

Strengthening Alginate/Polyacrylamide Hydrogels Using Various Multivalent Cations

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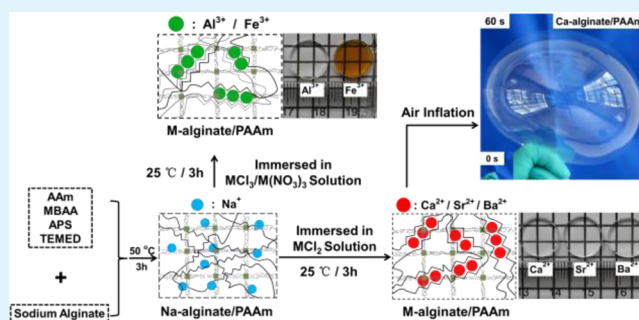
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S Supporting Information

ABSTRACT: We successfully synthesized a family of alginate/polyacrylamide hydrogels using various multivalent cations. These hydrogels exhibit exceptional mechanical properties. In particular, we discovered that the hydrogels cross-linked by trivalent cations are much stronger than those cross-linked by divalent cations. We demonstrate stretchability and toughness of the hydrogels by inflating a hydrogel sheet into a large balloon, and the elasticity by using a hydrogel block as a vibration isolator in a forced vibration test. The excellent mechanical properties of these hydrogels may open up applications for hydrogels.

KEYWORDS: alginate/polyacrylamide hydrogel, various multivalent cations, strength, stretchability, toughness, vibration



INTRODUCTION

Hydrogels are being developed for diverse applications, including tissue engineering, drug delivery, and soft machines.^{1–7} Most existing hydrogels, however, are weak, brittle, and not very stretchable. During the past decades, intense efforts have been devoted to creating strong, stretchable, tough hydrogels. Examples include double-network hydrogels, topological hydrogels, and nanocomposite hydrogels.^{8–14} It has been recently discovered that Ca-alginate/polyacrylamide (PAAm) hydrogel can be stretched beyond 20 times and achieve fracture energy as high as $\sim 9000 \text{ J m}^{-2}$.¹⁵ The value is much higher than that of pure alginate hydrogel ($\sim 25 \text{ J m}^{-2}$) or PAAm hydrogel ($\sim 150 \text{ J m}^{-2}$).¹⁵ Besides remarkable mechanical properties, the Ca-alginate/PAAm hydrogel also exhibits excellent biocompatibility.¹⁶

The Ca-alginate/PAAm hydrogels were fabricated by a one-step method. Water was mixed with all ingredients needed to form the two networks: sodium alginate and ionic cross-linker (calcium sulphate, CaSO_4) for the ionically cross-linked alginate; acrylamide, covalent cross-linker (N,N'-methylenebisacrylamide, MBAA), thermo-initiator (ammonium persulphate, APS) and accelerator (N,N,N',N'-tetramethylethylenediamine, TEMED) for the covalently cross-linked polyacrylamide. As a result, alginate chains will interpenetrate with the covalently cross-linked PAAm network, and the alginate network will be ionically cross-linked by Ca^{2+} cations, which

will zip the alginate network. The exceptional toughness of Ca-alginate/PAAm hydrogel is well-understood:¹⁵ alginate and PAAm severally provides a strengthening mechanism and have a cooperative effect. When a load is sustained, the loosely cross-linked long PAAm polymer chains are stretched; at the same time, the alginate component is unzipped from the ionically cross-linked points, supplying an energy dissipation mechanism. During the elongation, the unzipping of ionic cross-link increases the number of polymer chains which participate in load bearing, whereas the stretchable PAAm polymer chains stabilize deformation once the ionic cross-links are broken.

Accordingly, it is possible to enhance the mechanical properties of alginate/PAAm hydrogel by appropriately tuning alginate network or PAAm network. In fact, the mechanical properties of ionically cross-linked alginate can be adjusted by multivalent cations, such as divalent cations (Ca^{2+} , Sr^{2+} , and Ba^{2+}).¹⁷ Although alginate hydrogels cross-linked by different cations have been extensively studied, the effects of the chemistry of ionic cross-link on the mechanics of alginate/PAAm hydrogel are much less explored.

