large θ, as for twisting into a spiral), whereas the result of Shiga *et al.* (*17*) is based on a three-point bending model and is valid only for small bending. For small θ

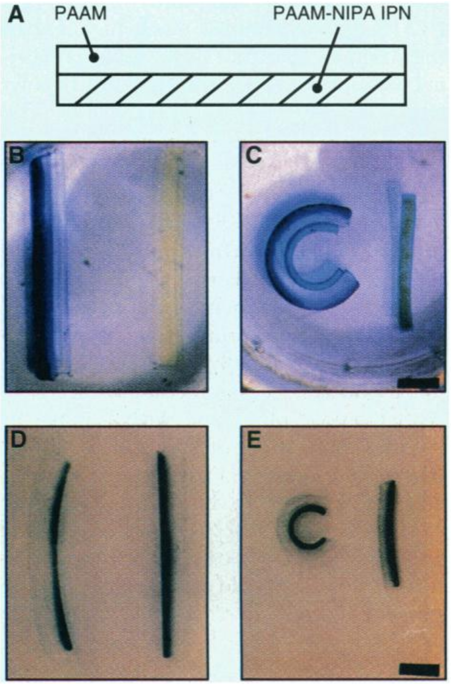

Fig. 1. (**A**) Sketch of the bigel strip with one PAAM gel (empty area) modulated by the interpenetration of one side of the PAAM gel with the NIPA gel, that is, a PAAM-NIPA interpenetrating polymer network (IPN) (shaded area). (**B** and **C**) Photos showing the bending of the bigel in water at a temperature of (B) 30.0°C and (C) 37.8°C. The PAAM gel of the bigel strip is coated with blue color for better visualization. The gel at the right of each picture is a pure NIPA gel as a reference. (**D** and **E**) Photos showing the bending of the bigel in a water-acetone mixture at an acetone concentration of (D) 20% and (E) 45% by weight. The gel at the right of each picture is a pure PAAM gel as a reference. Scale bar, 5 mm.

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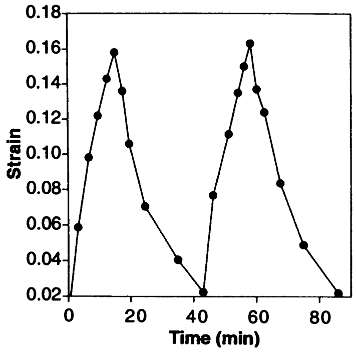

Fig. 2. Two cycles of the time dependence of the bending strain of the bigel. The increase of strain is obtained at 38°C and the decrease of strain at 22°C.

(small bending), our equation differs from that of Shiga *et al.* by a factor of 0.75, which arises from differences in assumptions regarding the shape of the sample cross section (circle versus rectangle).

Using this equation, we found that the maximum strain for the bigel is ~49% and that it occurs after the volume phase transition point of the ionic NIPA gel (~37°C). This strain is much higher than the strain of 20% that develops in poly(vinyl alcohol)–poly(sodium acrylate) copolymer gels under an electric field (*17*). The kinetics of bending is shown in Fig. 2. Starting from 22°C, we raised the sample temperature quickly to 38°C by transferring the sample from one water bath to another. The strain was obtained from photos taken of the sample at various times. The strain increases with time when the gel is immersed in the high-temperature bath. Upon cooling, the bigel gradually assumes its original shape and size. This process has been repeated in up to nine cycles with a change in the maximum strain of less than 5%.

The mechanism of bigel bending reported here is different from that brought about by an electric field (*11, 12, 17*) or infrared laser heating (*6*). In those cases, a gradient of the electric potential field or a gradient of the temperature field must be applied to trigger the bending of the gels, which are macroscopically homogeneous. Because of limitations associated with providing the complex external field gradient, a high degree of bending ($\theta > 180°$) cannot be easily obtained by those methods. In our experiment, the external environment is uniform, although the samples are internally modulated. Therefore, the sample bends directly in response to the temperature and solvent composition without the need for a gradient environment. A large degree of bending such as in a spiral can be achieved by either increasing the sample length or temperature.

The difference in the thermal expansion coefficients between two gels can be much larger than that between two metals. For example, the difference of expansion coefficients for a typical bimetallic strip of brass and steel is about 7×10^{-6} per degree Celsius. However, for the PAAM-NIPA bigel, such a difference can be as high as 0.5 per degree Celsius [the ionic NIPA gel made with 8 mM sodium acrylate shrinks to half its linear size per degree Celsius near the transition point at about 37°C (*16*), whereas the PAAM gel has no volume change in this temperature range], which is five orders of magnitude greater. Therefore, bigels can be far more sensitive to their environment than bimetals.

