

Supramolecular Materials

An “Ingredients” Approach to Functional Self-Synthesizing Materials: A Metal-Ion-Selective, Multi-Responsive, Self-Assembled Hydrogel

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Abstract: New methodology for making novel materials is highly desirable. Here, an “ingredients” approach to functional self-assembled hydrogels was developed. By designing a building block to contain the right ingredients, a multi-responsive, self-assembled hydrogel was obtained through a process of template-induced self-synthesis in a dynamic combinatorial library. The system can be switched between gel and solution by light, redox reactions, pH, temperature, mechanical energy and sequestration or addition of Mg^{II} salt.

Recent developments in dynamic combinatorial chemistry^[1] have led to the new concept of self-synthesizing materials,^[2] in which a self-assembly process drives the synthesis of the very molecules that self-assemble from a mixture of interconverting species. For cases in which self-assembly is based on non-covalent interactions, self-synthesis involves the formation of covalent bonds. This intriguing concept exploits the reversibility of bond formation in dynamic combinatorial libraries (DCLs), which are mixtures of molecules capable of exchanging building blocks such that the composition tends to be governed by thermodynamics. Molecular recognition events will bias the product distribution of DCLs towards those library members that yield the largest overall binding energy for the system. Originally, templates were used to bias the product distribution towards the formation of ligands for biomolecules^[1c,3] or synthetic receptors.^[1c,4] More recently it has been shown that, when no templates are added, self-selection in a dynamic combinatorial library, in which the library members bind to copies of themselves, may lead to the formation of materials that not only self-assemble, but thereby also self-synthesize.^[2] We now report the first example in which an externally added template drives the 1D self-assembly of a self-synthesizing material. While the template does not participate in dynamic covalent bond formation, it alters the library distribution in a small DCL

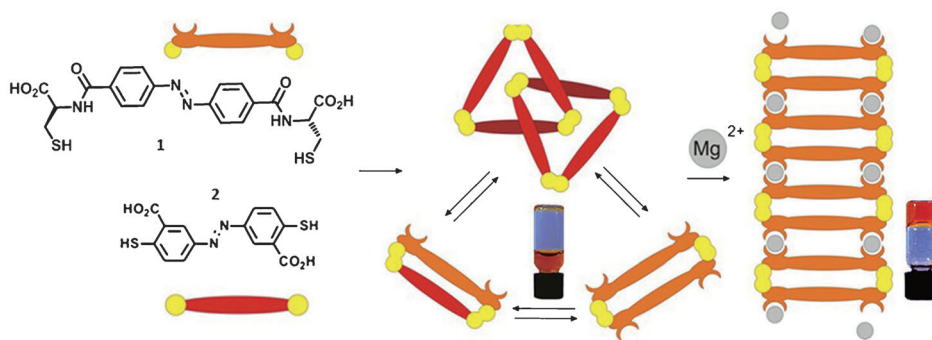
based on photoswitchable building blocks. We also demonstrate the potential of an “ingredients” approach to functional materials, in which it is sufficient to design building blocks to contain the ingredients for specific properties of the material, and allow the material to build itself from these building blocks. The result is a self-assembling and self-synthesizing hydrogel.

Hydrogels play an increasingly important role in a diverse range of applications, such as drug delivery, sensing, tissue engineering and wound healing.^[5] Desirable properties include stimuli-responsiveness and self-healing ability. While conventional gel chemistry is dominated by polymers, more recently interest in gels has extended to small organic molecules^[6] and their metal-ion complexes.^[7] We now describe the dynamic combinatorial development of a highly metal-ion-selective, self-assembled hydrogel that is self-healing and uniquely multi-responsive: it may be switched between gel and solution states by light, mechanical energy, redox chemistry, temperature changes and pH changes. Since the metal ion is an integral part of the gel, gelation also depends on the presence or absence/sequestration of the metal ion.

