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Supramolecular hydrogels prepared from fluorescent alkyl pyridinium acrylamide monomers and CB[8]†

Daniel J. Whitaker, Zehuan Huang, Brooke W. Longbottom, Renata L. Sala, Guanglu Wu and Oren A. Scherman *

We introduce a new facile synthetic methodology for the preparation of alkyl pyridinium-containing acrylamide monomers. Inclusion complexes of these new monomers with CB[8] facilitate supramolecular crosslinking in a series of hydrogels formed through *in situ* polymerisation. The resulting hydrogels not only show greatly enhanced mechanical properties over a purely acrylamide-based gel, but also by selecting fluorescent pyridine moieties, the materials are endowed with the fluorescence properties desirable for several sensing applications.

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Introduction

Owing to their unique mechanical properties, dynamic nature and diverse functionality, supramolecular hydrogels have been widely studied over the past few decades.^{1–10} Specifically, in the field of host–guest mediated supramolecular hydrogels there are two main approaches to prepare the final material. In the first approach, a polymer with pendent guest or host molecules is synthesised; a subsequent mixing step (with the addition of a free guest if required) then induces host–guest interactions that lead to gelation.^{11–15} In the second approach, pioneered by Harada *et al.*, an inclusion complex is first formed between the host and guest molecule(s). The resulting complex is then co-polymerised with a water-soluble monomer yielding a supramolecular hydrogel *in situ*.¹⁶

One molecular host, which has been utilised to introduce supramolecular crosslinks into polymer-based hydrogels, is cucurbit[8]uril (CB[8]), a barrel shaped molecule with a hydrophobic inner cavity.^{17–20} In recent reports from our group we prepared a range of hydrogels with high CB[8] loadings (2.5 mol%) and mass fractions (20 wt%) by performing *in situ* polymerisation of aqueous solutions of various monomers with 5 mol% 1-benzyl-3-vinylimidazolium, a polymerisable monomer exhibiting 2 : 1 complexation with CB[8].^{21–23} We also demonstrated that this benzyl-imidazolium motif could be simultaneously bound with a perfluorophenyl

moiety forming strong polar–π interactions within CB[8] mediated hydrogels.²⁴ Similarly, Zhang *et al.* demonstrated that an inclusion complex formed from an ester derivative of the tripeptide Phe–Gly–Gly and CB[8] could be polymerised to form both supramolecular hydrogels and microgels.^{25,26} They noted that supramolecular hydrogels formed using this approach were significantly more mechanically robust than their counterparts produced by first synthesising the polymers and then forming the CB[8] complex (a phenomenon which was suggested to be a result of the viscous polymer solution limiting CB[8] diffusion).²⁶ These examples demonstrate that performing *in situ* polymerisation of CB[8] inclusion complexes is a promising method to prepare supramolecular hydrogels; however, only two monomer architectures have been identified to date, which can be harnessed for this approach.

Side-chain functionalised polymers bearing fluorescent moieties, fluorescent gels and, specifically, fluorescent supramolecular hydrogels make up a wide field of interest across chemistry, biology and physics, with potential applications in energy conversion, biolabeling, tissue engineering and sensors.^{27–29} In most polymer-based preparations of fluorescent hydrogels three components are required: a backbone polymer, a dye and a gelator/crosslinker. By selecting pyridine moieties with known fluorescence properties for a generic monomer synthesis, we envisioned that we could reduce the number of components required for hydrogel formation as the crosslink-forming moiety and fluorescent dye could be combined as illustrated in Fig. 1. We propose that incorporation of new properties through the physical crosslink-forming unit enhances the functionality of the gel without significantly altering its overall structure.

Melville Laboratory for Polymer Synthesis, Department of Chemistry, University of Cambridge, Lensfield Road, Cambridge, CB2 1EW, UK. E-mail: oas23@cam.ac.uk

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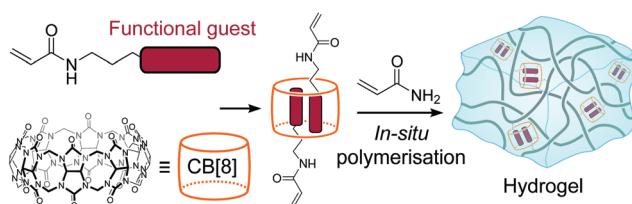


Fig. 1 Schematic representation of a supramolecular hydrogel prepared via *in situ* polymerisation of a pre-formed inclusion complex.