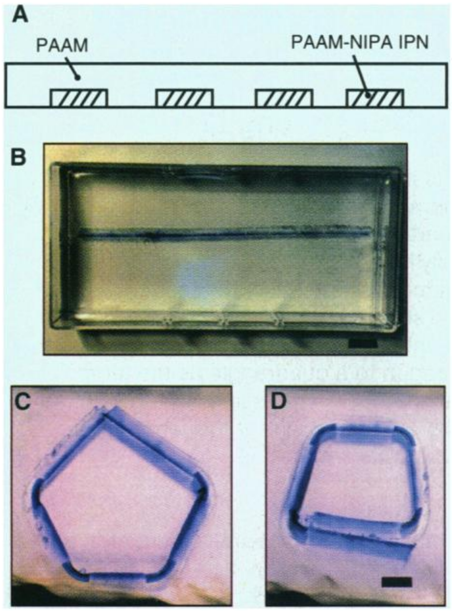

Fig. 3. (**A**) Sketch of the shape memory gel produced as a result of the modulation of the PAAM gel with NIPA gels at four locations (shaded areas). We prepared the sample by polymerizing the PAAM gel in the presence of four NIPA gel pieces that were placed on a glass plate. The separation between adjacent NIPA gel pieces is about 12 mm. (**B** through **D**) The gel shape at various temperatures: (B) 22°C, (C) 39°C, and (D) 41°C. Scale bar is 15 mm in (B) and 6 mm in (D); the length scales in (C) and (D) are the same.

A gel with a more complex modulated structure, a shape memory gel (Fig. 3A), was prepared in a manner similar to that used for the bigel sample. In this system the PAAM gel is modulated with the NIPA gel at four locations so that the gel can bend only at these modulated sites as the temperature is increased. At room temperature, the modulated gel is straight (Fig. 3B). As the temperature increases, the gel parts at modulated sites begin bending, forming a pentagon (39°C, Fig. 3C) and then a quadrangle (41°C, Fig. 3D). The change from pentagon to quadrangle is related to the higher shrinking ratio of NIPA at 41°C than at 39°C. As a result, the bigel at 41°C bends more (about 90°, that is, a quadrangle) than the bigel at 39°C (about 70°, that is, a pentagon). Transitions between different shapes are reversible. A variety of transitions, including a change from a straight line to a sinusoidal form, from a flat sheet to a hollow tube, and from a long strip to a spiral (*18*), of the gels at various temperatures can be obtained by proper design and control of the modulation pattern of the system, whereas the gel memory effect induced by chemical cross-linking under elongation is much more limited (*19*).

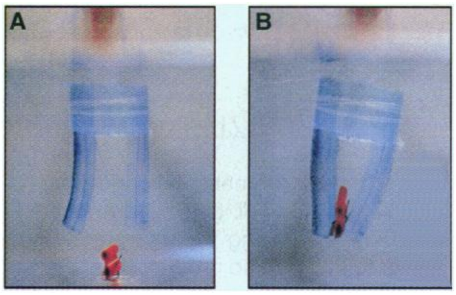

Fig. 4. A gel "hand" made from two bigel strips that have the same structure as that shown in Fig. 1A and are tied together at one end with a spacer. The NIPA-modulated sides are facing each other. The thicknesses of the PAAM gel and the NIPA-modulated side are 2.1 mm and 1.5 mm, respectively. (**A**) At 22°C, the "fingers" are open and a red object is released. (**B**) At 35°C, the "fingers" are closed and the object is caught.

To further demonstrate the potential of the modulated polymer gels, we made a gel "hand" consisting of two bigel strips, and it is shown immersed in water in Fig. 4. These bigel strips are identical to the bigels discussed earlier. At room temperature (Fig. 4A), the "fingers" of the "hand" are open and an object is released. At 35°C (Fig. 4B), the "fingers" are closed and the object is grasped.

The gel functions obtained from this modulation method are based on the fact that the volumes of different gels are sensitive to different aspects of the external environment. Applications of the modulation method could be extensive: for example, a modulated bigel of the pH-sensitive gel (polyacrylic acid) with PAAM should bend in a pH environment as well. Because a large amount of strain can be produced, the modulated gels may find use in gel display devices, switches, or valves.

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Importance of Historical Contingency in the Stereochemistry of Hydratase-Dehydratase Enzymes

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There are two stereochemical classes of hydratase-dehydratase enzymes. Those that catalyze the addition of water to α,β-unsaturated thioesters give *syn* addition-elimination stereochemistry, whereas those that catalyze the addition of water to conjugated carboxylate substrates give *anti* stereochemistry. This dichotomy could reflect different adaptive advantages or contingencies of separate evolutionary histories. Determination of the nonenzymatic stereochemistry of deuterium oxide addition to fumarate and to *S*-crotonyl *N*-acetylcysteamine has provided direct evidence for the importance of the contingencies of evolutionary history, rather than chemical efficiency, in the pathways of these hydratase-dehydratase enzymes.

