Supramolecular anion recognition in water: synthesis of hydrogen-bonded supramolecular frameworks†

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The interaction of tetratopic amidinium-containing receptors with terephthalate anions leads to porous framework materials assembled through charge-assisted hydrogen bonds. The frameworks form in good yield within minutes in water at room temperature, but no framework material is obtained if other anions (Cl\(^-\), Br\(^-\), NO\(_3\)^\(-\), SO\(_4\)^\(-\), or isophthalate\(2^\text{-}\)) are used in place of terephthalate. Two forms of the framework can be prepared: one with a connected pore network, and a more dense phase with discrete voids. We demonstrate that these are the kinetic and thermodynamic products, respectively. Either framework can be prepared independently and can be converted to the other form in response to stimuli. Furthermore, the frameworks can be controllably disassembled and reassembled in response to acid/base triggers suggesting that this new class of materials may have applications in the selective encapsulation and release of guests.

Introduction

Encumbered by the difficulties associated with binding anions in protic solvents, the field of anion recognition has lagged behind that of cation recognition. Even after decades of research, there are few supramolecular hosts that can bind anions in water, and fewer still that can achieve selective recognition in this medium.

Given these difficulties, it is perhaps unsurprising that the field of anion-templated self-assembly is very much in its infancy, particularly when compared with the impressive successes of transition metal imidazolate analogues.

However, despite the significant challenges, notable successes have been reported including the anion-templated syntheses of interlocked structures (Beer),\(^1\) stimuli-responsive pseudorotaxanes and threaded architectures (Sessler),\(^2\) and very recently, cages (Kruger and Gunnlaugsson, and Wu).\(^3\)

Inspired by recent developments in the field of hydrogen-bonded framework materials, in particular Ward’s pioneering work on guanidinium--sulfonate frameworks,\(^4\) and Friščič’s demonstration that imidazolium sulfate salts are “mirror images” of the transition metal imidazolate analogues,\(^5\) we have investigated the use of simple anions to assemble supramolecular framework materials.\(^6\) Herein, we describe the use of terephthalate anions to prepare porous frameworks, which we believe to be an unprecedented demonstration of anion-induced self-assembly in water.\(^7,8\)

While the amidinium group has been elegantly exploited to prepare self-assembled systems,\(^9,10\) it has received relatively little attention within anion recognition chemistry.\(^11\) This is perhaps surprising, given its similarity to the thoroughly-explored guanidinium functionality.\(^11,12\) Attracted by the amidinium motif’s relatively high p\(K_a\),\(^13\) strong hydrogen bonding capability and ease of synthesis, we sought to investigate whether the favourable interaction between this motif and carboxylate anions could be used to prepare self-assembled structures.

Results and discussion

While complex systems assembled by amidinium--carboxylate interactions have been reported,\(^11,12\) little information regarding the strength of a simple 1 : 1 amidinium--carboxylate interaction is available. Therefore, we initially investigated the solution anion recognition properties of simple model receptor 1-BPh\(_4\) (Fig. 1): \(^1\)H NMR titration experiments revealed that this simple host displays strong anion recognition in CD\(_3\)CN (\(K_a\) for Cl\(^-\) > 10\(^9\) M\(^{-1}\), addition of oxoanions results in precipitation). Moving to a more competitive medium, isothermal calorimetry (ITC), \(^13\)C NMR experiments and molecular dynamics (MD) simulations all showed strong benzoate anion binding in 95 : 5 acetonitrile : water (\(K_a\) ~ 2900 M\(^{-1}\), \(^1\)H NMR experiments were
precluded by disappearance of N–H resonances in this solvent mixture, see ESI† for details of anion recognition experiments). Negligible association was observed between 1+ and chloride anion in this competitive aqueous medium.

This strong oxoanion binding is remarkable given that 1+ contains only one amidinium motif, and an electron-donating tert-butyl group, and presumably it arises due to the highly complementary hydrogen bonding interactions possible between the amidinium N–H donors and carboxylate oxygen atoms. Single crystal X-ray diffraction (SCXRD) studies and molecular dynamics (MD) simulations reveal that in both the solid state and in solution short hydrogen bonds between the “forward-facing” amidinium N–H groups and carboxylate oxygen atoms are present (Fig. 1). Given the strong binding exhibited by simple receptor 1+, it seems likely that more complex and sophisticated anion receptors containing amidinium groups offer a route to potent anion recognition in aqueous media.

