# Amidinium–carboxylate frameworks: Predictable, robust, water-stable hydrogen bonded materials

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In the last few years, the amidinium–carboxylate interaction has emerged as a powerful tool for the relatively predictable construction of families of three dimensional hydrogen bonded organic frameworks. These frameworks can be prepared in water and are surprisingly stable, including to heating in polar organic solvents and water. This feature article describes the design and synthesis of these materials, discusses their structures and stability, and highlights their recent applications for enzyme encapsulation and as precursors for the synthesis of molecularly thin hydrogen bonded 2D nanosheets.

## Introduction

### Hydrogen bonded frameworks

In the last decade or so, hydrogen bonded frameworks have emerged as a class of materials complementary to more established metal organic frameworks/coordination polymers and covalent organic frameworks.[1,2] Perhaps inevitably, they are often designated as "HOFs," by analogy with metal organic frameworks[3-6] (MOFs) and covalent organic frameworks[7,8] (COFs), although this nomenclature may not be ideal.[9]

While it might be thought that the weakness of hydrogen bonds would give very unstable materials, well-designed materials can actually be quite robust, and materials with high stability to *e.g.* heat,[10,11] water,[10,12] and concentrated acid[12,13] have been reported. In fact, the weakness of hydrogen bonds can represent an advantage, as it typically leads to highly crystalline materials that can be prepared in much milder conditions than many other framework solids.[1]

Many hydrogen bonded frameworks are prepared from a single component, *i.e.* one organic molecule. This approach was pioneered by authors including Ermer[14,15] and Wuest. In particular, Wuest prepared large, rigid tetrahedral molecules containing divergent 2-pyridone groups, which could "recognise" one another through self-complementary hydrogen bonding and form channel-containing 3D frameworks (Figure 1).[16,17] Subsequently, they and many other groups have prepared molecules containing self-complementary hydrogen bonding groups such as carboxylic acids or diaminotriazine motifs, and careful selection of crystallisation conditions has allowed the synthesis of porous 3D organic materials.[18-24] While impressive properties have been realised using this single component approach including impressive gas storage[22,23] and separation,[25,26] there are some less ideal features. Notably, while the hydrophobic nature of the building blocks means that many of these single component HOFs are water-stable, the relatively weak nature of the neutral hydrogen bonds means that they often dissolve in polar organic solvents.[1] Additionally, the process of screening solvents to find conditions that give a crystalline material can be tedious and time-consuming.

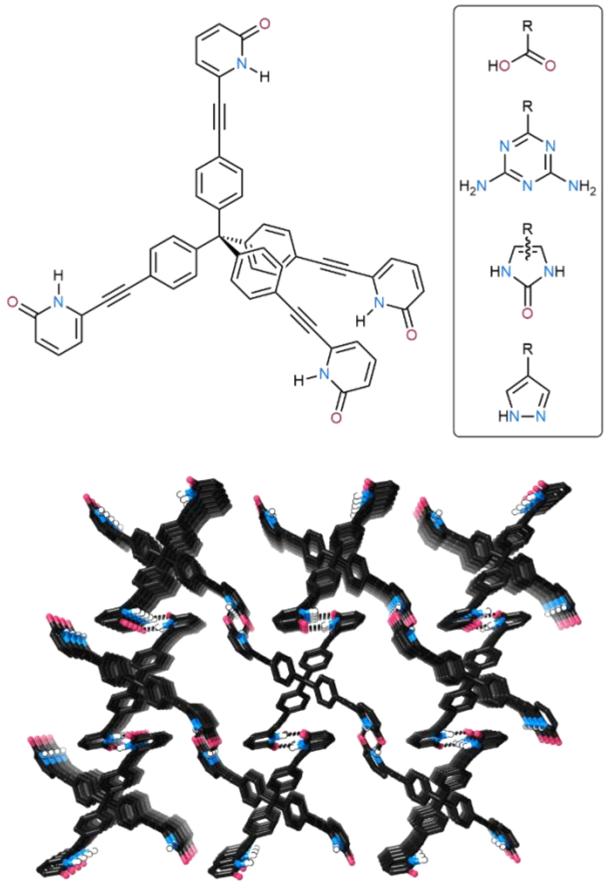


**Figure 1** Structure of organic molecule used by Wuest to prepare hydrogen bonded frameworks, and crystal structure of the framework (CCDC: 1285772). The inset shows common hydrogen bonding motifs used to prepare single component hydrogen bonded frameworks.

### Charge-assisted hydrogen bonded frameworks

An alternative approach to forming hydrogen bonded frameworks is to use charged building blocks. This means that both a cationic and anionic component are needed, which gives "node-and-linker" frameworks that have conceptual similarities to MOFs.[27] Potentially this offers scope to use the isoreticular synthesis concept to prepare series of related materials by varying the size/functionality of a single component while keeping the geometry constant.[6] The other advantage of these interactions is that the hydrogen bonds tend to be significantly stronger than those without charge assistance.

Hydrogen bonded frameworks assembled by charge-assisted interactions were pioneered by Ward, who reported in 1994 that unsubstituted guanidinium cations assembled with sulfonate anions into pseudo-hexagonal 2D hydrogen bonded sheets (Figure 2).[28] Subsequently Ward's group have reported a series of 2D and 3D extended structures using this guanidinium-sulfonate interaction, always using the unsubstituted guanidinium cation but incorporating a huge variety of polysulfonate anions.[29-32]

In the last decade or so, other authors have used the interactions between protonated amine or pyridine groups and anions to assemble porous extended structures.[33-39] For example, in 2015 Friščić showed that (benz)imidazolium cations could be assembled into open 2D grids with tetrahedral sulfate and selenate anions, representing interesting charge-inverted analogues of metal (benz)imidazolate coordination networks.[37] In 2018 Ben showed that diammonium salts could form open networks with tetracarboxylate and tetrasulfonate anions. These frameworks showed some permanent porosity as well as high proton conductivity.[39]

While some fascinating structures with interesting properties have been prepared, generally these systems do not have well defined hydrogen bonding vectors, which means that it is difficult to predict what kind of structures will form. To try and gain a degree of predictability, we searched for a charge-assisted hydrogen bonding pair that could achieve the well-defined hydrogen bonding geometries exhibited by Ward's guanidinium-sulfonate systems, but that would allow us to vary both components. As will be discussed in this article, we have found that the amidinium-carboxylate pair is very well-suited for this purpose and have used this to prepare a range of frameworks over the last few years. The interaction of amidinium cations and carboxylate anions results in a well-defined hydrogen bonding vector running along the axis of the hydrogen bond (*i.e.* the R–amidinium and carboxylate–R bonds in Figure 2 are aligned) resulting in straightforward prediction of network structure. In guanidinium-sulfonate frameworks, the hydrogen bonding typically propagates at right angles to the axis of the benzenesulfonate component (Figure 2a and 2b), while many other charge-assisted hydrogen bonding motifs have several possible hydrogen bonding geometries and thus framework structure is less predictable (Figure 2c).

We note that in 2018 and 2019, Ben, Comotti and co-workers reported related frameworks assembled through the interactions of amidinium cations with sulfonate anions, with one of these displaying impressive $CO_2$ uptake and selectivity.[40,41] In the weeks leading up to the submission of this work, two reports of amidinium-carboxylate frameworks from other groups[42,43] appeared and these are discussed in the Recent Developments section.

## Amidinium-carboxylate interactions for self-assembly

Beginning in the 1990s, Wais Hosseini reported bisamidinium tectons where the amidinium motif is rigidified within cyclic groups and demonstrated that these could be used to form 1D and 2D hydrogen bonded networks with either carboxylate[44-46] or cyanometallate anions (Figure 3).[47,48] While 3D frameworks were not prepared, these results were a clear demonstration that amidinium groups are suitable for preparing extended hydrogen bonded structures. In the solution phase, the interaction of amidinium cations with carboxylate anions has been used for anion recognition applications,[49-53] and to assemble supramolecular macrocycles,[54] cages[55-57] and helices.[58-60] Typically the cation and anion interact through a paired parallel hydrogen bonding arrangement (*i.e.* $R_2^2(8)$ in graph notation) as shown in Figure 3, although other hydrogen bonding geometries have been observed.[61-63]