Since our understanding of self-assembly processes in water is still incomplete, the reliable design of self-assembled hydrogelators remains a challenge. In the dynamic combinatorial approach to such materials it is not necessary to design every step of the assembly process or even to design the self-assembling molecule. It is sufficient to only provide the system with building blocks that contain the right ingredients. The self-assembly process then instructs the system to synthesize the appropriate molecules from these building blocks. We decided to use this “ingredients” approach to develop a hydrogel that is responsive to light, redox chemistry, metal-ion chelation and ideally also mechanical energy. The necessary ingredients for achieving this many functions had to be contained in the design of the building blocks: We envisaged that light-responsiveness could be achieved by incorporating the known azobenzene photoswitch.^[8] Redox responsiveness may be realized by the use of disulfide bonds, which function as reversible covalent linkages at the same time.^[9] Metal-ion affinity may be provided by incorporating carboxylate and carbonyl groups.^[7a,b] Metal-ligand coordination may also be sensitive to pH. Finally, mechanical and temperature sensitivity may be realized by ensuring that the hydrogel self-assembles from small molecular constituents through relatively weak interactions. Potential ingredients for driving the self-assembly process are already contained in the design elements described above and

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Scheme 1. DCLs of building block 1 and 2 with or without MgCl_2 .

include hydrophobic and π - π interactions between the azobenzene units^[10] and metal ions that may potentially bridge between carboxylate groups. These considerations led us to design and synthesize building blocks 1 and 2 (Scheme 1, for synthesis, see Supporting Information).

A small DCL was prepared by dissolving building blocks 1 (5.0 mM) and 2 (2.0 mM) in aqueous borate buffer (50 mM, pH 8.1). The DCL was placed in a capped vial in a dark environment for seven days in the presence of oxygen from the air to allow oxidation of the thiols into disulfides. Residual thiolate mediates the disulfide exchange reaction that enables equilibration of the DCLs.^[9] The resulting free-flowing solution was analyzed by HPLC-MS (Figure 1 a), which revealed that the

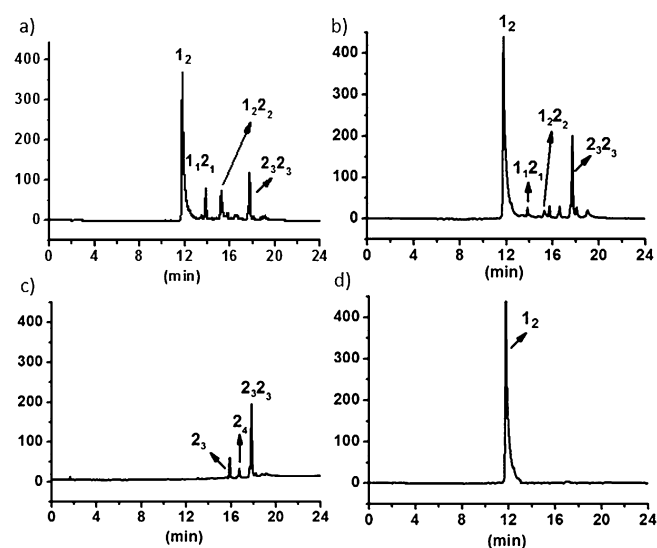


Figure 1. HPLC-MS analysis of a DCL made from building block 1 (5.0 mM) and 2 (2.0 mM) a) without; b) with MgCl_2 (20 mM); DCL made from only c) building block 1 (5.0 mM); and d) building block 2 (2.0 mM) with MgCl_2 (20 mM) in an aqueous borate buffer (50 mM, pH 8.1).

main species in the library were homo-dimer 1_2 , hetero-dimer $1_2 1_1$, tetramer $1_2 2_2$ and a [2]catenane $2_3 2_3$ built from two mechanically interlocked trimers of building block 2 (Scheme 1).^[11]

We then investigated the response of the DCL to the introduction of metal ions. Most of the metal salts we introduced

(CaCl_2 ; SrCl_2 ; BaCl_2 ; AlCl_3 ; ZnCl_2 ; CdCl_2 ; HgCl_2 ; CuCl_2 ; NiCl_2 ; FeCl_2) failed to induce gelation, with one notable exception: a transparent hydrogel was obtained in the presence of MgCl_2 (Figure 2). Analysis by HPLC-MS shows that in the presence of this template the concentrations of 1_2 and $2_3 2_3$ increased at the expense of $1_2 1_1$ and $1_2 2_2$ (Figure 1 b). The disappearance of the mixed