The diversity inherent in the primary, secondary, and tertiary structures of proteins fosters catalysis of unparalleled precision and efficiency. The specificity that enzymes show in substrate recognition and the rate at which the subsequent chemical transformations are performed are extraordinary. With billions of years of evolutionary history, can we safely assume that enzymes will always use the most favorable pathways for the transformations that they catalyze? Dorit *et al.* have argued that modern protein diversity represents only a very limited exploration of sequence space—an exploration constrained by the success of earlier motifs—and that some proteins may well lie at local optima (*1*). Do the pathways of some natural enzymatic processes represent local rather than global optima?

Because of ambiguities in our understanding of the precise mechanistic and kinetic details of most complex enzymatic reaction pathways, it is difficult to find convincing evidence pertaining to this important question by examining the rates of enzymatic reactions; however, stereochemistry offers a more promising opportunity. The stereospecificity of enzyme-catalyzed reactions has been a fruitful source of information about the mechanisms of enzymatic catalysis, but stereochemical investigations have also generated interesting puzzles. One of these concerns the *syn* or *anti* stereochemistry of addition-elimination reactions, which play fundamental roles in most metabolic pathways.

All hydratase-dehydratase reactions in which the abstracted proton of the substrate is α to a carboxylate group, such as fumarate hydratase, aconitate hydratase, and enolase, proceed with *anti* stereochemistry. Seven examples are known (*2, 3*). In general, *syn* pathways are not favored in most nonenzymatic elimination reactions because of the eclipsed geometry necessary in the transition state, and *anti* elimination is favored by stereoelectronic effects (*4*); therefore, this *anti* stereochemical pattern is no surprise. However, there is also a group of eight dehydratases that produce the *syn* elimination of water, including enoyl–coenzyme A (CoA) hydratase, fatty acid synthetase, and β-hydroxydecanoyl thioester dehydratase; in these reactions, the proton abstracted is α to a carbonyl group of a thioester or a ketone (*2, 3*). It has been shown that enoyl-CoA hydratase favors the *syn* pathway by more than 8.8 kcal/mol (*5*).

Functional theories often argue that evolutionary selection pressures have produced enzymes that are optimally adapted to catalyze their specific reactions. Indeed, some enzymes act with a catalytic efficiency close to chemical perfection (*6*). In an effort to provide an adaptive explanation for the *syn* stereochemistry in addition-elimination reactions, it has been suggested that the acidity of the proton attached to the α carbon might influence which is the most efficient pathway. Because the α protons of thioesters ($pK_a \sim 22$ to 23, where K_a is the acid dissociation constant) are more acidic than those of carboxylate salts or carboxylic acids ($pK_a \geq 25$), it has been argued that this increased acidity could tilt the stereochemistry toward *syn* addition-elimination, with catalytic group economy in having a single acid-base enzymatic group that could interact both with the α proton and with the β leaving group (*2, 7*).

However, the stereochemical preference need not have a basis in mechanistic advantage. There are two other evolutionary possibilities. In the first, the stereochemistry may be functionally significant, and in each stereochemical class of dehydratases the pattern simply represents divergent evolution from two ancestral progenitors with conservation of active site structure. A second possibility is that the functional difference is insignificant and therefore neutral to natural selection. Selective pressures might not be strong enough to favor one stereochemical outcome over the other, because the energetic difference between the *syn* and *anti* elimination pathways involving unhindered acyclic substrates is rarely, if ever, more than 3 kcal/mol (*4*).

We chose to try to understand this *syn-anti* dichotomy by determining the innate chemical stereoselectivity for the addition of water across the conjugated double bond of a substrate from each stereochemical class, under nonenzymatic conditions. The two substrates that we used are disodium fumarate (**1**) and *S*-crotonyl *N*-acetylcysteamine (**3**), shown in Fig. 1. Of course, fumarate is the actual substrate of fumarate hydratase, and **3** is identical to the substrate of enoyl-CoA hydratase near the site of the addition reaction. Although the actual substrate is the CoA thioester, Lynen found that **3** is also catalytically processed by the enzyme (*8*), which produces *syn* elimination on the *S*-pantetheine thioester of crotonate as well (*9*). In addition, β-hydroxydecanoyl thioester dehydratase gives *syn* elimination from the *N*-acetylcysteamine substrate (*10*).

The stereoselectivity of conjugate addition to α,β-unsaturated esters can be quite high, on the order of 10:1 *anti*/*syn* for the addition of deuterated ethyl alcohol

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