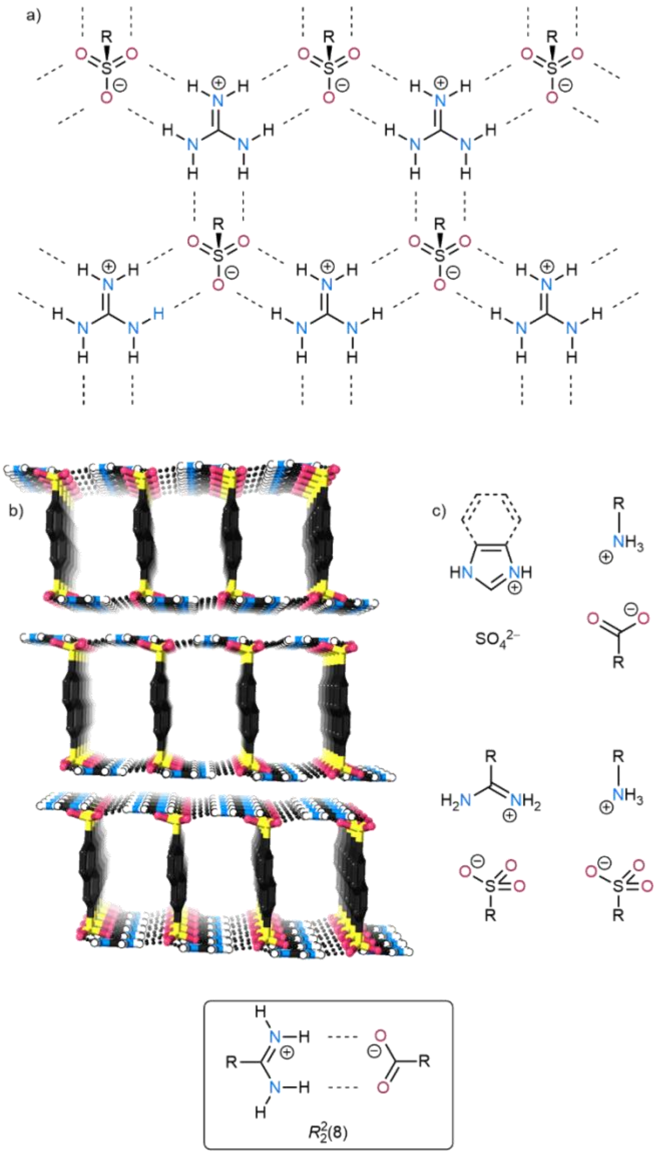


Figure 2 Motifs used to prepare charge-assisted hydrogen bonded frameworks: a) hydrogen bonding arrangement used by Ward to prepare guanidinium-sulfonate frameworks; b) crystal structure of one of these frameworks (CCDC: 114766); c) examples of other hydrogen bonding motifs used to prepared charge-assisted hydrogen bonded frameworks. The inset shows the most commonly observed geometry of the hydrogen bonding interaction between amidinium and carboxylate components.

Inspired by this prior art, we sought to use the amidinium–carboxylate interaction to form 3D framework materials. As well as a well-defined hydrogen bonding geometry, this pair both have ideal p$K_a$ values for assembly: that is, the p$K_a$ of benzamidinium is 11.6 [64] so it is a potent hydrogen bond donor but remains protonated at sensible pH values. Similarly, the p$K_a$ of benzoic acid is 4.2 [65] so benzoate is a strong hydrogen bond acceptor but remains deprotonated at sensible pH values, such that both components of the interaction remain charged in water.[66]

My group has used this amidinium–carboxylate interaction to prepare a range of 3D hydrogen bonded frameworks. These can be prepared with reasonably high levels of predictability, and are stable in a surprising range of conditions including in boiling water. This Feature Article will give an overview of the types of frameworks we have been able to prepare, and the scope and limitations of our approach. It will then discuss the properties of the frameworks and their applications in enzyme encapsulation and their exfoliation to give molecularly thin nanosheets.

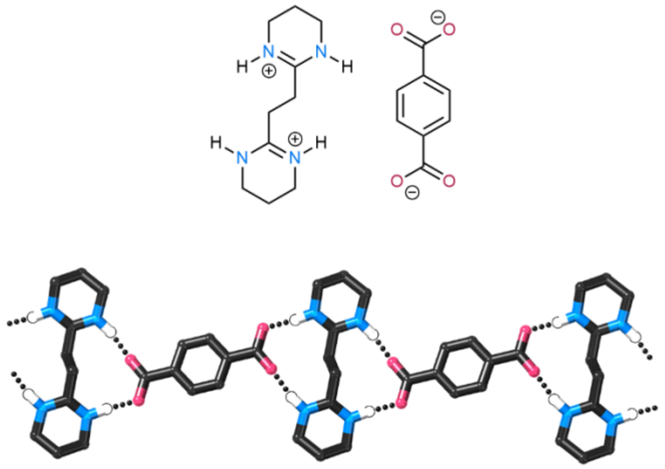


**Figure 3** Structure of cyclic amidinium and carboxylate components used by Wais Hosseini to prepare an early example of a 1D hydrogen bonded chain, and crystal structure of the framework (CCDC:1235940).

## Synthesis of amidinium–carboxylate frameworks

### Initial synthesis

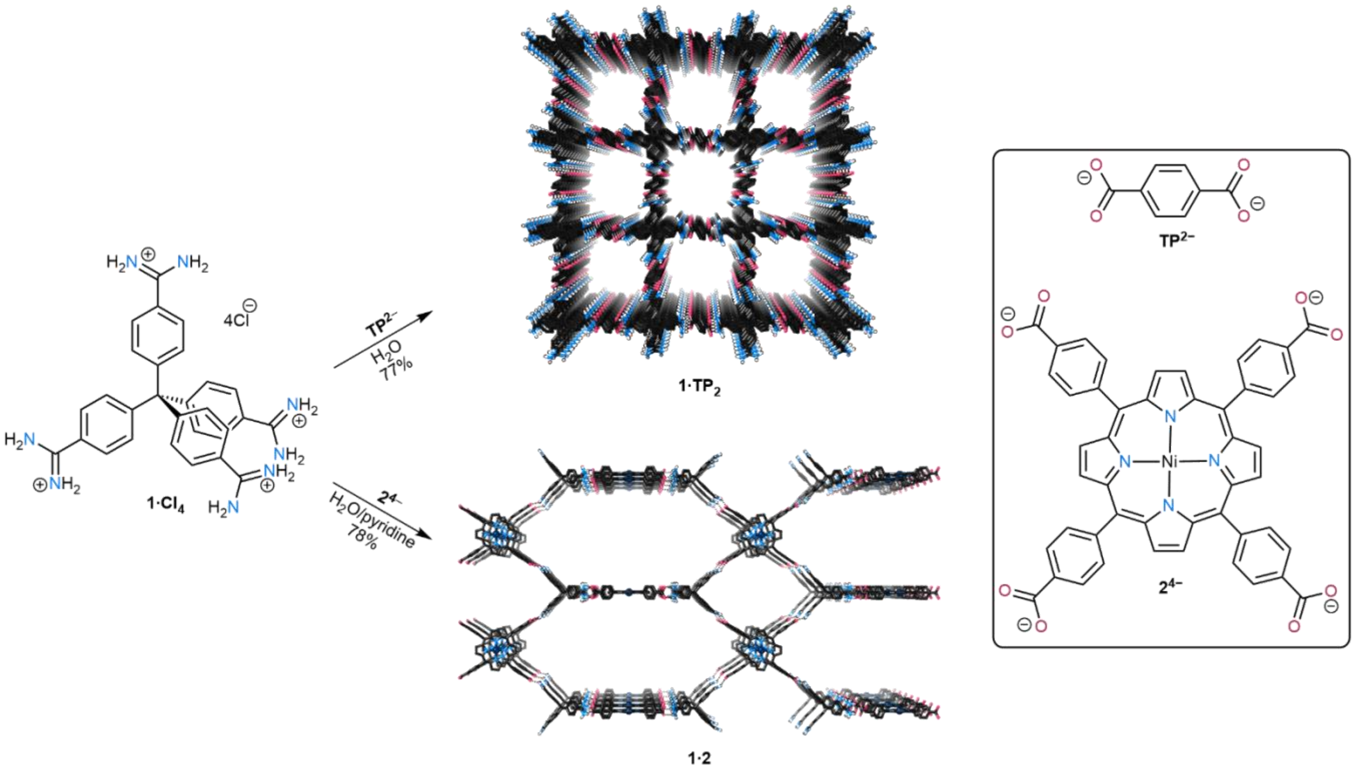
We initially designed the tetrahedral tetraamidinium tecton $\mathbf{1}^{4+}$ (Scheme 1), which has formed the basis for much of our work in this area. This key building block can be prepared from the corresponding tetranitrile in one step by simply reacting with a THF solution of LiHMDS followed by acidic work-up.[67] We initially studied framework formation using the linear dicarboxylate, terephthalate ($\mathbf{TP}^{2-}$, *i.e.* benzene-1,4-dicarboxylate), expecting that this would link molecules of $\mathbf{1}^{4+}$ into diamondoid hydrogen bonded frameworks.[67]

We first attempted to form frameworks in organic solvents, thinking that this would maximise the strength of the amidinium–carboxylate hydrogen bond and thus favour framework formation. To do this we used the organic-soluble tetraphenylborate salt of $\mathbf{1}^{4+}$, *i.e.* $\mathbf{1}\cdot\mathbf{(BPh_4)_4}$, and mixed this with organic-soluble tetrabutylammonium terephthalate ($\mathbf{TBA_2{\cdot}TP}$). We tried this in a variety of solvents, and in all cases obtained an amorphous, insoluble powder. Studying this material by $^1$H NMR spectroscopy (after acid digestion) revealed a 1:2 ratio of $\mathbf{1}^{4+}$:terephthalic acid, which was encouraging, but without a crystalline product it was difficult to determine much about the structure of these materials. We tried to use various “tricks” to obtain crystalline products, including slowly diffusing reagents into one another and solvothermal syntheses, but without any success. Finally, out of desperation, we attempted framework synthesis in water using the water-soluble salt $\mathbf{1{\cdot}Cl_4}$ (Scheme 1). We found that adding a solution of $\mathbf{TBA_2{\cdot}TP}$ in water to an aqueous solution of $\mathbf{1{\cdot}Cl_4}$ immediately results in a slight cloudiness, but within 30–60 seconds crystals start to form and after approximately an hour crystallisation is complete (a video of this process is available as part of the supporting information of Ref. 67).