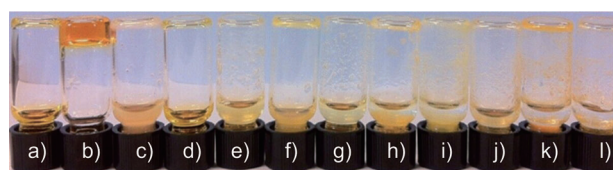


Figure 2. Appearance of DCLs made from a) building block 1 (5.0 mM) in borate buffer (50 mM, pH 8.1) and with 20 mM metal salts: b) MgCl_2 ; c) CaCl_2 ; d) SrCl_2 ; e) BaCl_2 ; f) AlCl_3 ; g) ZnCl_2 ; h) CdCl_2 ; i) HgCl_2 ; j) CuCl_2 ; k) NiCl_2 ; l) FeCl_2 .

dimer and tetramer indicates that MgCl_2 induces the sorting of the DCL.

In order to clarify which component was responsible for gelation, two DCLs were made by dissolving building block 1 (5.0 mM) or 2 (2.0 mM) with MgCl_2 (20 mM) in borate buffer (50 mM, pH 8.1). Only the DCL prepared from 1 turned into a hydrogel, whereas that made from 2 and MgCl_2 remained a free-flowing solution. HPLC-MS analysis (Figure 1 d) of the hydrogel only showed one peak, the mass of which corresponds to 1_2 , suggesting that gelation is the consequence of the formation of coordinative bonds between 1_2 and Mg^{2+} . Further evidence for this mode of assembly was obtained by adding a known strong chelator, ethylene diamine tetraacetic acid (EDTA; 5.0 mM) to the hydrogel, which resulted in the immediate conversion into a non-viscous solution. When another portion of MgCl_2 (20 mM) was added, the solution reverted back to the hydrogel over a period of two days.

In order to provide more detailed structural insights we attempted to obtain crystals of the 1_2 - Mg^{2+} assembly that were suitable for X-ray diffraction studies. While all attempts using Mg^{2+} as a template failed, similar experiments with Ca^{2+} were successful. The Ca^{2+} complex crystallizes in space group $P2_1$ as $(1_2)_2\text{Ca}_2(\text{H}_2\text{O})_{15}$, $Z=2$. In its crystal structure two distinct organizational motifs can be recognized. Firstly, linear stacks of azobenzene moieties are formed (Figure 3 a). The stacks show a spacing between the aromatic rings that alternates between 3.3 Å for the azobenzene units within a macrocycle and 3.6 Å for the corresponding distance between two adjacent macrocycles. Secondly, the crystal structure reveals a chain that is composed of calcium ions coordinated by the amide carbonyl oxygen and the carboxylate oxygen atoms of macrocycle 1_2 (Figure 3 b and Figure S6 in the Supporting Information). Water