Herein a general monomer architecture was designed containing both an acrylamide and a fluorescent alkyl pyridinium subunit connected *via* a short carbon chain. The complexation of these molecules with CB[8] is then investigated by isothermal calorimetry (ITC) and ^1H NMR spectroscopy. A series of hydrogels are then prepared, and their mechanical properties characterised by strain and frequency dependent oscillatory rheology. Finally, the fluorescence properties of the monomers and hydrogels are explored using UV/Vis and fluorescence spectroscopy.

Results and discussion

Alkyl pyridinium moieties were selected for this study as it has been demonstrated that these compounds often make excellent guests for both cucurbit[7]uril (CB[7]) and CB[8].^{30–35} The strong binding constant ($K_1 = 10^5\text{--}10^7 \text{ M}^{-1}$) between CB[7] or CB[8] and the alkyl pyridinium moiety is attributed both to an electrostatic interaction of the electron deficient aromatic system with the electron rich carbonyl groups of the CB portal and the complementary size of the relatively bulky aromatic ring within the CB cavity.³⁶ The alkyl pyridinium monomers were synthesised *via* a generic, straightforward, column-free procedure shown in Fig. 2.

An alkyl linker three carbon atoms in length was selected as it was postulated that a shorter chain might hinder the accessi-

bility of the acrylamide once the inclusion complex is formed. On the other hand, a longer alkyl linker might lead to the formation of a U-shaped 1:1 inclusion complex with CB[8] rather than a 2:1 homodimer.³⁷ Though N-heterocyclic structures linked to acrylate moieties are known,^{38,39} they were not selected for this study as acrylates are susceptible to hydrolysis and their synthetic strategies (formation of the bromoalkyl acrylate followed by nucleophilic substitution to form the quaternary amine) do not yield pure monomers evidenced by baseline impurities in ^1H NMR.³⁸ It was found that alkyl-pyridinium acrylamides could not be formed in high purity or good yield from a bromoalkyl acrylamide as the conditions of the nucleophilic substitution (reflux for several days) led to degradation of both the starting material and product. As such, a different synthetic approach was sought.

After initial nucleophilic substitution with 3-bromopropylamine hydrobromide, cooling the reaction mixture readily allowed the crystallisation of the pure alkyl pyridinium intermediate. A salt metathesis with ammonium hexafluorophosphate followed to allow solubility in aprotic acetonitrile. Activation of the primary amine with a weakly basic resin and a reaction with acryloyl chloride formed the acrylamide monomer. It is noted that a similar tactic was used by Nordhaus *et al.*⁴⁰ who employed trifluoroacetate anions to afford alkyl pyridinium solubility in DMF. A related synthesis was also reported by Katz *et al.*⁴¹ who added *N*-(acryloxy)succinimide in DMSO to a HEPES buffered solution of propylamine substituted pyridinium, but in our hands this was not found to yield the desired product.

As a resin immobilised base was employed in the previous step, the product was obtained by simple filtering and precipitation, negating the need to separate the cationic product from a cationic conjugate acid. Finally, the counter ion was exchanged back to the chloride *via* an ion exchange column for greater water solubility. To the best of our knowledge, this provides the first generic strategy for forming alkyl pyridinium acrylamide type monomers.

To test the generality of this synthetic approach, a range of pyridine derivatives were selected (Fig. 2 bottom). 4-Phenylpyridine (PhPy) was selected as it has been shown to form 1:1 complexes with CB[7] and homoternary 2:1 complexes with CB[8] after methylation of the pyridyl nitrogen.^{35,42} Furthermore, PhPy derivatives in the absence of CB exhibit strong fluorescence.⁴³ Isoquinoline (IsoQ) has some structural similarity to 4-phenylpyridine and so it was predicted that, once quaternised, it would also form a 2:1 homodimer with CB[8]. Previous work^{44,45} has shown that alkyl-pyridinium derivatives of isoquinoline bind in a 1:1 manner with CB[7]. 2-(Pyridin-4-yl)benzo[d]thiazole (BTPy) was selected for the interesting photophysical behaviour of benzothiazole derivatives, which depends strongly on the local environment, enabling their use in the monitoring of pH and the sensing of metal cations.^{46,47} Additionally, benzothiazole derivatives have been demonstrated to form 1:1 complexes with CB[7].^{48–51} The final pyridine explored, 1-methyl-[4,4'-bipyridin]-1-ium (MV), forms a viologen derivative upon alkylation of the