The one-step method, however, is difficult to apply to the fabrication of alginate/PAAm hydrogels cross-linked by various

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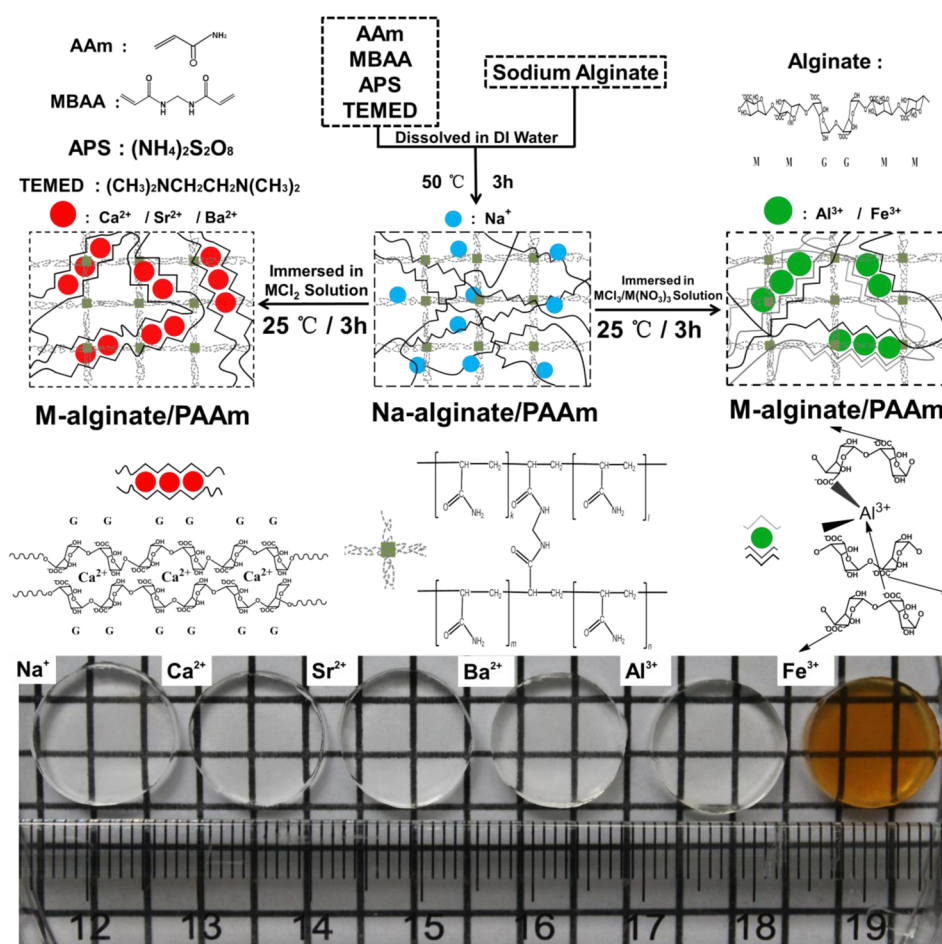


Figure 1. Two-step method to synthesize alginate/PAAm hydrogels cross-linked by multivalent cations. The photos show various kinds of transparent hydrogels.

multivalent cations. In fabricating Ca-alginate/PAAm hydrogel, CaSO_4 was used due to its low solubility in water, so that alginate could be gradually cross-linked by dissociated Ca^{2+} cations, resulting in a homogeneous hydrogel. By contrast, high soluble CaCl_2 would fast cross-link alginate, and failed to produce homogeneous hydrogel. It would be time-consuming to identify a suitable salt and optimal processing conditions for each kind of multivalent cation.

In this contribution, we propose a facile two-step strategy to tune the cross-link of alginate, obtaining alginate/PAAm hydrogels cross-linked by various multivalent cations. The mechanical properties of these hydrogels are greatly enhanced compared with the hydrogels prepared by one-step method. Specially, the hydrogels containing trivalent cations are much stronger than those containing divalent cations. To demonstrate stretchability and toughness of these hydrogels, we inflate a sheet of Ca-alginate/PAAm hydrogel into a large balloon. We also show that the hydrogels are effective as vibration isolators by using a Ca-alginate/PAAm hydrogel block as a vibration isolator in a forced vibration test. We envision that hydrogels of much improved mechanical properties will open up applications, such as artificial tissues, soft robotics, and structural materials.