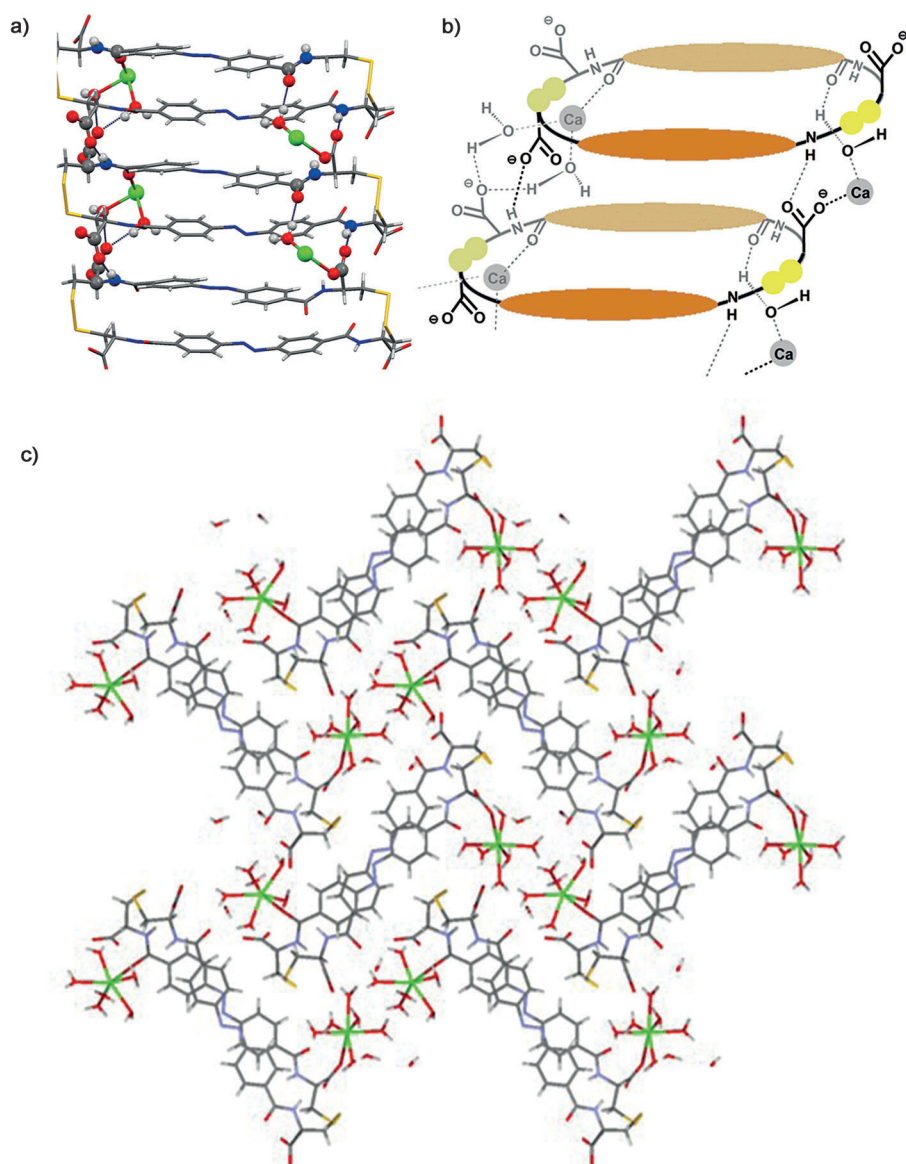


Figure 3. X-ray crystal structure of $(1_2)Ca_2(H_2O)_{15}$. a) Stacking of the azobenzene moieties and b) interactions between neighbouring 1_2 moieties are mediated by calcium ions and water. c) Packing of the 1_2 moieties (blue-gray) and the hydrated calcium cations (green and red) (view along the *a* axis).

molecules are involved as bridging ligands, mediating the interactions between every second amide carbonyl or carboxylate group and the calcium ion. Similar bridging water molecules are also frequently encountered in protein–ligand binding.^[12] In addition, neighbouring molecules of 1_2 are also interacting directly by hydrogen bonding between amide NH and carboxylate groups.

The fact that we could obtain crystals for the Ca- 1_2 complex, but not for the Mg²⁺ complex may hold a clue as to why gelation occurs only with Mg²⁺, but not with the closely similar Ca²⁺. The Ca- 1_2 complex appears to be capable of assembling into fibre like structures that appear to be similar to those formed by the Mg- 1_2 complex (vide infra). However, for Ca²⁺ the assembly process does not stop at the fibre stage, and the fibres assemble laterally into the three-dimensional arrange-

ment shown in Figure 3c. In this assembly the Ca²⁺ ion is coordinated by seven ligands. Mg^{II} has more rigid coordination preferences than Ca^{II} and is usually six-coordinate,^[13] and we speculate that this difference is at the heart of the difference in gelation behaviour between the two complexes.

Closer inspection of the packing in Figure 3c suggests that the water molecules play a crucial role in the lateral association of the stacks of 1_2 by bridging adjacent Ca²⁺ ions. We reasoned that if we could replace some of these water ligands by charged ligands we may be able to introduce electrostatic repulsion between the stacks and prevent their lateral association, which should promote gelation. Indeed, oxidizing building block **1** (5.0 mM) in the presence of glycine (500 mM) and CaCl₂ (20 mM) led to a turbid hydrogel. However, the stability of this gel was inferior to that made with MgCl₂ in the absence of glycine and after standing for three days we obtained a free-flowing suspension. Given the metastable nature of the calcium gel we did not further characterize this material, but focused our attention on the magnesium hydrogel and assessed to what extent its structure resembles that of the stacks of 1_2 observed in the crystal structure of the calcium complex of 1_2 .