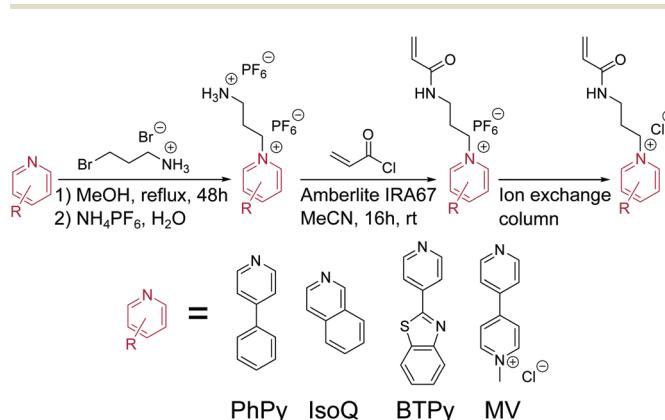


Fig. 2 General synthetic route towards alkyl pyridinium monomers. PhPy = 4-phenylpyridine, IsoQ = isoquinoline, BTPy = 2-(pyridin-4-yl)benzo[d]thiazole and MV = 1-methyl-[4,4'-bipyridin]-1-ium.



second nitrogen. It was predicted that this molecule will form a 1:1 complex with CB[8] similar to other viologen derivatives.^{52–55} As crosslinking in these CB[8]-based gels is mediated by two guests on different chains forming a homoternary 2:1 complex with CB[8], forming a 1:1 complex cannot facilitate a crosslink. Thus, MV was therefore selected as an ideal control.

In total, four novel alkyl pyridinium monomers each with a propylacrylamide (PrAm) moiety were synthesised: 1-(3-acrylamidopropyl)-4-phenylpyridin-1-ium chloride (PhPyPrAm), 2-(3-acrylamidopropyl)isoquinolin-2-ium chloride (IsoQPrAm), 1-(3-acrylamidopropyl)-4-(benzo[d]thiazol-2-yl)pyridin-1-ium chloride (BTPyPrAm) and 1-(3-acrylamido-propyl)-1'-methyl-[4,4'-bipyridine]-1,1'-diium chloride (MVPrAm).

Isothermal titration calorimetry (ITC) was employed to explore the binding of the alkyl pyridinium guests with CB[8] (Fig. 3). Typical titration profiles for a 2:1 binding stoichiometry were observed for PhPyPrAm, IsoQPrAm and BTPyPrAm, while 1:1 binding was observed with MVPrAm.³⁷ The thermodynamic parameters shown in Table S2† were in good agreement with previously described homoternary CB[8] complexes.⁵⁶ Furthermore, the calculated binding constants ($K_1 \approx 10^7 \text{ M}^{-1}$, $K_2 \approx 10^5 \text{ M}^{-1}$) observed for PhPyPrAm, IsoQPrAm and BTPyPrAm match closely with the values for 1-benzyl-3-vinylimidazolium ($K_1 = 4.21 \times 10^7 \text{ M}^{-1}$, $K_2 = 4.25 \times 10^5 \text{ M}^{-1}$), indicating that the three monomers are good candidates to form CB[8] mediated dynamic crosslinks in a hydrogel network.

To understand the homoternary complex formation in greater depth, a series of ^1H NMR titrations were performed in which aqueous solutions of guest compound (2.0 mM) were titrated into an aqueous solution of CB[8] (0.1 mM) (Fig. S6–8†). Analysis of the NMR spectra further confirmed

the 2:1 binding stoichiometry, as the peaks from the unbound alkyl pyridinium only begin to appear once a guest:CB[8] ratio of 2:1 has been surpassed. In all cases, a 2:1 binding mode is observed by ^1H NMR, indicating that any 1:1 binding dynamics were faster than the timescale of the NMR measurement. For IsoQPrAm the signals are broadened throughout, hindering the ability to fully assign the spectra and indicating that all binding dynamics were fast compared to the timescale of the measurement. Additionally, for BTPyPrAm some splitting of the pyridinium protons is observed. This is attributed to desymmetrisation upon complexation presumably arising from the loss of free rotation.