Analysis of these crystals by single crystal X-ray diffraction (SCXRD) revealed that the desired diamondoid network $\mathbf{1{\cdot}TP_2}$ had formed with relatively short “paired” charge-assisted hydrogen bonds linking the tectons together (Scheme 1). The structure is constructed of eleven interpenetrating networks, but despite this contains large channels, occupied by well-resolved water molecules in the crystal. Calculations reveal a calculated surface area of ~ 1500 m$^2$ g$^{-1}$, although we were not able to activate the material and demonstrate porosity (this will be discussed in the structure and stability section). Despite being assembled by hydrogen bonds, the frameworks are robust and do not dissolve in any tested solvents. Unsurprisingly, the frameworks can be broken apart by adding acid to protonate the carboxylate anions. This leads to an interesting behaviour where crystals can be suspended in water, and then acid can be added to destroy the crystals; neutralisation with base results in the crystals re-forming within a few minutes.[67]

### Synthesis of families of frameworks

Having shown that we could prepare a diamondoid framework from $\mathbf{1}^{4+}$ and terephthalate, we next investigated whether other framework topologies were realisable. We showed that mixing tetrahedral $\mathbf{1}^{4+}$ with the porphyrin tetracarboxylate $\mathbf{2}^{4-}$, which has a square planar geometry, gave framework $\mathbf{1{\cdot}2}$ with the expected PtS geometry (Scheme 1).[68] In this case, only four interpenetrating nets are present; 75% of the unit is occupied by solvent and the structure has a calculated solvent accessible surface area of 5,770 m$^2$ g$^{-1}$. This meant that at the time the structure was one of the most open hydrogen bonded frameworks known.[69] However, this “porosity” is purely virtual, and the very low stability of the materials to solvent loss suggests that this particular framework has little potential use as a porous material.



**Scheme 1** Synthesis of diamondoid amidinium–carboxylate framework **1·TP**$_2$ and its crystal structure (CCDC: 1523338), and of PtS framework **1·2** and its crystal structure (CCDC: 1574946). For clarity, only one of the four interpenetrated nets in the structure of **1·2** is shown. The inset shows the structure of dicarboxylate **TP**$^{2-}$ and tetracarboxylate **2**$^{4-}$.

While many hydrogen bonded frameworks have been prepared, the ability to prepare large families of these materials is very rare.[30,70] Based on the initial synthesis of **1·TP**$_2$, we next investigated how general our approach was and whether we could make large families of related materials. In particular we were interested to see whether the isoreticular approach that has proven so powerful in metal organic framework chemistry,[6] could be generalised to hydrogen bonded materials. We showed that we could prepare a range of diamondoid materials from **1**$^{4+}$ and dicarboxylate anions, including extended dicarboxylates such as **3**$^{2-}$, aminoterephthalate **4**$^{2-}$, which contains a “free” amine group, and anthracenedicarboxylate **5**$^{2-}$ (Figure 4).[71] We also demonstrated that we could “reverse” our initial terephthalate framework and construct it from tetrahedral tetracarboxylate **6**$^{4-}$ and the linear bisamidinium **7**$^{2+}$, or use the larger tetraamidinium component **8**$^{4+}$ to make predictable open materials. Frameworks could also be made from tetrahedral tetraamidiniums **1**$^{4+}$ or **8**$^{4+}$ with tetrahedral tetracarboxylate **6**$^{4-}$, and as expected these also gave diamondoid networks.[71]

In all of these cases, we obtained crystalline materials simply by mixing the two components in water or water/alcohol mixtures at room temperatures. These structures typically contain large channels and are nearly all diamondoid, however they are not strictly isoreticular. Differing degrees of interpenetration are obtained and the networks crystallise in a range of different space groups (monoclinic, orthorhombic, tetragonal and hexagonal).[71] Thus while this level of predictability and the ability to make families of related materials is unusual for hydrogen bonded frameworks, the level of fine control structure does not yet reach the level that can be obtained for certain metal–organic materials.

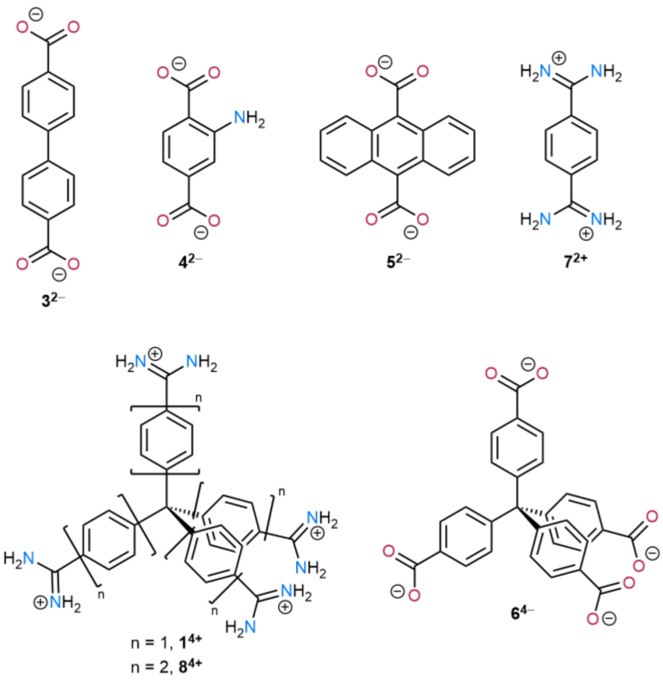


**Figure 4** Structure of amidinium and carboxylate tectons used to make a family of diamondoid frameworks.

### Frameworks assembled using anti-electrostatic hydrogen bonds

It is known that protic anions are able to interact with each other in both solution and the solid state through anti-electrostatic hydrogen bonds (AEHBs).[72] In these cases, the favourability of the hydrogen bonding arrangement can outweigh the Coulombic repulsion between the two charged anions, often aided by the solvent or receptors that can help to "screen" this charge. The bicarbonate $HCO_3^-$–$HCO_3^-$ dimer adopts a planar geometry and has a $2^-$ charge, so may be thought of as analogous to a dicarboxylate anion. When receptor **1**$^{4+}$ was combined with an excess of $NaHCO_3$ in water, we found that we could obtain 3D frameworks held together by the interaction of amidinium groups with anti-electrostatically hydrogen bonded bicarbonate dimers (Figure 5).[73] Remarkably these AEHBs can assemble a framework, even in water. The material does not have the structure we envisaged, where each bicarbonate dimer links two amidinium moieties to give a charge-neutral network. Instead, four amidinium groups hydrogen bond to a dimer, giving an overall cationic framework, which is charge-balanced by additional bicarbonate dimers located within the pores of the material.

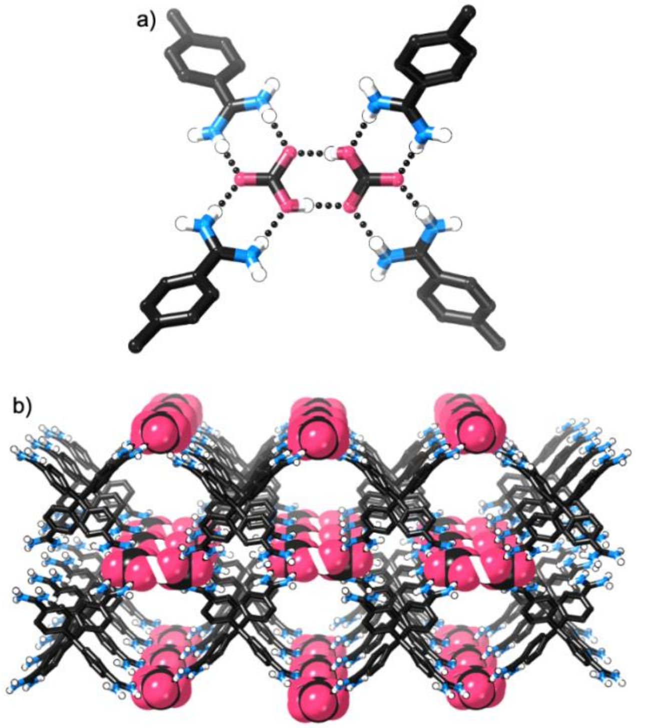


**Figure 5** Structure of framework assembled using antielectrostatic hydrogen bonds (CCDC: 1949479): a) image highlighting the AEHB motif that assembles the framework, b) view of one of the diamondoid nets (charge-balancing AEHB bicarbonate anions in the channels omitted for clarity).