IR spectra (see Figure 4) were recorded for 1_2 , the Ca- 1_2 complex and the hydrogel made from 1_2 and Mg²⁺.^[14] In the IR spectrum of 1_2 , the C=O and C–O stretching vibrations of the carboxylate groups are observed at 1721 and 1218 cm⁻¹ respectively. In the spectrum of the Mg- 1_2 complex these bands are shifted by +12 and +9 cm⁻¹, respectively, and have a much reduced intensity. The spectrum of the Ca- 1_2 sample is very similar to that of the Mg- 1_2 complex, suggesting similar assembly modes in the Ca²⁺ and Mg²⁺ complexes of 1_2 .

The magnesium hydrogel was studied by using cryo-TEM (Figure 5a), which revealed the presence of thin fibres with a diameter of approximately 2 nm, which matches the diameter of the calculated minimum energy conformation of macrocycle 1_2 in the gas phase and the diameter of the 1_2 in the Ca²⁺ complex. The analysis of powder XRD data of the lyophi-

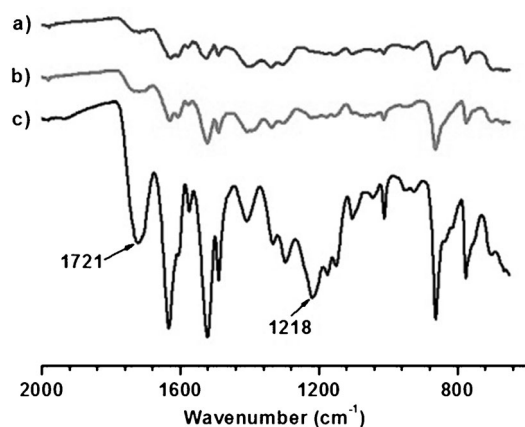


Figure 4. IR spectra of lyophilized samples of a) the Ca-1₂ complex, b) the hydrogel made from 1₂ and Mg²⁺ and c) 1₂.

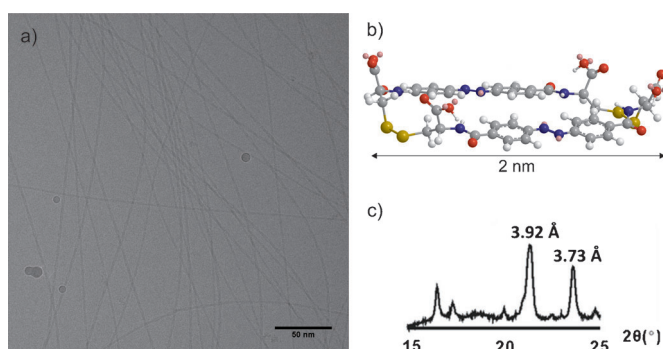


Figure 5. a) Cryo-TEM micrograph of the hydrogel, b) molecular modelling of 1₂ by Chem 3D, c) powder XRD of the dry sample of hydrogel made from 1₂ (2.5 mM) and MgCl₂ (20 mM).

lized gel (Figure 5c) revealed the typical distance of 3.73 and 3.92 Å, which may be attributed to two different kinds of π - π stacking arrangements, reminiscent of those in the crystal structure of the Ca-1₂ complex (Figure 3a). Taken together, these observations suggest an assembly mode for the Mg²⁺ gel that is similar to the stacks of 1₂ that are encountered in the crystal structure of the Ca²⁺-1₂ complex, as depicted in Figure 3a and 3b.

We then investigated the responsiveness of the hydrogel to different stimuli. We have already discussed the responsiveness to Mg^{II} chelation above. Since the 1₂ macrocycles that form the hydrogel are linked by disulfide bonds, the hydrogel should also be redox-responsive. Indeed, adding two equivalents of a dithiothreitol (DTT) reducing agent to the hydrogel converted it into a solution containing monomer 1 (Figure S7 in the Supporting Information). A hydrogel could be re-formed by oxidation through exposing the solution to oxygen from the air for seven days.