Encouraged by the strength of the interaction between our model compound and benzoate, we designed the new tетratopic tetra-catonic receptor 24+ (Scheme 1). This receptor was prepared in high yield (81%) by treating the corresponding tetra-nitrile17 with LiHMDS in THF, followed by work-up with ethanolic HCl, giving 2-4Cl. The potentially-coordinating chloride anions could be readily exchanged for non-coordinating anions by simple precipitation from water with sodium tetraphenylborate.

We next investigated whether terephthalate anions19 could be used to link 24+ receptors into a porous framework material. We initially used 2-4BPh4 and TBA2·TP, which are both soluble in a range of moderately-polar and polar organic solvents [TBA2·TP = n-tetraethylammonium terephthalate], reasoning that using organic solvents and the non-coordinating tetraphenylborate anion and terephthalammonium cation would minimize unwanted interactions and maximise the strength of the amidinium::terephthalate interaction, thus favouring extended network formation. However, mixing 2-4BPh4 and TBA2·TP in a range of solvents resulted in the immediate precipitation of insoluble amorphous solids under all tested conditions, even when using highly polar solvents such as DMF and DMSO and/or solvothermal reactions. While the solids formed were insoluble in all tested solvents, 1H NMR analysis of the acid-digested material was consistent with the insoluble solid having the formulation [2·(TP)2]n. We hypothesize that a polymeric aggregate between 24+ and TP2− forms very rapidly in these solvents, and this speed precludes an ordered crystalline structure.

In an effort to modify the kinetics of framework formation, we next investigated the use of water as solvent; this required the use of 2-4Cl, as 2-4BPh4 is insoluble in water. Mixing aqueous solutions of 2-4Cl and TBA2·TP resulted in the formation of large needle-like crystals. Crystals were visible within 1–2 minutes, and crystal growth was complete within an hour (see ESI Video†).

The crystals were analysed by SCXRD studies, which show that the material possesses a distorted diamondoid topology with the formula [2·(TP)2]n·water (Fig. 2). The framework is constructed from parallel hydrogen bonds between the two “forward-facing” amidinium N–H groups and the two carboxylate oxygen atoms. These hydrogen bonds are short [N···O distances: 2.787(3) and 2.832(3) Å, N–H···O: 171 and 165°, H···O distances: 1.91 and 1.99 Å, and 71 and 74% of the sum of the van der Waals radii18 of H and O].

The framework crystallises in the I-centered tetragonal space group I41/a, and is significantly interpenetrated, with 11 interpenetrating nets (Fig. S23†). Despite this, the material contains accessible pores, which exist as square channels with a diameter of approximately 1.3 nm running down the crystallographic c-axis. In the crystalline state, the channels are filled with water molecules, which can be resolved down the crystallographic c-axis. The framework synthesis was repeated on a preparative scale, giving access to “bulk” quantities of [2·(TP)2]n, in good yield (77%). In addition, the material was further characterized by powder X-ray diffraction (PXRD) experiments, IR spectroscopy, thermogravimetric analysis (TGA), elemental analysis (EA) and by 1H NMR spectroscopy of an acid-digested sample (see ESI†).

![Diagram of tetratopic receptor 2-4Cl and its anion exchange reactions.](Image)
Given that the material is prepared from TBA₂-TP, it is conceivable that the large TBA cations could have a templating effect on the structure – however, this was ruled out by preparing the framework from sodium terephthalate. Any possible structure directing effect of the chloride anions was also ruled out by preparing the framework from 2-4Br, and from 2-4NO₃.

It is noteworthy that 2⁺ does not precipitate from water in the presence of Cl⁻, Br⁻, NO₃⁻ or even SO₄²⁻ or isophthlate²⁻ anions, suggesting that no extended structures form in water with these anions. We suggest that the interaction between all these anions and 2⁺ in water is negligible, so no insoluble aggregates form. Conversely, when terephthalate is used, the interaction between this anion and the tetra-amidinium receptor is strong enough that small "clusters" of receptors and anions can form that nucleate crystal growth. Remarkably, the framework could be prepared in 50 mM NaCl(aq), even though this corresponds to a greater than 100-fold excess of chloride anions relative to terephthalate anions. Surprisingly, when [2-(TP)₃]ₙ was prepared in this way, no evidence of incorporation of NaCl into the channels was observed by SCXRD.

A key advantage to preparing frameworks from terephthalate anions is that [2-(TP)₃]ₙ is prepared from solution at room temperature, unlike metal organic frameworks (MOFs) and covalent organic frameworks (COFs), which typically (although not always) require solvothermal synthesis. We sought to use these mild synthetic conditions to our advantage by reversibly "breaking" and re-forming our frameworks. Suspending crystals of [2-(TP)₃]ₙ in water and adding dilute HCl(aq) or trifluoroacetic acid caused the dissolution of the crystals, presumably due to protonation of the carboxylate anion breaking apart the favourable hydrogen bonding interactions. Neutralising the solution using NaOH(aq) caused the framework to reform within minutes. The ability to selectively "trigger" the destruction of a framework in response to a stimulus, and importantly, to recreate it, suggests that carboxylate anion-based materials may have future applications in controlled release systems, where encapsulated guests are freed by disassembling the extended network in response to acid.