EXPERIMENTAL SECTION

The stretchable tough hydrogels are synthesized by a two-step method. In brief, in the first step, all ingredients except the ionic

cross-linker are dissolved in deionized water to obtain a homogeneous and transparent solution. The solution is transferred into a mold and placed in an oven at 50 °C for 3 h to produce Na-alginate/PAAm hydrogel. In the second step, the Na-alginate/PAAm hydrogel is immersed in an aqueous solution containing multivalent cations for 3 h, resulting in hydrogel cross-linked by multivalent cations. Here the 3 h soaking time is sufficient to obtain hydrogel with stable mechanical properties, which is confirmed by both approximately calculation and experiments (see Figure S1 in the Supporting Information).

Other details regarding detail synthetic process, mechanical characterizations, air inflation experiment, and calculation of natural frequency are supplied in the Supporting Information.

RESULTS AND DISCUSSION

In the first step, a Na-alginate/PAAm hydrogel is synthesized (Figure 1) in which the PAAm is cross-linked by covalent bonds and the Na-alginate is well-dispersed but not cross-linked. Alginate is a linear copolymer of α -L-guluronic acid (G unit) and β -D-mannuronic acid (M unit). The monovalent Na^+ cations do not cross-link alginate, whereas multivalent cations cross-link alginate by simultaneously associating with carboxylic groups on different units of alginate chains.^{18–20} In the second step, the Na-alginate/PAAm hydrogel is immersed in an aqueous solution of CaCl_2 , SrCl_2 , BaCl_2 , AlCl_3 or $\text{Fe}(\text{NO}_3)_3$, resulting in a highly homogeneous and transparent alginate/

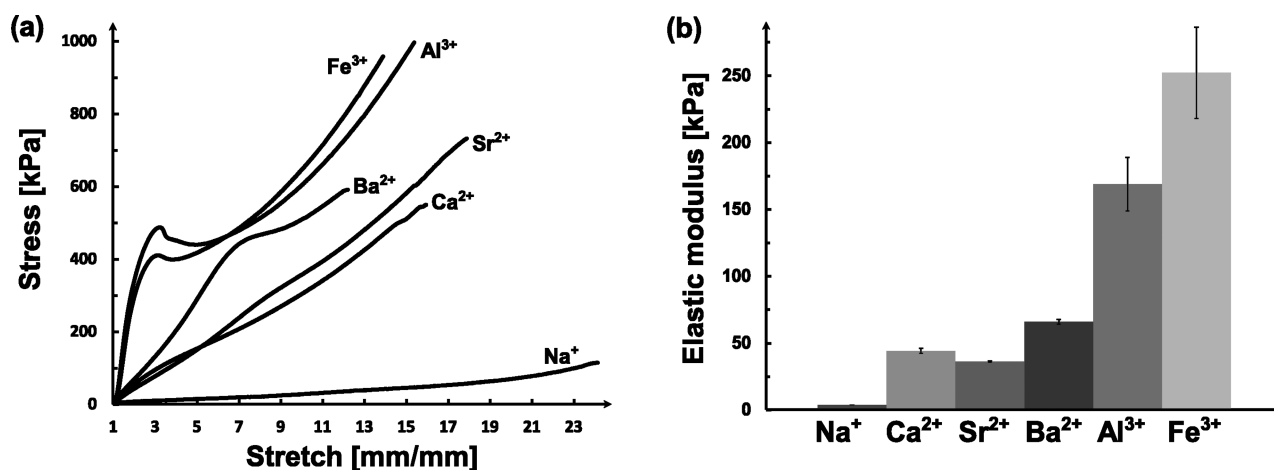


Figure 2. (a) Stress–stretch curves of various hydrogels, each elongated to rupture. (b) Elastic modulus of various hydrogels. Error bars show standard deviation.