For each of the three guest monomers, at all CB[8]:guest ratios a large upfield shift was observed for the aromatic protons, especially those far from the cyclic nitrogen, implying that the aromatic region is included within the cavity. Conversely, only a slight downfield shift was observed for the vinyl and alkyl protons indicating that they are close to the CB[8] portal but not in the cavity. As a result, the vinyl and alkyl protons are accessible and able to undergo polymerisation. Together with the ITC results these data confirm that the alkyl pyridinium monomers in 2:1 complexes with CB[8] form excellent candidates for the introduction of supramolecular bonds into hydrogel networks *via* an *in situ* polymerisation approach.

To investigate the monomers' ability to crosslink supramolecular gels each monomer was first pre-complexed with CB[8] and copolymerised with acrylamide (5:95 mol%) in water (2 M) *via* a thermoinitiated free radical polymerisation at 50 °C. To ensure good reproducibility each hydrogel was prepared three times and for each rheological measurement three samples of the same gel were used (giving a total of 9 datasets per averaged result). A guest:CB[8] ratio of 2:1 was used in all guest containing hydrogels.

Small-amplitude oscillatory rheological analysis was employed to explore the mechanical properties of the hydrogels (Fig. 4). In an amplitude sweep experiment (Fig. 4a) each of the materials prepared displayed a broad linear viscoelastic region with the storage modulus (G') higher than the loss modulus (G''), indicating that they are gels under the conditions analysed. Statistical analysis (Fig. S9†) demonstrated that within the viscoelastic region the storage moduli (G') of the three gels containing 2:1 binding monomers were statistically similar ($p = 0.01–0.37$), demonstrating that they presented similar elastic like solid behaviour. The storage modulus of the two control samples (100% AAm and 95% AAm with 5% of the 1:1 binding MVPrAm guest) showed no significant change between them ($p = 0.68$), indicating that the 1:1 binding MVPrAm guest did not form supramolecular crosslinks. Additionally, the hydrogels with 2:1 binding guests had (G') and (G'') more than one order of magnitude higher than those of the control samples, indicating the formation of robust hydrogels by the introduction of supramolecular crosslinks.

Towards the end of the linear viscoelastic regime, G'' of the BTPyPrAm hydrogel shows a slight increase with strain before hydrogel deformation: a weak strain overshoot. This is a

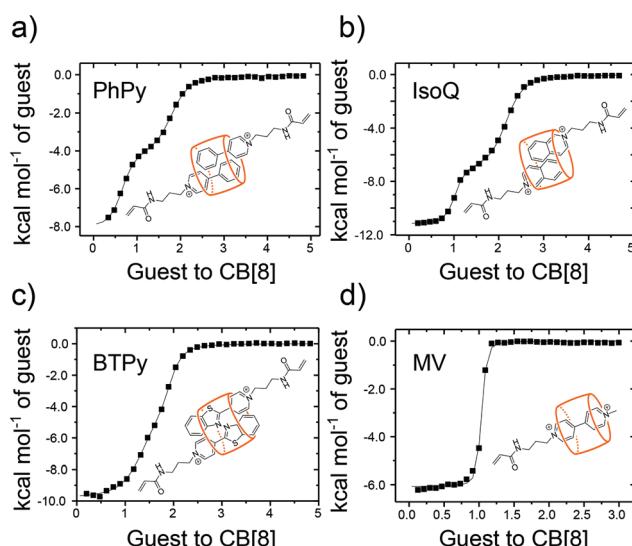


Fig. 3 ITC titration plots (H_2O , 298 K) of four alkyl-pyridinium guests titrated into cucurbit[8]uril (0.1 mM). (a) PhPyPrAm (2.0 mM), (b) IsoQPrAm (2.0 mM), (c) BTPyPrAm (2.0 mM) and (d) MVPrAm (1.0 mM). Counterions omitted for clarity.