We could also switch between solution and gel states by light.^[15] After 30 min of UV irradiation at 375 nm, the *trans* form of the azobenzene moiety was partially converted to the *cis* form (Figure S9 in the Supporting Information), destroying the hydrogel, presumably by disrupting π - π stacking and fibre

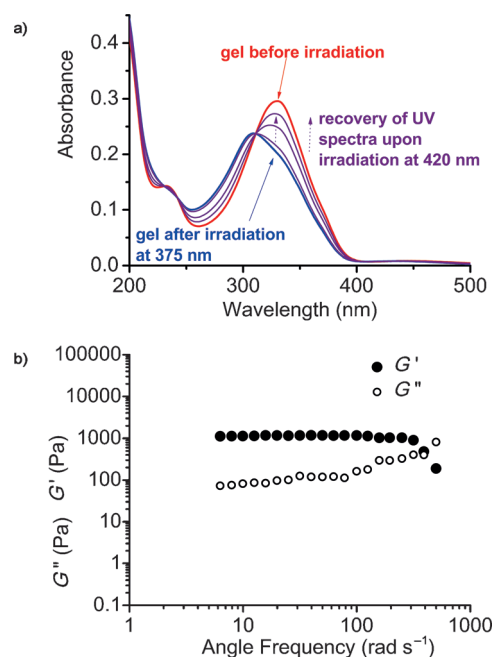


Figure 6. a) Change in the UV/Vis spectrum of 1₂ (1.0×10^{-5} M) hydrogel made by 1 (5.0 mM) and MgCl₂ (20 mM) in 50 mM borate buffer pH 8.1 upon irradiation at 375 nm and recovery of the spectrum upon irradiation at 420 nm. b) Frequency sweep rheology data for the hydrogel made from 1₂ and MgCl₂.

organization. The hydrogel is re-formed by letting the sample rest in a dark environment for five days. Recovery of the hydrogel can be accelerated to two days by irradiating the sample at 420 nm. The switching process was monitored by UV/Vis spectroscopy (Figure 6a).

We also found that the hydrogel is temperature responsive. Upon heating the gel to 40 °C for 30 min, it turned into a clear solution. When the temperature was reduced back to 20 °C, the sample gelled again in the course of two days. Similarly, upon changing the pH to 5.0, the hydrogel was destroyed. When adjusting the pH back to 8.1, the hydrogel was re-formed after two days.

Finally, we tested the responsiveness of the hydrogel to mechanical energy and the potential for self-healing. The hydrogel could be disrupted by vigorous shaking and self-heals when rested for two days. We further investigated this behaviour by using oscillatory rheology measurements. At low oscillatory frequencies, the storage modulus (G') is one order of magnitude larger than the loss modulus (G''). When the angle frequency was increased beyond 390 rad s⁻¹ the hydrogel was disrupted (Figure 6b). After resting the disrupted hydrogel for two days, the rheology experiment was repeated and gave identical results (Figure S8 in the Supporting Information). Repeating the disruption–healing sequence a second time gave, again, identical results, suggesting that the processes of rupture and healing are fully reversible.

In conclusion, we have shown that incorporating the appropriate ingredients in the design of the building blocks, dynamic combinatorial chemistry may lead to the self-synthesis of a new self-assembled material that combines within it all the

functional elements that were contained in the building block design. Note that it is not readily predictable (or necessary to know beforehand) which library member will emerge to have the desired functional properties. In this case the dimer made from **1** was selected by the system over the closely related building block **2**. The result is a Mg²⁺ selective self-healing hydrogel that is responsive to an exceptionally large number of stimuli: it may be switched between gel and solution state by light, sequestration or addition of Mg²⁺, reduction or oxidation, pH or temperature changes and mechanical energy. These results demonstrate the power of an “ingredients” approach for the development of new self-synthesizing materials with properties that may be specifically targeted.

Experimental Section

The synthesis of building blocks **1** is described in the Supporting Information. Building block **2** was prepared as reported previously.^[11] Dynamic combinatorial libraries (typical volume 0.5 mL) were prepared by dissolving building blocks **1** and/or **2** in borate buffer (50 mM, pH 8.1) at the required concentrations in the presence or absence of metal salts (20 mM). The final pH of the solution was adjusted to 8.1 by addition of 1.0 M KOH solution. The DCLs were placed in capped 2 mL HPLC vials in a dark environment at room temperature for seven days in the presence of oxygen from the air and monitored by HPLC. Procedures for HPLC and UPLC/LC-MS analysis of the libraries, HPLC analysis of the effect of DTT on the molecular composition of the hydrogel sample and procedures and data for the rheology experiments are described in the Supporting Information.

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