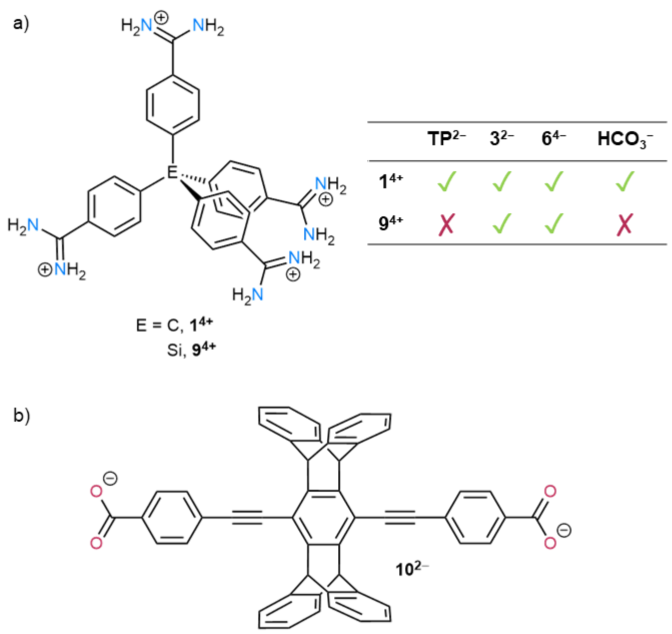
### Scope and limitations of synthesis

As noted in the previous section, a reasonable amount of control can be achieved over framework synthesis, and families of related amidinium–carboxylate materials can be prepared. In addition, the actual synthetic methodology is typically trivial – simply mixing two solutions of an appropriate concentration and waiting for crystals to form. However, we have experienced some limitations regarding flexibility and size of tectons, and the dimensionality of the materials. The first is perhaps the least surprising, we have not yet been able to prepare frameworks from flexible tectons such as dicarboxylates derived from amino acids.[71] Moving from the parent tetraamidinium **1**$^{4+}$ to the larger building block **8**$^{4+}$ gave several channel-containing networks, but non-diamondoid structures were obtained when **8**$^{4+}$ was combined with some dicarboxylates. Generally moving from the small and rigid tetraamidinium **1**$^{4+}$ to larger and more flexible **8**$^{4+}$ appears to reduce the predictability of forming the desired network.[71]

When we attempted to prepare frameworks from the silicon-centred tetraamidinium **9**$^{4+}$, we also saw an interesting and unexpected effect of flexibility (Figure 6).[74] While the carbon-centred building block **1**$^{4+}$ readily gave diamondoid networks with terephthalate[67] anions and bicarbonate dimers,[73] we were unable to obtain these frameworks with silicon-centred building block **9**$^{4+}$.[74] When the biphenyldicarboxylate anion **3**$^{2-}$ or tetracarboxylate **6**$^{4-}$ were used, we did obtain diamondoid materials, but overall the results suggest a reduced level of predictability for the silicon tetraamidinium **9**$^{4+}$ compared with the carbon tetraamidinium **1**$^{4+}$.

Interestingly, silicon centred tetratopic ligands also seem to give a wider variety of framework types (*i.e.* reduced predictability) than carbon centred tetratopic ligands in MOF chemistry. Perhaps counterintuitively, tetraphenylsilane derivatives are significantly less flexible than tetraphenylmethane derivatives as demonstrated by high level computational studies, as well as a survey of the Cambridge Structural Database.[74] That highly rigid building blocks made it harder to predict the nature of a framework surprised us at first, however, it is now apparent that a small amount of flexibility is advantageous, as it allows the diamondoid networks to pack more effectively. Silicon's preference for a strictly tetrahedral geometry can make it harder to reach these arrangements and so alternative frameworks form instead.[74]

In terms of the size of the components that can be used, we have shown that potentially quite large tectons are suitable. The ~ 2 nm long pentiptycene based dicarboxylate **10**$^{2-}$ (Figure 6) gave a 2D honeycomb network and a 3D diamondoid material with tetraamidinium **8**$^{4+}$, although interestingly the desired framework material was not obtained when the smaller tetraamidinium **1**$^{4+}$ was used.[75] While we have not yet conducted detailed testing, it appears that quite large building blocks can be incorporated into these frameworks, although perhaps with some reduction in predictability due to increased flexibility (*cf.* **8**$^{4+}$ *vs.* **1**$^{4+}$). Our bigger difficulty has come when trying to make frameworks using the oxalate anion, the smallest dicarboxylate. We have never been able to obtain our target frameworks from this anion, which appears to be due to its ability to bind through either possible pair of oxygen atoms (two atoms on the same carbon, or on adjacent carbon atoms).[71,76]



|  | $TP^{2-}$ | $3^{2-}$ | $6^{4-}$ | $HCO_3^-$ |
|---|---|---|---|---|
| $1^{4+}$ | ✓ | ✓ | ✓ | ✓ |
| $9^{4+}$ | ✗ | ✓ | ✓ | ✗ |

**Figure 6** a) Comparison of carbon-centred and silicon-centred tetraamidinium tectons and their framework-forming ability. Ticks in the table indicate that a diamondoid framework was obtained for a given cation/anion combination, crosses indicate a diamondoid framework was not obtained. b) Structure of pentiptycene dicarboxylate $10^{2-}$.

It appears to be easier to form higher dimensionality solid state frameworks than lower dimensionality polymeric structures, or discrete assemblies. For example, the square planar porphyrin tetracarboxylate did not form either 2D frameworks with a linear bisamidinium linker, or cages with a bent bisamidinium, but did form 3D PtS networks.[68] Combinations of linear or bent bisamidiniums and linear or bent dicarboxylates did not give solid state macrocyclic structures, but did give 1D polymers.[63] In this case, solution NMR spectroscopy and computational molecular dynamics simulations were consistent with a range of acyclic, cyclic and oligomeric structures existing in polar solvents and so presumably crystallisation "sorts" the mixture to its least soluble, *i.e.* polymeric, state.

## Structure and stability of amidinium-carboxylate frameworks

### Interpenetration

The majority of frameworks we have prepared have had diamondoid topologies, although we have obtained some 2D sheet[63,71] and PtS materials.[68] In all cases, these materials have exhibited levels of interpenetration ranging from four-fold to 32-fold. Two different frameworks have exhibited 32-fold interpenetration: both are made from the large tetraamidinium $\mathbf{8}^{4+}$ and one contains the biphenyldicarboxylate anion $\mathbf{3}^{2-}$ [71] while the other contains the pentiptycene based anion $\mathbf{10}^{2-}$.[75] To the best of our knowledge, these are the most interpenetrated hydrogen bonded structures known, although an even more highly interpenetrated MOF has been reported.[77] Generally we see far higher levels of interpenetration in our frameworks than is common for MOFs, and we attribute this to two causes. Firstly, many of our frameworks have diamondoid topologies, and diamondoid materials are inherently highly prone to interpenetration.[78] Secondly, in our materials, both the cationic and anionic components are relatively large, whereas in MOFs the metal ions/secondary building units are typically relatively small. When both components are large, the nodes are thus far apart giving plenty of space for interpenetration to occur.

### Stability

There seems to be a trade-off in our frameworks between the amount of "open" space and stability. As previously mentioned, we prepared the porphyrin-based PtS structure **1·2**, which had only four-fold interpenetration and a calculated surface area of nearly 6000 $m^2\,g^{-1}$, but which was extremely unstable and lost crystallinity as soon as it was removed from solvent.[68] The first amidinium-carboxylate framework that we prepared (**1·TP**$_2$) had a relatively large calculated surface area (~1500 $m^2\,g^{-1}$) but lost crystallinity upon drying.[67] Most of the frameworks we have prepared have intermediate calculated surface areas (~400–1100 $m^2\,g^{-1}$) and retain their crystallinity upon drying.[71] Generally, it seems that frameworks with larger components have higher degrees of interpenetration meaning that the calculated surface areas typically remain broadly similar across a range of component sizes. When high levels of interpenetration do not occur and very open frameworks form, it appears that the channels simply become too large to be supported by the relatively weak hydrogen bonding that assembles the materials leading to poor stability.