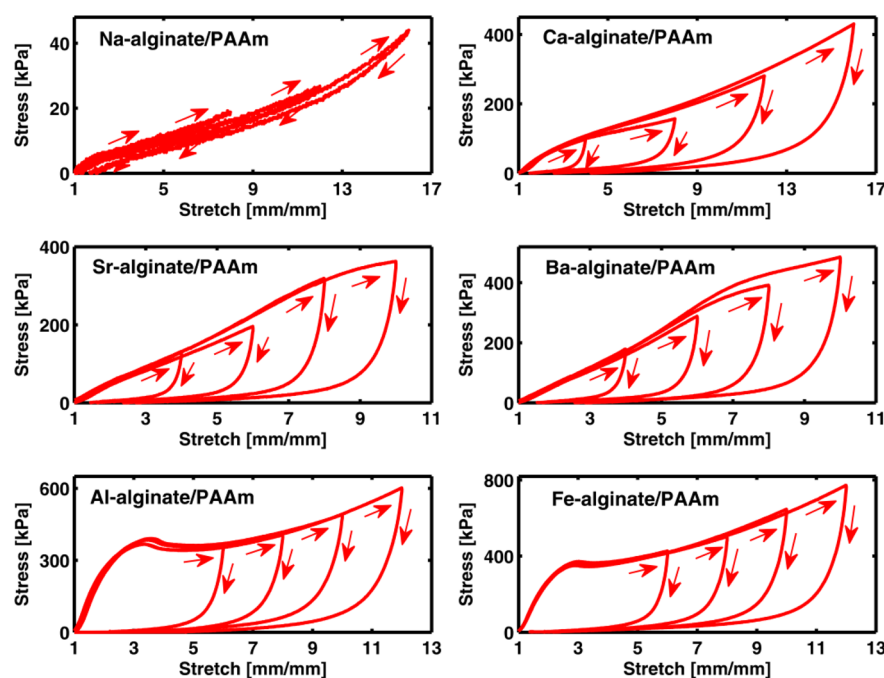


Figure 3. Hysteresis curves of various kinds of alginate/PAAm hydrogels.

PAAm hydrogel cross-linked by multivalent cations (Figure 1). This result is remarkable, given that highly soluble salts like CaCl_2 are known to produce inhomogeneous hydrogels when pure alginate is involved.^{21,22}

Alginate hydrogel microbeads are used as matrix for three-dimensional cell immobilization, and Ca^{2+} , Sr^{2+} , Ba^{2+} , and Al^{3+} are commonly used as cross-linkers.^{23,24} Note that Ca^{2+} binds to GG and GM blocks, Ba^{2+} to GG and MM blocks, whereas Sr^{2+} to GG blocks uniquely.¹⁷ Alginate hydrogels cross-linked by Ba^{2+} or Al^{3+} exhibit higher stability in biological environment than those cross-linked by Ca^{2+} .²⁴

We compare the mechanical properties of alginate/PAAm hybrid hydrogels cross-linked by various cations (Figure 2a, b). As expected, both divalent and trivalent cations greatly increase strength and stiffness of the hydrogels. In particular, Al-alginate/PAAm hydrogel and Fe-alginate/PAAm hydrogel reach strength of 939.1 ± 47.6 kPa and 942.5 ± 22.0 kPa, and stiffness of 169.0 ± 20.0 kPa and 252.2 ± 34.0 kPa,

respectively. However, Na-alginate/PAAm hydrogel shows low strength (116.2 ± 0.8 kPa), low elastic modulus (3.8 ± 0.1 kPa), but high stretchability (24.4 ± 0.8), which are similar to those of pure PAAm hydrogel (see Figure S2 in the Supporting Information). Though less stretchable than Na-alginate/PAAm hydrogel, the hydrogels containing divalent or trivalent cations can be stretched more than 10 times, which should be enough for many applications.

The much better mechanical properties of Al-alginate/PAAm and Fe-alginate/PAAm hydrogel are understood as follows: mechanical properties of alginate/PAAm hydrogels depend on the interaction between multivalent cations and GG blocks, MM blocks, and GM blocks in alginate polymers. Molecular modeling and ^{13}C nuclear magnetic resonance (NMR) spectroscopy studies have shown that both charge and ion radius of multivalent cations can affect the interaction, and the charge may be more significant.²⁵ Accordingly, the cross-linking degree of alginate depends on the properties of the cross-linker