To further investigate the formation of the frameworks, we next investigated the preparation of [2-(TP)₃]ₙ in the presence of an organic co-solvent. When 2-4Cl and TBA₂-TP were mixed in

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**Fig. 2** Views of the solid state structure of [2-(TP)₃]ₙ: (a) view showing hydrogen bonding interactions, (b) view of one of the interpenetrating nets, (c) view down the c-axis highlighting N₂-accessible pores (solvent molecules and some hydrogen atoms are omitted for clarity, see Fig. S23 † for additional views of the structure).

**Fig. 3** Views of the SCXRD structure of [2-(TP)₃]ₙ water prepared from water/acetone mixtures: (a) depiction of hydrogen bonding interactions in both terephthalate anion disorder positions; (b) view along the crystallographic a-axis (solvent molecules and most hydrogen atoms are omitted for clarity).
isolated, with no inclusion of SO₄

Intriguingly, the kinetic product

Conclusions

In this paper, we have demonstrated that a simple amidinium receptor can recognise carboxylate anions in aqueous media, and have then used these amidinium...carboxylate interactions to synthesise supramolecular frameworks in water. At room temperature, 2-4ClI and terephthalate anions rapidly form an open porous framework material, \( \text{tet}-[2 \cdot (\text{TP})_2]_n \), while other anions (halides, SO₄²⁻, isophthalate²⁻) give no framework. Formation is tolerant to the highly competitive solvent, and even to a huge excess of competing chloride anions. By varying the reaction conditions in one of several ways, we can prepare an alternative less-open framework, \( \text{ortho}-[2 \cdot (\text{TP})_2]_n \). Alternatively, \( \text{ortho}-[2 \cdot (\text{TP})_2]_n \) can be prepared by the single-crystal-to-single-crystal transformation of \( \text{tet}-[2 \cdot (\text{TP})_2]_n \) in response to an organic solvent, or to temperature. Both \( \text{tet} \) and \( \text{ortho}-[2 \cdot (\text{TP})_2]_n \) can be disassembled upon addition of an acid stimulus, and neutralisation of the acid results in re-assembly of the kinetic product, \( \text{tet}-[2 \cdot (\text{TP})_2]_n \) when starting from either phase of the framework.

We are now investigating whether more robust materials can be prepared using this anion-mediated approach with the aim of making these stable to solvent removal and thus suitable for gas/guest adsorption. We envisage that the ability to deliberately dis-assemble these frameworks and later re-assemble them will be attractive for guest storage and controlled release.

Experimental

General remarks

Tetra(4-cyanophenyl)methane was prepared from tetraphenylmethane as previously described. Additional synthetic details and characterisation data are provided in the ESI.†

Synthesis of 2-4Cl

Tetra(4-cyanophenyl)methane (0.500 g, 1.19 mmol) was dissolved in dry THF (10 mL). It was cooled to -78 °C under a nitrogen atmosphere, and LiHMDS solution (1.0 M in THF, 7.1 mL, 7.1 mmol) was added resulting in the immediate formation of a precipitate. The mixture was allowed to warm to room temperature and stirred overnight, during which time the precipitate dissolved to give a yellow-orange solution. This was cooled to 0 °C and ethanolic HCl (prepared by cautiously adding 2 mL of acetyl chloride to 10 mL ethanol) was added, which resulted in the formation of a pale precipitate. This was isolated by filtration, and then suspended in ethanol (10 mL) and sonicated for 1 hour. The solid was again isolated by filtration, washed thoroughly with ethanol (5 × 10 mL) and dried in vacuo to give 2-4ClI as a cream-coloured powder. Yield: 0.612 g (0.964 mmol, 81%).
1H NMR (D2O): 7.80 (d, J = 8.3 Hz, 8H), 7.66 (d, J = 8.3 Hz, 8H)) ppm. 13C NMR (D2O): 160.0, 150.8, 131.3, 127.8, 126.3, 65.5 ppm. HRESI-MS (pos.) 489.2530, calc. for [C29H42N8O10]⁺ (i.e. loss of 3H⁺ and 4Cl⁻) = 489.2521 Da. IR (inter alia) 1677 (C≡N stretch) cm⁻¹.