When these materials do lose crystallinity upon drying, they can typically be "resuscitated" by addition of a drop of solvent.[67,74] This does not appear to be a bulk recrystallisation process (the frameworks being highly insoluble). Instead, we attribute this to solvent entering the partially collapsed frameworks and "re-ordering" them. It appears that for at least some of the frameworks, several different structures are possible and have similar energies. For example, two different forms of the framework assembled from silicon tetraamidinium $\mathbf{9}^{4+}$ and $\mathbf{TP}^{2-}$ were identified by SCXRD studies, as well as another four phases identified by PXRD studies.[74]

We have not yet found a way to activate our materials for gas sorption studies, so have not been able to determine surface areas in this manner. However, we have demonstrated that these materials are genuinely porous, for example by use of confocal laser scanning microscopy to show that fluorescein can move throughout the entire framework.[79]

In terms of stability more generally, our frameworks are very resistant to water and to polar organic solvents. There are a relatively high number of HOFs that are stable to water, presumably because the hydrophobic organic building blocks have no interest in dissolving in water. In our frameworks, both building blocks are typically water-soluble (often very much so), but the materials are robust enough to resist water, including boiling water. We note that the strength of an individual amidinium-carboxylate interaction is negligible in water, so it is not that the interactions are so strong that they can resist water. Rather, it appears that the net result of a large number of charge-assisted hydrogen bonds, potentially coupled with some hydrophobic interactions between the organic building blocks is enough to overcome the significant entropic penalty of framework formation.

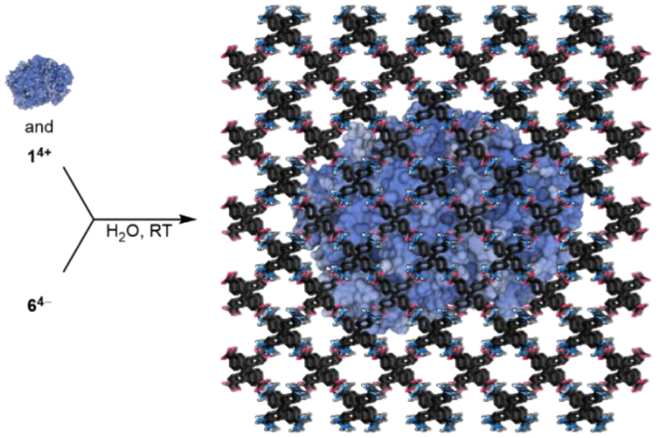
The frameworks demonstrate reasonable stability to acids and bases,[79] although strong acids protonate the carboxylate moieties destroying the framework,[67] while strong bases also appear to break the framework apart.[79,80] This may result from either deprotonation of the amidinium group in highly basic conditions, and/or hydrolysis of the amidinium group, which occurs slowly in moderately basic conditions but becomes rapid in strong base.[80] For example, frameworks **1·6** and **7·TP** show almost no degradation after a week at room temperature in 1% $NH_3$ (pH ~ 11.5), but are unstable at pH 13 or higher.[79,80]

## Applications of amidinium–carboxylate frameworks

### Enzyme encapsulation

As mentioned in the previous section, we have not yet demonstrated gas sorption in amidinium–carboxylate frameworks but we have demonstrated that they are porous in solution. Given the high stability of the materials, in particular to water, we wondered whether they may be suitable for use in biotechnological applications.[81] It has been elegantly demonstrated that a small number of MOFs are can form crystalline composites with proteins and other biomolecules in water (typically zeolitic imidazolate frameworks, ZIFs).[82-85] When enzymes are encapsulated, they are stabilised against a range of adverse conditions, but retain activity because substrates and reaction products can diffuse throughout the porous material. While this approach is promising, there are some drawbacks associated with using MOFs for this: notably some enzymes are deactivated upon encapsulation, and typical MOFs used have small pore apertures that limit reaction scope. Additionally, there are significant stability issues associated with the MOFs in biological media.[86,87]

In collaboration with the groups of Doonan, Falcaro and Sumby, we have investigated the encapsulation of enzymes in the amidinium–carboxylate framework **1·6** (Scheme 2).[79] Simply mixing an aqueous solution containing **1·Cl**$_4$ and catalase, alcohol oxidase, or bovine serum albumin (BSA) with a solution containing **6**$^{4-}$ resulted in the rapid precipitation of a microcrystalline composite (Scheme 2). A range of techniques were used to reveal that this composite has the same structure as "normal" **1·6**, but with enzymes located throughout the crystals in mesopores. Synchrotron small angle X-ray scattering experiments on the BSA/framework composite revealed that crystallisation is very rapid, with crystal nuclei forming within 0.1 seconds, and that this is not affected by the presence or absence of BSA. This suggests a crystallisation mechanism where the biomolecule is "caught up" in a rapidly crystallising framework. This mechanism is in contrast to enzyme encapsulation by ZIFs, which occurs by a "biomimetic mineralisation" mechanism, where the enzyme promotes crystallisation by concentrating cations at its surface.[88]



**Scheme 2** Schematic representation of encapsulation of enzymes inside hydrogen bonded amidinium–carboxylate framework **1·6**. We note that the composites formed are not single enzymes inside hydrogen bonded shells, but rather framework crystals with enzymes distributed throughout.

Enzymes retain their catalytic activities upon encapsulation in the frameworks, albeit with reduced rates. Notably, alcohol oxidase remained active in our hydrogen bonded material, but showed a complete loss of activity when encapsulated in ZIFs.[79] Importantly, encapsulation offers significant protection against a range of conditions including heat, non-neutral pHs, a proteolytic agent (trypsin) and chaotropic substance (6 M urea). That is, these substances do not significantly degrade the encapsulated enzymes, but do degrade the free enzymes, or enzymes which are simply adsorbed on the surface of the hydrogen bonded framework. We attribute this to confinement within pores in the framework preventing the enzyme from unfolding. As amidinium–carboxylate frameworks have larger pore apertures than ZIFs and appear to show higher biocompatibility, these materials appear to offer significant promise for encapsulation.[89] Given the relatively large family of amidinium–carboxylate frameworks that have been prepared to date and the scope to expand this family significantly, we are hopeful that "designer" frameworks can be prepared to tune encapsulation properties.

### Hydrogen bonded nanosheets

Two dimensional materials, *i.e.* materials that are large in two dimensions but only a few atoms/molecules thick are the subject of huge research interest. These materials typically have relatively strong interactions such as covalent[90-92] or coordination[93-95] bonding in two dimensions and much weaker interactions in the third, which allows the strongly-bonded layers to be separated from one another. Perhaps unsurprisingly, making freestanding 2D materials using hydrogen bonding alone is much harder, consistent with the much weaker nature of the interaction. The small number of hydrogen bonded 2D materials that have been made have typically been prepared through a bottom-up approach, which is often quite time consuming.[96-99] An alternative approach is to take 3D crystals that contain weak interactions in one dimension and exfoliate these using a force such as ultrasonication in a top-down process. Working with the Foster, group we have recently demonstrated that this approach can be used to prepare monolayer 2D nanosheets that are held together solely by hydrogen bonding interactions (Figure 7).[100]

Amidinium-carboxylate frameworks were prepared from either bisamidinium $\mathbf{7}^{2+}$ and terephthalate, or from the single component **11** (Figure 7), which contains an amidinium and carboxylate group attached to the same benzene ring.[101] X-ray crystallography revealed that both frameworks had very similar close-packed structures with short, parallel hydrogen bonds linking the structures into 1D chains (H–O: 1.90–1.94 Å) and slightly longer hydrogen bonds linking these into 2D sheets (H–O: 2.00–2.08 Å). No close contacts were observed between the sheets (interlayer distances > 3.7 Å). Exfoliation using ultrasonication in polar organic solvents gave crystalline single layer nanosheets with micron dimensions and sub-nanometre thickness. Both the aspect ratio and yields of nanosheets are remarkably high – significantly higher than other molecular nanosheet materials.

Stability testing revealed that the exfoliated nanosheets retained their structure after extended heating in water (3 days at 80 °C). This is remarkable given that the building blocks used to make the materials are highly water soluble, and that the 2D nature of the materials means that the hydrogen bonds used to assemble them are necessarily exposed to the highly polar solvent. The nanosheets exhibited efficient quenching of the organic dye molecule Rhodamine B, suggesting that these types of materials may have potential sensing applications.

## Recent developments

In the weeks leading up to submission of this article, two reports describing amidinium-carboxylate frameworks by other research groups have appeared. In both cases, interesting applications of the frameworks have been described. He, Sessler and Wang reported a family of amidinium-carboxylate frameworks assembled from the tetraphenylethene-based tetraamidinium $\mathbf{12}^{4+}$ and four different dicarboxylate anions (Figure 8a).[42] Interestingly, in the structure containing bipyridinedicarboxylate anion $\mathbf{13}^{2-}$, all amidinium groups hydrogen bond to the anions in a "paired" $R_2^2(8)$ manner, while in other structures other hydrogen bonding arrangements are observed, sometimes involving water solvent molecules. It is notable that all of these structures were obtained from either pure water or mixtures of water and a polar organic solvent, and that the authors were able to break apart and re-form their frameworks using acid/base stimuli. The frameworks displayed moderately high fluorescent quantum yields of 5–15%, although this was lower than the non-framework amidinium salt $\mathbf{12}\cdot\mathrm{Cl}_4$ (38%).