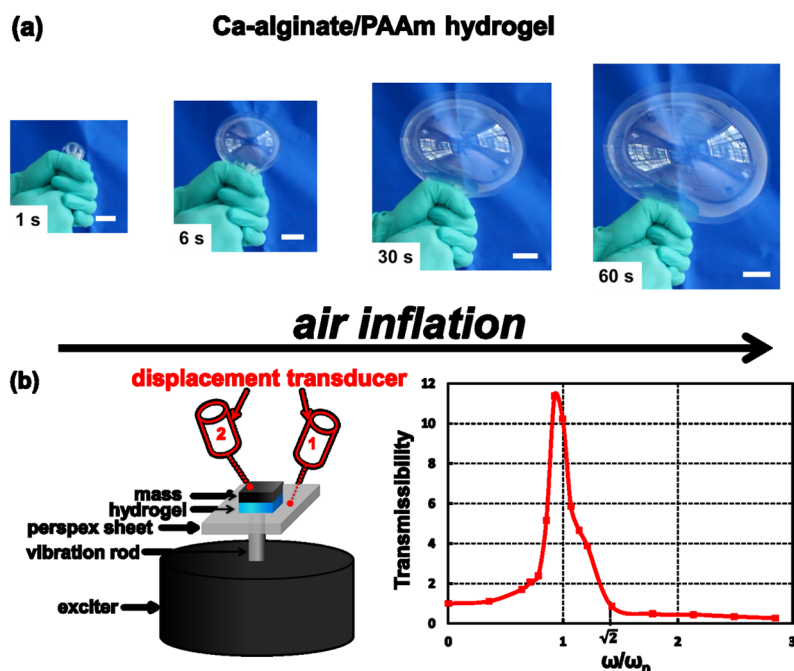


Figure 4. (a) Air inflation experiment of a Ca-alginate/PAAm hydrogel balloon (scale bars: 4 mm). (b) Schematic representation of the vibration isolation experiment set-up (left) and the transmissibility versus frequency ratio ω/ω_n (right).

ions (i.e., charge and ion radius of multivalent cations). In the case of divalent cations, egg box model has illustrated that the cations bond with the blocks of alginate polymers in a planar two dimensional manner, and the extent of binding increases with an increasing of ionic radius.²⁵ It has been reported that Ba^{2+} cations with larger ion radius (1.35 Å) can form a tighter structure compared with Ca^{2+} cations with smaller ion radius (1.0 Å),²⁶ because Ba^{2+} cations are expected to fill a larger space between the blocks of alginate polymers, resulting a tighter arrangement of cross-linked alginate polymers.²⁷ Compared with divalent cations, the binding extent of trivalent cations with alginate is enhanced. Trivalent cations could interact with three carboxylic groups of different alginate chains at the same time, lead to a larger coordination number ($(\text{COO})_3\text{M}$) and form a three dimensional valent bonding structure, resulting in a more compact networks. So alginate/PAAm hydrogels cross-linked by trivalent cations exhibit higher mechanical properties. In addition, Fe-alginate/PAAm hydrogel exhibits a higher stiffness than Al-alginate/PAAm hydrogel, because Fe^{3+} (6.45 Å) has a larger ion radius than Al^{3+} (5.35 Å).²⁶ Interaction between multivalent cations and alginate has been studied, and the existing conclusions are consistent with our argument.^{24,27} Furthermore, we have tried more kinds of divalent cations (Zn^{2+} , 7.4 Å; Cu^{2+} , 7.3 Å; and Co^{2+} , 6.5 Å) and trivalent cation (Eu^{3+} , 9.47 Å) to verify our argument.²⁶ And the experimental results also support the conclusion that the trivalent cations cross-linking will yield better mechanical properties (see Figure S3 in the Supporting Information).

We observed that hydrogels containing trivalent cations (Al^{3+} or Fe^{3+}) exhibited distinct yield points, whereas those containing divalent cations (Ca^{2+} , Sr^{2+} , or Ba^{2+}) did not (Figure 2a). The Al-alginate/PAAm hydrogel and Fe-alginate/PAAm hydrogel underwent homogeneous deformation until the yield point was reached (see Figure S3 in the Supporting Information). After this point, deformation became inhomogeneous: un-necked region and necked region coexisted, with the necked region being deformed more than the un-necked

region. On further stretching, the necked region enlarged at the expense of the un-necked region. Ultimately the sample deformed homogeneously again. This phenomenon is reminiscent of the Luders band in low-carbon steel, and of necking in double-network hydrogels.²⁸ Again, difference of mechanical behavior of hydrogels cross-linked by divalent and trivalent cations might be due to their difference of bonding with alginate.²⁷