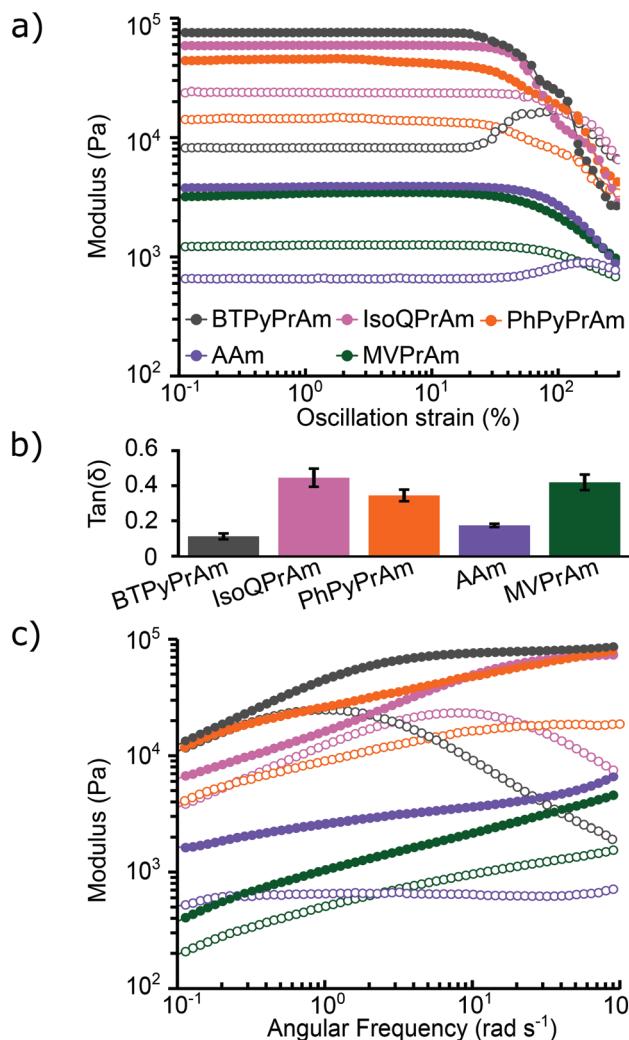


Fig. 4 Oscillatory rheological analysis of hydrogels prepared from either copolymers of alkyl pyridinium guests and acrylamide or pure acrylamide. (a) Storage (G' , shaded circle) and loss moduli (G'' , hollow circle) obtained from an amplitude sweep performed at 10 rad s^{-1} . (b) $\tan \delta$ (G''/G') taken from the linear viscoelastic region of the amplitude sweep, error bars plotted as 95% confidence intervals. (c) Storage and loss moduli obtained from a frequency sweep performed at 1% strain.

known phenomenon for fluids with extended polymer chains with a complex inter-chain structure, which resists deformation up to a certain strain (observed by increasing G''). As this structure breaks down, chains can align with the direction of flow and G'' decreases.⁵⁷ The AAm control hydrogel presented a less pronounced strain overshoot, which has been observed by others.^{58,59} This behaviour, observed in AAm-based hydrogels, may be related to the presence of an additional structure associated by hydrogen bonding that imposes some resistance to deformation.⁵⁷ In all other gels a strain thinning behaviour is observed, in which as strain is increased polymer chains disentangle to align with the direction of flow. This implies that the supramolecular interactions in the BTPyPrAm hydrogel induced the formation of additional

weak structural complexes throughout the polymer networks that were not observed in PhPyPrAm and ISOQPrAm hydrogels. We postulate that as BTPyPrAm has the largest area of π -conjugation it may be able to induce some additional weak stacking interactions between chains.

$\tan \delta$ (G''/G') taken from the linear viscoelastic region provides a good metric for the tough and elastic-like behaviour of hydrogels; Fig. 4b shows $\tan \delta$ for all of the gels tested. BTPyPrAm hydrogels have a significantly lower $\tan \delta$ than the others containing supramolecular crosslinks suggesting that it is more highly elastic and has properties closer to those of a tough material. It is also apparent that the pure AAm gel has more tough material-like properties than the control formed from the 1 : 1 binding MVPrAm. We believe that this is due to an increase in free volume (and a related decrease in hydrogen bonding) in the MVPrAm containing gels. In the pure AAm gel, polymer chains can readily hydrogen bond with one another, while in the MVPrAm gels pendant MV molecules increase the inter-chain distance through both repulsive interactions between the dications and the steric bulk of the pendant viologens (especially when complexed with CB[8]) leading to less hydrogen bonding.