**Synthesis of tet-[2-(TP)]₂**

A solution of TBA₂·TP (0.103 g, 0.159 mmol) in water (20 mL) was added to a solution of 2·4Cl (0.050 g, 0.079 mmol) in water (20 mL). Within approximately one minute crystals began to grow, and crystallisation was complete within one hour (a video of this process is supplied as ESI†). The large, colourless needle-like crystals were isolated by filtration, washed with water, and air-dried to give tet-[2-(TP)]₂. Yield: 0.056 g (0.061 mmol, 77%).

1H NMR (d6-DMSO containing a drop of conc. DCl(aq)): δ 9.55 (s, 1H), 9.34 (br. s), 8.03 (s, 8H), 7.74 (d, J = 8.3 Hz, 8H) ppm. IR (inter alia) 1669 (C≡N stretch) cm⁻¹. M. Pt: decomposition begins ~225 °C. EA, found: C 61.0, H 6.5, N 12.6; calc. for [C29H42N8O10]: C 61.1, H 6.5, N 12.1 %.

The structure was determined by SCXRD, and PXRD used to confirm phase purity (see ESI†).

**Synthesis of ortho-[2-(TP)]₂**

A solution of TBA₂·TP (0.064 g, 0.099 mmol) in water : acetone (2:1 v/v, 5 mL) was added to a solution of 2·4Cl (0.030 g, 0.047 mmol) in water : acetone (2:1 v/v, 5 mL). Crystals developed overnight, which were isolated by filtration, washed with water, and air-dried to give ortho-[2-(TP)]₂. Yield: 0.031 g (0.033 mmol, 69%).

1H NMR (d6-DMSO containing a drop of conc. DCl(aq)): δ 9.53 (s, 1H), 9.27 (br. s), 8.04 (s, 8H), 7.57 (d, J = 8.3 Hz, 8H) ppm. IR (inter alia) 1680 (C≡N stretch), 1523 (C≡O stretch) cm⁻¹. M. Pt: 238 °C. EA, found: C 61.0, H 5.7, N 12.2; calc. for [2-(TP)]₂: 4H₂O (C₄H₂H₄N₈O₁₀): C 60.5, H 5.4, N 12.6 %.

The structure was determined by SCXRD, and PXRD used to confirm phase purity (see ESI†).

**Notes and references**

† MMol and % yield calculated accounting for 11 weight% water present after drying, as indicated by TGA.


For example, the pKa of unsubstituted benzamidinium is 11.6; A. Albert, R. Goldacre and J. Phillips, *J. Chem. Soc.*, 1948, 2240.


This strong binding has some precedent: Kusukawa has shown very strong interactions in DMSO between bis(amidine) receptors and dicarboxylic acids (Ka > 105 M⁻¹). These interactions involve proton transfer to form amidinium/carboxylate pairs (a) T. Kusukawa, S. Tanaka and K. Inoue, *Tetrahedron*, 2014, 70, 4049. Similarly, Guidi and colleagues have reported that the association constant between a porphyrin amidine and fullereNE carboxylic acid (again involving proton transfer) is ~107 M⁻¹ in 9 : 1 toluene : acetonitrile: (b) L. Sanchez, M. Sierra, N. Martin, A. J. Myles, T. J. Dale, J. Rebek, W. Seitz and D. M. Guidi, *Angew. Chem., Int. Ed.*, 2006, 45, 4637.


2-Cl, 2-Br and 2-NO₂ are all soluble in water, which would not be expected if they had an extended network structure. Similarly, their ³H NMR spectra in d₄-DMSO are sharply resolved, suggesting limited/no aggregation in this solvent (See Fig. S3, S8 and S97). Addition of two equivalents of TBA₂SO₄ or TBA₂isophthalate to 2·4Cl in the same manner used to prepare 2·(TP)₂ gave no precipitate even after several weeks.
23 For a similar crystal growth mechanism in a MOF, see M. Jian, B. Liu, R. Liu, J. Qu, H. Wang and X. Zhang, RSC Adv., 2015, 5, 48433.

24 It is perhaps surprising that the orthorhombic form, which contains disordered and less linear hydrogen bonds is more stable than the tetragonal form containing linear hydrogen bonds. However, the orthorhombic form is considerably more dense, so is presumably preferred as it minimises void space. This conclusion is supported by the far greater stability of the orthorhombic phase, particularly to solvent removal.

25 While the start and end points of this transformation are single crystals, we do not rule out the possibility that this process goes via an intermediate amorphous phase (see for example: T. D. Bennett, A. K. Cheetham, Acc. Chem. Res., 2014, 47, 1555).