Tough hydrogels reveal remarkable dissipation of energy, which can be characterized by hysteresis. Hydrogels containing divalent or trivalent cations demonstrate large hysteresis (Figure 3). The area enclosed by the loading and unloading curves is the energy dissipated in the cycle. The Na-alginate/PAAm hydrogel shows negligible hysteresis. However, for a cycle with a maximum stretch of 8, the energy dissipated is $588.1 \pm 62.4 \text{ kJ m}^{-3}$ for Ca-alginate/PAAm hydrogel, $784.2 \pm 89.5 \text{ kJ m}^{-3}$ for Sr-alginate/PAAm hydrogel, $1231.8 \pm 90.8 \text{ kJ m}^{-3}$ for Ba-alginate/PAAm hydrogel, $2159.4 \pm 155.2 \text{ kJ m}^{-3}$ for Al-alginate/PAAm hydrogel, and $2107.1 \pm 73.2 \text{ kJ m}^{-3}$ for Fe-alginate/PAAm hydrogel. Hysteresis exists even before the yield point for both Al-alginate/PAAm hydrogel and Fe-alginate/PAAm hydrogel (see Figure S4 in the Supporting Information). The large hysteresis in the hydrogels containing divalent and trivalent cations maybe due to the unzipping of the ionic cross-links. The remarkable enhancement of mechanical properties of alginate/PAAm hybrid hydrogels is possibly attributable to the synergy of two mechanisms: bridging by the network of covalent cross-links and hysteresis by unzipping the network of ionic cross-links.^{15,29} Upon this stage, the mechanical properties of hydrogels cross-linked by multivalent cations are summarized and compared (Table 1, Supporting Information).

To demonstrate stretchability and toughness of the hydrogels, we inflate a hydrogel membrane into a large balloon by using an air pump (see Figure S5 in the Supporting Information). We cover an air pipe (inner diameter: 4 mm) with a sheet of Ca-alginate/PAAm hydrogel (150.0 mm \times 150.0 mm \times 1.0 mm), and then inflate the sheet (see Figure 4a

in the Supporting Information, Movie 1). The area strain of the hydrogel balloon is estimated from the photographs to be about 760% at 60 s.

To demonstrate elasticity of the hydrogels, we test them as vibration isolators by using a setup commonly adopted for testing rubbers and other polymer compounds (Figure 4b).³⁰ We fasten a mass (50g) and a block of Ca-alginate/PAAm hydrogel (30.0 mm × 20.0 mm × 8.0 mm) on a vibration exciter. The amplitude of vibration of the mass is recorded as a function of the frequency of excitation ω . The transmissibility is defined as the amplitude of vibration of the mass (measured by displacement transducer 2) divided by the amplitude of vibration of the exciter (measured by displacement transducer 1), and the frequency of excitation is normalized by the natural frequency ω_n . The natural frequency is estimated to be approximately 70 Hz (for calculation of natural frequency, see the Supporting Information). The transmissibility is lower than 1 when $\omega/\omega_n > \sqrt{2}$, as expected for a forced vibration of a viscous-damped system.³¹ The results indicate that the novel tough hydrogel is an effective vibration isolator.

CONCLUSIONS

In summary, we report a facile two-step method to synthesize alginate/PAAm hydrogels with excellent mechanical properties. The Na-alginate/PAAm hydrogels are prepared first, and then immersed in aqueous solutions containing divalent or trivalent cations. Ionic cross-linking of alginate is regulated by a convenient ion-exchange approach, which results in hydrogels of high strength and remarkable toughness. Trivalent cations lead to hydrogels of significantly higher strength and modulus than divalent cations. The two-step method also enables us to explore how the chemistry of ionic cross-link affects the mechanics of alginate/PAAm hybrid hydrogels. We inflate a sheet of hydrogel into a large balloon and demonstrate a block of hydrogel as a vibration isolator, which imply that such strong and tough hydrogels might have potential applications as structural materials.

ASSOCIATED CONTENT

Supporting Information

Details regarding detail synthetic process, mechanical characterizations, air inflation experiment, and calculation of natural frequency. This material is available free of charge via the Internet at <http://pubs.acs.org>.

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Notes

The authors declare no competing financial interest.

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