Frequency dependent rheological analysis performed within the linear viscoelastic region is shown in Fig. 4c. G' of the AAm hydrogel slightly increased in the frequency range investigated, presenting a slope of 0.24 when the power law is applied, while PhPyPrAm and MVPrAm showed similar behaviour but with a larger value for the slope 0.35 and 0.40 respectively. The rheological behaviour observed for the AAm sample can only be a result of the polymer entanglements since no crosslinker moieties were added; these have finite relaxation time and so the elastic contribution would increase with frequency.⁶⁰ The behaviour was instead influenced by the associative network formed by hydrogen bonding between acrylamide groups.^{61,62} Again, this was partially disrupted in the presence of MVPrAm pendant groups complexed with CB[8], reducing the G' of the MVPrAm hydrogel in Fig. 4c. Though PhPyPrAm showed higher moduli than the control samples its G' showed a similar frequency dependence in the linear viscoelastic regime, indicating that the storage modulus was mainly dominated by polymer entanglement. Additionally, the G'' profile of the AAm, MVPrAm and PhPyPrAm hydrogels exhibits the same power law as their G' profiles, meaning that their $\tan \delta$ does not vary significantly with frequency (Fig. S10†). $\tan \delta$ values that are independent of frequency in this way are characteristic of a critical gel and has been observed in weakly crosslinked polyacrylamide gels previously.⁶⁰

Conversely, BTPyPrAm and IsoQPrAm exhibited a distinct profile of G' , G'' and $\tan \delta$ (Fig. 4c and S10†). At lower frequency, G' and G'' have similar values and at higher frequencies G' reaches a plateau, followed by a drastic decrease of $\tan \delta$ due to the reduction of G'' , which is typical of solid-like behaviour. Additionally, the loss moduli reach their maximum value at 1.01 rad s^{-1} (or 6.20 s) and 8.05 rad s^{-1} (or 0.80 s) for BTPyPrAm and IsoQPrAm, respectively, which relates to the relaxation time of the supramolecular crosslinkers and the rate



of dissociation of the host–guest interactions. A longer time, as observed for the BTPyPrAm hydrogels, implies that the 2:1 guest:CB[8] complex is less dynamic.^{63,64} Although the three hydrogels have the same crosslinking density and CB[8] guests of a similar binding constant, different rheological properties were observed, possibly related to distinct microstructural homogeneity arising from their varied chemical structure. While polymer entanglements control the hydrogel network relaxation in PhPyPrAm, supramolecular crosslinks dominate the relaxation profile of BTPyPrAm and IsoQPrAm.⁶⁴

Overall, these results demonstrate that supramolecular crosslinks enabled by the inclusion of 2:1 binding CB[8] guests endow the hydrogels studied with superior mechanical properties; by selecting appropriate guest molecules the elastic properties of the hydrogel can be tuned independent of their storage modulus. This additional degree of tunability of the loss modulus may be of particular relevance to model biological systems where viscoelasticity can uniquely affect how cells interact with a surface.⁶⁵

UV-Vis and fluorescence spectroscopy were used to verify the absorption and emission properties of the alkyl pyridinium monomers (Fig. 5a). The guests were found to have a good variation in absorption profiles spanning from the UVC to UVA range (250–400 nm). The emission profiles also varied, covering nearly the entire visible light spectrum and having maxima in the violet and green regions. Fluorescence quantum yields (ϕ_f) were also calculated for the monomers

and these were found to be 0.0007, 0.017 and 0.34 for BTPyPrAm, PhPyPrAm and IsoQPrAm, respectively. To verify whether fluorescence properties might be retained upon complexation with CB[8], emission spectra were recorded for 2:1 guest:CB[8] ratios (Fig. S16–18†). For IsoQPrAm and BTPyPrAm a slight decrease in integrated emission was observed (68% and 66% of their uncomplexed form, respectively). We suggest that this could be due to the formation of a charge-transfer complex between molecules bound by CB[8], which is consistent with previous reports.⁶⁶ Conversely, for PhPyPrAm a tremendous 341% increase in integrated emission was observed upon binding, which we postulate is the result of the free rotation around the bond connecting the phenyl and pyridine subunits becoming restricted, leading to more efficient, planar π -conjugation than in the unbound state.⁶⁷ X-ray crystallography analysis of PhPyPrAm as a PF_6^- salt indicated a 12.62° torsion angle around this bond in its unbound state, providing some qualitative evidence to support this hypothesis (Fig. S19 and 20†). Furthermore, encapsulation of PhPyPrAm inside both CB[7] and CB[8] results in a bathochromic shift in emission. This change can be attributed to the stabilization of the excited state, thus deactivating non-radiative pathways and decreasing the HOMO–LUMO band gap upon inclusion of the phenyl moiety in the cucurbituril cavity.^{68–70} We suggest that the difference in fluorescence emission for bound and unbound PhPyPrAm may also enable its use as a fluorescent reporter in a self-reporting hydrogel preparation. To determine if fluorescence is indeed retained upon hydrogel formation, samples were illuminated using a long-wave (365 nm) UV lamp. For all three 2:1 binding monomers fluorescence could be visibly observed in the gels (Fig. 5b).