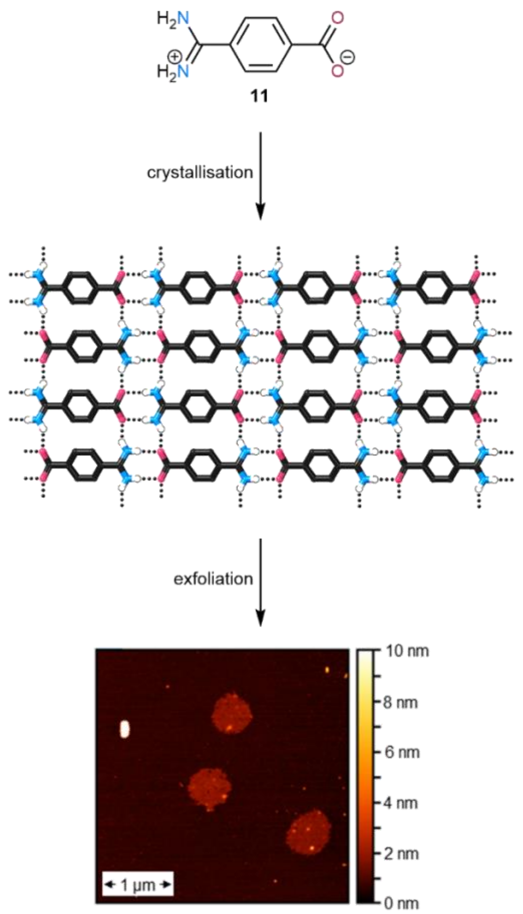


**Figure 7** Example of formation of 2D hydrogen bonded nanosheets from **11** (CCDC: 20472426). Nanosheets were prepared from **7·TP** in the same manner.

Wang has very recently reported the synthesis of new amidinium-carboxylate frameworks for enzyme encapsulation.[43] The frameworks were prepared from tetraamidinium $\mathbf{1}^{4+}$ and the diazo-containing dicarboxylate $\mathbf{14}^{2-}$ (Figure 8b), and in the absence of a protein form nanorods with lengths of approximately 200 nm. Encapsulation of several different proteins in the amidinium-carboxylate framework was demonstrated, and resulted in slightly larger crystallites (400–2000 nm). Due to the small size of the crystallites, the exact structure of the framework was not determined, but PXRD showed that both the framework and protein/framework composite have some crystallinity. The authors showed that encapsulation of proteins within the framework allowed the composite to be internalised by cells. Remarkably, when a catalase/framework composite was used, it was demonstrated that this could protect cells from oxidative stress by catalysing the decomposition of hydrogen peroxide.

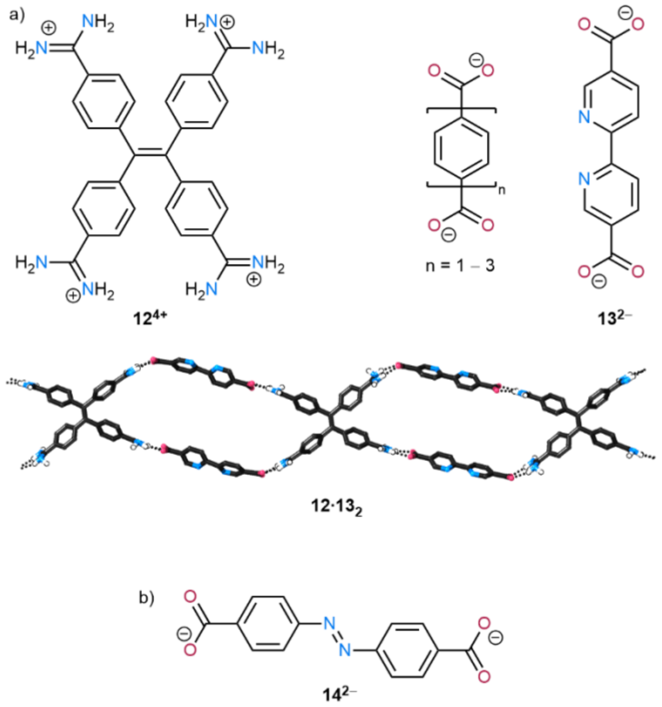


**Figure 8** Recent advances in amidinium-carboxlyate frameworks: a) structure of tetraphenylethylene tetraamidinium **$12^{4+}$** and dicarboxylate anions used by He, Sessler, and Wang to form fluorescent hydrogen bonded framework, as well as crystal structure of **$12{\cdot}13_2$** (CCDC: 2056902); b) diazodicarboxlate **$14^{2-}$** used by Wang to encapsulate proteins and internalise them within cells.

## Outlook and conclusions

Inspired by early work from the groups of Wuest, Wais Hosseini and Ward, my group has developed the synthesis of a family of amidinium-carboxylate hydrogen bonded frameworks. We have been able to form a range of materials in a relatively predictable manner, using an operationally simple method of mixing two components at room temperature in water or water:organic mixtures. Most of the frameworks have open structures, are stable to drying, and robust to all tested solvents. While we have not been able to observe uptake of gases within these frameworks, they are porous in solution. Working with collaborators we have demonstrated that some of these frameworks can encapsulate and protect enzymes, while others can be exfoliated into 2D nanosheets. There appears to be considerable scope for the development of new amidinium-carboxylate frameworks, as demonstrated by the very recent results reported by He, Sessler, and Wang,[42] and by Wang.[43]

A key challenge from a crystal engineering perspective will be to understand the conditions that lead to exclusive formation of the "paired" $R_2^2(8)$ hydrogen bonding motif. This will further enhance the predictability of the already (relatively) predictable framework structures. If a methodology could be found to tune the degree of framework interpenetration (and thus porosity), this would represent a huge advance.

It is interesting that even though amidinium-carboxylate frameworks are surprisingly robust under conditions that destroy many HOFs (*e.g.* boiling water, DMSO), gas sorption has not yet been demonstrated for these materials. It may be that this is due to the difficulty of removing the highly polar solvents that need to be used to prepare these frameworks from the pores of the material, and it is notable that generally it has been far harder to observe gas sorption in charge-assisted hydrogen bonded frameworks than in those prepared from neutral components. Given the other applications of these materials, perhaps the requirement to study their gas sorption properties is less pressing, although studying the presence or absence of gas sorption further may provide insights into structural properties of these materials.

It is clear that these kind of frameworks are excellent candidates for biological applications as they are robust, predictable and can be prepared in water.[43,79] Early signs suggest the frameworks are well-tolerated by biological systems, as exemplified by Wang's demonstration that they can be used to encapsulate enzymes which can then be internalised in cells.[43] To date the amidinium-carboxylate frameworks that have been exfoliated into nanosheets contain only simple building blocks, and the frameworks do not contain any pores. Future work will investigate whether functional building blocks containing *e.g.* catalytically active groups or sensing motifs can be incorporated in order to really take advantage of the high aspect ratios of the nanosheets.

Given the first 3D amidinium-carboxylate framework was only reported in 2017, there is still considerable room for new applications of these materials to be developed. The rate of development of these systems is likely to increase dramatically now that other research groups are also exploring their synthesis and applications, and it will be interesting to see what new uses people find for them.

## Conflicts of interest

There are no conflicts to declare.