Together these results demonstrate that alkyl pyridinium monomers prepared *via* our general synthetic route were able to endow the resultant hydrogels with fluorescence properties. Furthermore, combining the crosslink-forming unit with the dye results in a simplified approach for the formation of supramolecular fluorescent hydrogels. To the best of our knowledge, this is the first example of fluorescence being introduced to CB[8]-mediated hydrogels directly through the crosslink-forming unit. We envision that supramolecular hydrogels prepared by this method could find widespread use in both physical and biomedical applications.

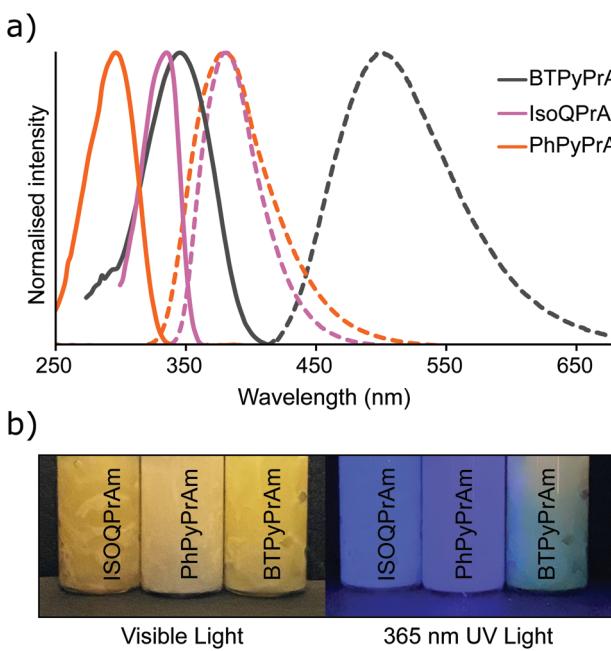


Fig. 5 (a) Normalised steady-state absorption (solid line) and emission (dashed line) for alkyl pyridinium molecules BTPyPrAm (blue), IsoQPrAm (orange) and PhPyPrAm (pink). (b) Photographs of hydrogels made from alkyl pyridiniums under visible light (left) and 365 nm UV light (right).

Conclusions

A facile, generic, column-free synthetic pathway is reported for the preparation of alkyl pyridinium containing acrylamide monomers on a gram scale. ITC and NMR spectroscopy analysis confirmed that these monomers have a high affinity to form complexes with CB[8] and, when complexed, the acrylamide moieties are still readily available for polymerisation. A series of hydrogels with a broad viscoelastic region were prepared *via* *in situ* polymerisation of an inclusion complex of these monomers with CB[8]. It was demonstrated that the presence of supramolecular crosslinks greatly enhances the

mechanical properties of the gel, increasing the storage and loss moduli by more than an order of magnitude. Moreover, by varying the guest, the elastic and solid-like properties of the hydrogel can be tuned independent of the storage modulus. Finally, it was demonstrated that by selecting pyridine moieties with known fluorescence properties the generic synthesis yielded fluorescent monomers, which could then be polymerised into fluorescent hydrogels. This approach reduces the number of components necessary to create fluorescent supramolecular hydrogels by combining the dye and crosslink forming monomer into a single unit.

The preparation of fluorescent supramolecular hydrogels, which may find use in biolabeling, as sensors or in tissue engineering, is just one example of this generic synthetic route. By varying the pyridine used for monomer synthesis any number of potential new uses could be imagined from corrosion inhibition, to use as an electrolyte in batteries, or even in the preparation of antimicrobial materials.⁷¹ Furthermore, by selecting an acrylamide as the polymerisable unit, these 2:1 binding alkyl pyridinium moieties have a very similar polymerisation activity to the acrylamide monomer used to form the backbone. This will enable the use of controlled radical polymerisation in future material preparation, a topic which will be the subject of further papers from our group.

Conflicts of interest

There are no conflicts to declare.

Acknowledgements

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