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## Notes and references

1. R.-B. Lin, Y. He, P. Li, H. Wang, W. Zhou and B. Chen, *Chem. Soc. Rev.*, 2019, **48**, 1362-1389.
2. I. Hisaki, C. Xin, K. Takahashi and T. Nakamura, *Angew. Chem., Int. Ed.*, 2019, **58**, 11160-11170.
3. B. F. Hoskins and R. Robson, *J. Am. Chem. Soc.*, 1989, **111**, 5962-5964.
4. S. S.-Y. Chui, S. M.-F. Lo, J. P. H. Charmant, A. G. Orpen and I. D. Williams, *Science*, 1999, **283**, 1148-1150.
5. H. Li, M. Eddaoudi, M. O'Keeffe and O. M. Yaghi, *Nature*, 1999, **402**, 276.
6. O. M. Yaghi, M. O'Keeffe, N. W. Ockwig, H. K. Chae, M. Eddaoudi and J. Kim, *Nature*, 2003, **423**, 705-714.
7. A. P. Côté, A. I. Benin, N. W. Ockwig, M. O'Keeffe, A. J. Matzger and O. M. Yaghi, *Science*, 2005, **310**, 1166-1170.
8. H. M. El-Kaderi, J. R. Hunt, J. L. Mendoza-Cortés, A. P. Côté, R. E. Taylor, M. O'Keeffe and O. M. Yaghi, *Science*, 2007, **316**, 268-272.
9. The term HOF is used somewhat indiscriminately in the literature. Sometimes it is used to refer to frameworks with demonstrated permanent porosity, while at other times it simply refers to open hydrogen bonded frameworks. Several alternative terms including SOF (supramolecular organic framework) and CPOS (crystalline porous organic salt) are also used, which can further add to the confusion. A more detailed view on the nomenclature of these materials has recently been provided by Ward: A. Yusov, A. M. Dillon and M. D. Ward, *Mol. Syst. Des. Eng.* 2021, DOI: 10.1039/D1ME00055A.
10. X.-Z. Luo, X.-J. Jia, J.-H. Deng, J.-L. Zhong, H.-J. Liu, K.-J. Wang and D.-C. Zhong, *J. Am. Chem. Soc.*, 2013, **135**, 11684-11687.
11. H. Yamagishi, H. Sato, A. Hori, Y. Sato, R. Matsuda, K. Kato and T. Aida, *Science*, 2018, **361**, 1242.
12. K. Ma, P. Li, J. H. Xin, Y. Chen, Z. Chen, S. Goswami, X. Liu, S. Kato, H. Chen, X. Zhang, J. Bai, M. C. Wasson, R. R. Maldonado, R. Q. Snurr and O. K. Farha, *Cell Rep. Phys. Sci.*, 2020, **1**, 100024.
13. I. Hisaki, Y. Suzuki, E. Gomez, Q. Ji, N. Tohnai, T. Nakamura and A. Douhal, *J. Am. Chem. Soc.*, 2019, **141**, 2111-2121.
14. O. Ermer, *J. Am. Chem. Soc.*, 1988, **110**, 3747-3754.
15. O. Ermer and A. Eling, *Angew. Chem., Int. Ed.*, 1988, **27**, 829-833.
16. M. Simard, D. Su and J. D. Wuest, *J. Am. Chem. Soc.*, 1991, **113**, 4696-4698.
17. X. Wang, M. Simard and J. D. Wuest, *J. Am. Chem. Soc.*, 1994, **116**, 12119-12120.
18. P. Brunet, M. Simard and J. D. Wuest, *J. Am. Chem. Soc.*, 1997, **119**, 2737-2738.
19. J.-H. Fournier, T. Maris, J. D. Wuest, W. Guo and E. Galoppini, *J. Am. Chem. Soc.*, 2003, **125**, 1002-1006.
20. W. Yang, A. Greenaway, X. Lin, R. Matsuda, A. J. Blake, C. Wilson, W. Lewis, P. Hubberstey, S. Kitagawa, N. R. Champness and M. Schröder, *J. Am. Chem. Soc.*, 2010, **132**, 14457-14469.
21. Y. He, S. Xiang and B. Chen, *J. Am. Chem. Soc.*, 2011, **133**, 14570-14573.
22. M. Mastalerz and I. M. Oppel, *Angew. Chem., Int. Ed.*, 2012, **51**, 5252-5255.
23. A. Pulido, L. Chen, T. Kaczorowski, D. Holden, M. A. Little, S. Y. Chong, B. J. Slater, D. P. McMahon, B. Bonillo, C. J. Stackhouse, A. Stephenson, C. M. Kane, R. Clowes, T. Hasell, A. I. Cooper and G. M. Day, *Nature*, 2017, **543**, 657-664.
24. P. Li, P. Li, M. R. Ryder, Z. Liu, C. L. Stern, O. K. Farha and J. F. Stoddart, *Angew. Chem., Int. Ed.*, 2019, **58**, 1664-1669.
25. F. Hu, C. Liu, M. Wu, J. Pang, F. Jiang, D. Yuan and M. Hong, *Angew. Chem., Int. Ed.*, 2017, **56**, 2101-2104.
26. Y. Yang, L. Li, R.-B. Lin, Y. Ye, Z. Yao, L. Yang, F. Xiang, S. Chen, Z. Zhang, S. Xiang and B. Chen, *Nature Chem.*, 2021, DOI: 10.1038/s41557-021-00740-z.
27. We note that in rare cases it is possible to prepare hydrogen bonded frameworks from more than one neutral component, e.g. J. Lü, C. Perez-Krap, M. Suyetin, N. H. Alsmail, Y. Yan, S. Yang, W. Lewis, E. Bichoutskaia, C. C. Tang, A. J. Balke, R. Cao and M. Schröder*, J. Am. Chem. Soc* 2014, **136**, 12828-12831.
28. V. A. Russell, M. C. Etter and M. D. Ward, *J. Am. Chem. Soc.*, 1994, **116**, 1941-1952.
29. V. A. Russell, C. C. Evans, W. Li and M. D. Ward, *Science*, 1997, **276**, 575-579.
30. M. J. Horner, K. T. Holman and M. D. Ward, *J. Am. Chem. Soc.*, 2007, **129**, 14640-14660.
31. Y. Liu, C. Hu, A. Comotti and M. D. Ward, *Science*, 2011, **333**, 436-440.
32. T. Adachi and M. D. Ward, *Acc. Chem. Res.*, 2016, **49**, 2669-2679.
33. H. Wahl, D. A. Haynes and T. le Roex, *Chem. Commun.*, 2012, **48**, 1775-1777.
34. A. Yamamoto, S. Uehara, T. Hamada, M. Miyata, I. Hisaki and N. Tohnai, *Cryst. Growth Des.*, 2012, **12**, 4600-4606.
35. A. Yamamoto, T. Hirukawa, I. Hisaki, M. Miyata and N. Tohnai, *Tetrahedron Lett.*, 2013, **54**, 1268-1273.
36. N. Roques, G. Mouchaham, C. Duhayon, S. Brandès, A. Tachon, G. Weber, J. P. Bellat and J.-P. Sutter, *Chem. Eur. J.*, 2014, **20**, 11690-11694.
37. C. Mottillo and T. Friscic, *Chem. Commun.*, 2015, **51**, 8924-8927.
38. T. Miyano, N. Okada, R. Nishida, A. Yamamoto, I. Hisaki and N. Tohnai, *Chem. Eur. J.*, 2016, **22**, 15430-15436.
39. G. Xing, T. Yan, S. Das, T. Ben and S. Qiu, *Angew. Chem., Int. Ed.*, 2018, **57**, 5345-5349.
40. G. Xing, I. Bassanetti, T. Ben, S. Bracco, P. Sozzani, L. Marchiò and A. Comotti, *Cryst. Growth Des.*, 2018, **18**, 2082-2092.
41. G. Xing, I. Bassanetti, S. Bracco, M. Negroni, C. Bezuidenhout, T. Ben, P. Sozzani and A. Comotti, *Chem. Sci.*, 2019, **10**, 730-736.
42. J. L. Sessler, H. Jiang, L. Xie, Z. Duan, K. Lin, Q. He, V. M. Lynch and H. Wang, *Chem. Eur. J.*, 2021, DOI: 10.1002/chem.202102296.
43. M. Wang, J. Tang, J. Liu, Q. Zheng, W. Li, J. Sheng and L. Mao, *Angew. Chem., Int. Ed.*, 2021, DOI: 10.1002/anie.202105634.
44. O. Félix, M. W. Hosseini, A. De Cian and J. Fischer, *Angew. Chem., Int. Ed.*, 1997, **36**, 102-104.
45. M. W. Hosseini, R. Ruppert, P. Schaeffer, A. De Cian, N. Kyritsakas and J. Fischer, *J. Chem. Soc., Chem. Commun.*, 1994, 2135-2136.
46. C. Carpanese, S. Ferlay, N. Kyritsakas, M. Henry and M. W. Hosseini, *Chem. Commun.*, 2009, 6786-6788.
47. S. Ferlay, O. Félix, M. W. Hosseini, J.-M. Planeix and N. Kyritsakas, *Chem. Commun.*, 2002, 702-703.
48. S. Ferlay, V. Bulach, O. Félix, M. W. Hosseini, J.-M. Planeix and N. Kyritsakas, *CrystEngComm*, 2002, **4**, 447-453.
49. Y. Deng, J. A. Roberts, S.-M. Peng, C. K. Chang and D. G. Nocera, *Angew. Chem., Int. Ed.*, 1997, **36**, 2124-2127.
50. P. A. Gale, *Tetrahedron Lett.*, 1998, **39**, 3873-3876.
51. L. Sebo, B. Schweizer and F. Diederich, *Helv. Chim. Acta*, 2000, **83**, 80-92.

52. L. Sebo, F. Diederich and V. Gramlich, *Helv. Chim. Acta*, 2000, **83**, 93-113.
53. T. Kusukawa, S. Tanaka and K. Inoue, *Tetrahedron*, 2014, **70**, 4049-4056.
54. T. Kusukawa, K. Matsumoto, H. Nakamura, W. Iizuka, K. Toyama and S. Takeshita, *Org. Biomol. Chem.*, 2013, **11**, 3692-3698.
55. F. Corbellini, L. Di Costanzo, M. Crego-Calama, S. Geremia and D. N. Reinhoudt, *J. Am. Chem. Soc.*, 2003, **125**, 9946-9947.
56. H. Katagiri, Y. Tanaka, Y. Furusho and E. Yashima, *Angew. Chem., Int. Ed.*, 2007, **46**, 2435-2439.
57. C. M. Thomas, É. M. Foyle, S. E. Walker and N. G. White, *Aust. J. Chem.*, 2021, DOI: https://doi.org/10.1071/CH21101.
58. W. Makiguchi, J. Tanabe, H. Yamada, H. Iida, D. Taura, N. Ousaka and E. Yashima, *Nature Commun.*, 2015, **6**, 7236.
59. M. Ikeda, Y. Tanaka, T. Hasegawa, Y. Furusho and E. Yashima, *J. Am. Chem. Soc.*, 2006, **128**, 6806-6807.
60. Y. Tanaka, H. Katagiri, Y. Furusho and E. Yashima, *Angew. Chem., Int. Ed.*, 2005, **44**, 3867-3870.
61. N. Kamali, M. Aljohani, P. McArdle and A. Erxleben, *Cryst. Growth Des.*, 2015, **15**, 3905-3916.
62. L. Pop, N. D. Hadade, A. van der Lee, M. Barboiu, I. Grosu and Y.-M. Legrand, *Cryst. Growth Des.*, 2016, **16**, 3271-3278.
63. M. Thomas, T. Anglim Lagones, M. Judd, M. Morshedi, M. L. O'Mara and N. G. White, *Chem. Asian J.*, 2017, **12**, 1587-1597.
64. A. Albert, R. Goldacre and J. Phillips, *J. Chem. Soc.*, 1948, 2240-2249.
65. J. G. Clayden, Nick and S. Warren, *Organic Chemistry*, Oxford University Press, 2nd Edn., 2012.
66. I note that these p$K_a$ values are given in water, and will be significantly different in organic solvents.
67. M. Morshedi, M. Thomas, A. Tarzia, C. J. Doonan and N. G. White, *Chem. Sci.*, 2017, **8**, 3019--3025.
68. M. Morshedi, J. S. Ward, P. E. Kruger and N. G. White, *Dalton Trans.*, 2018, **47**, 783-790.
69. Y.-F. Han, Y.-X. Yuan and H.-B. Wang, *Molecules*, 2017, **22**, 266.
70. Y. Suzuki, M. Gutiérrez, S. Tanaka, E. Gomez, N. Tohnai, N. Yasuda, N. Matubayasi, A. Douhal and I. Hisaki, *Chem. Sci.*, 2021, **12**, 9607-9618.
71. S. A. Boer, M. Morshedi, A. Tarzia, C. J. Doonan and N. G. White, *Chem. Eur. J.*, 2019, **25**, 10006-10012.
72. W. Zhao, A. H. Flood and N. G. White, *Chem. Soc. Rev.*, 2020, **49**, 7893-7906.
73. D. A. Cullen, M. G. Gardiner and N. G. White, *Chem. Commun.*, 2019, **55**, 12020-12023.
74. S. A. Boer, L.-J. Yu, T. L. Genet, K. Low, D. A. Cullen, M. G. Gardiner, M. L. Coote and N. G. White, *Chem. Eur. J.*, 2021, **27**, 1768-1776.
75. S. A. Boer, P.-X. Wang, M. J. MacLachlan and N. G. White, *Cryst. Growth Des.*, 2019, **19**, 4829-4835.
76. M. Morshedi and N. G. White, *CrystEngComm*, 2017, **19**, 2367-2371.
77. H. Wu, J. Yang, Z.-M. Su, S. R. Batten and J.-F. Ma, *J. Am. Chem. Soc.*, 2011, **133**, 11406-11409.
78. S. R. Batten and R. Robson, *Angew. Chem., Int. Ed.*, 1998, **37**, 1460-1494.
79. W. Liang, F. Carraro, M. B. Solomon, S. G. Bell, H. Amenitsch, C. J. Sumby, N. G. White, P. Falcaro and C. J. Doonan, *J. Am. Chem. Soc.*, 2019, **141**, 14298-14305.
80. L.-J. Yu, D. A. Cullen, M. Morshedi, M. L. Coote and N. G. White, *J. Org. Chem.* 2021, DOI: 10.1021/acs.joc.1c01955.
81. W. Liang, P. Wied, F. Carraro, C. J. Sumby, B. Nidetzky, C.-K. Tsung, P. Falcaro and C. J. Doonan, *Chem. Rev.*, 2021, **121**, 1077-1129.
82. F. Lyu, Y. Zhang, R. N. Zare, J. Ge and Z. Liu, *Nano Lett.*, 2014, **14**, 5761-5765.
83. K. Liang, R. Ricco, C. M. Doherty, M. J. Styles, S. Bell, N. Kirby, S. Mudie, D. Haylock, A. J. Hill, C. J. Doonan and P. Falcaro, *Nature Commun.*, 2015, **6**, 7240.
84. S. Li, M. Dharmarwardana, R. P. Welch, Y. Ren, C. M. Thompson, R. A. Smaldone and J. J. Gassensmith, *Angew. Chem., Int. Ed.*, 2016, **55**, 10691-10696.
85. K. Liang, J. J. Richardson, J. Cui, F. Caruso, C. J. Doonan and P. Falcaro, *Adv. Mater.*, 2016, **28**, 7910-7914.
86. M. A. Luzuriaga, C. E. Benjamin, M. W. Gaertner, H. Lee, F. C. Herbert, S. Mallick and J. J. Gassensmith, *Supramol. Chem.*, 2019, **31**, 485-490.
87. M. d. J. Velásquez-Hernández, R. Ricco, F. Carraro, F. T. Limpoco, M. Linares-Moreau, E. Leitner, H. Wiltsche, J. Rattenberger, H. Schröttner, P. Frühwirt, E. M. Stadler, G. Gescheidt, H. Amenitsch, C. J. Doonan and P. Falcaro, *CrystEngComm*, 2019, **21**, 4538-4544.
88. N. K. Maddigan, A. Tarzia, D. M. Huang, C. J. Sumby, S. G. Bell, P. Falcaro and C. J. Doonan, *Chem. Sci.*, 2018, **9**, 4217-4223.
89. We note that a very recent paper shows that other hydrogen bonded frameworks potentially offer remarkable bioencapsulation properties: G. Chen, S. Huang, Y. Shen, X. Kou, X. Ma, S. Huang, Q. Tong, K. Ma, W. Chen, P. Wang, J. Shen, F. Zhu and G. Ouyang, *Chem*, 2021, DOI: 10.1016/j.chempr.2021.07.003.
90. M. J. Allen, V. C. Tung and R. B. Kaner, *Chem. Rev.*, 2010, **110**, 132-145.
91. L. H. Li and Y. Chen, *Adv. Funct. Mater.*, 2016, **26**, 2594-2608.
92. D. Rodríguez-San-Miguel, C. Montoro and F. Zamora, *Chem. Soc. Rev.*, 2020, **49**, 2291-2302.
93. X. Huang, Z. Zeng and H. Zhang, *Chem. Soc. Rev.*, 2013, **42**, 1934-1946.
94. M. Zhao, Y. Huang, Y. Peng, Z. Huang, Q. Ma and H. Zhang, *Chem. Soc. Rev.*, 2018, **47**, 6267-6295.
95. D. J. Ashworth and J. A. Foster, *J. Mater. Chem. A*, 2018, **6**, 16292-16307.
96. R. Davis, R. Berger and R. Zentel, *Adv. Mater.*, 2007, **19**, 3878-3881.
97. X. Hou, M. Schober and Q. Chu, *Cryst. Growth Des.*, 2012, **12**, 5159-5163.
98. W. Bai, Z. Jiang, A. E. Ribbe and S. Thayumanavan, *Angew. Chem., Int. Ed.*, 2016, **55**, 10707-10711.
99. R. Makiura, K. Tsuchiyama, E. Pohl, K. Prassides, O. Sakata, H. Tajiri and O. Konovalov, *ACS Nano*, 2017, **11**, 10875-10882.
100. J. Nicks, S. A. Boer, N. G. White and J. A. Foster, *Chem. Sci.*, 2021, **12**, 3322-3327.
101. We note that Jackson and Nocera prepared a 2D layered framework from a compound related to **11**, where the amidinium and carboxylate groups are located *meta* to one another: D. Papoutsakis, J. P. Kirby, J. E. Jackson and D. G. Nocera, *Chem. Eur. J.* 1999, **5**, 1474-1480.