Crystal engineering with urea and thiourea hydrogen-bonding groups

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The utilization of *N*,*N*′-disubstituted ureas and thioureas as design elements in the synthesis of crystalline organic solids is reviewed. These hydrogen-bonding units are versatile yet predictable building blocks that can be rationally employed in both crystal assembly and functionalization.

Introduction

Crystal engineering[1] has as a main objective the understanding of intermolecular interactions and packing principles in molecular crystals, and the use of the knowledge thus generated for the deliberate design of novel materials with targeted structures and properties. Towards this end goal, one can employ a multitude of noncovalent interactions to assemble molecular crystals, among which hydrogen bonds occupy a prominent position due to their pronounced directionality and relatively high strength.[2] Compared to covalent bonds though, hydrogen bonds are typically much weaker, and therefore less predictable, which often undermines the process of crystal design using these interactions. While in molecular synthesis one can often plan with confidence synthetic schemes for very complex molecules, in the synthesis of crystalline organic solids one can rarely invoke the term *engineering* in its true sense. More often, the crystal 'design' process involves empirical observations and *a posteriori* crystal structure analyses, which in ideal situations may lead to somewhat predictable synthetic protocols that typically apply to a limited number of crystals within a homologous series.[3] For this reason, the crystal engineering discipline remains for the moment more an exploratory endeavor rather than an exact science. Furthermore, success in this area is generally dependent on the ability to grow single crystals, which is often described as more of an art than a science. Despite these inherent difficulties the field offers a cornucopia of research opportunities, both experimental and theoretical, that can address the basic understanding of structures, energetics, and growth of molecular crystals, and lead to formulation of structure-properties relationships in crystalline solids. Such studies have the potential to identify robust supramolecular motifs (synthons)[4] and building blocks (tectons),[5] which may eventually be employed in *bona fide* engineering of novel crystalline materials.

One such robust building block that forms persistent hydrogen-bonded chains in a variety of environments, from solutions,[6] to gels and fibers,[7] as well as crystals,[8] is the urea group. Symmetrical or asymmetrical *N*,*N*′-disubstitution of urea can provide a wide variety of building blocks for the construction of crystalline organic solids, a strategy that has been extensively explored since the early crystallographic studies of disubstituted ureas in the late 1960s. *N*,*N*′-Disubstituted ureas can act as both hydrogen-bond donors through their two NH protons, and acceptors through the lone pairs of the C=O group. The good complementarity between the two groups results in self-association into robust one-dimensional hydrogen-bonded chains (Fig. 1), which have been explored repeatedly for the construction of crystalline networks, and, more recently, nanostructured materials based on tubular or columnar architectures. In comparison to ureas, thioureas have been far less explored for the rational assembly of crystalline solids,[9] despite the fact that they can also form relatively robust hydrogen-bonding motifs.[10] Along a different line, both ureas and thioureas have long been exploited as anion binding groups in synthetic receptors, by taking advantage of their ability to form strong hydrogen bonds to a wide variety of anions (Fig. 1).[11] This inspired us to use *N*,*N*′-disubstituted ureas and thioureas as functional groups in crystalline frameworks for anion binding and separation.[12] The utilization of ureas and thiourea for functionalization of crystalline frameworks rather than their assembly is an intriguing possibility requiring different design strategies that

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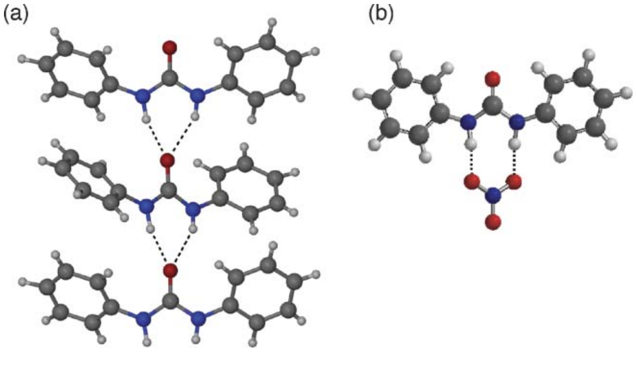


Fig. 1 The duality of *N*,*N*′-disubstituted ureas, which can function as either: (a) building units for the assembly of hydrogen-bonded chains, as illustrated by the crystal structure of diphenylurea[13] or (b) anion-binding groups, as exemplified by the calculated complex of diphenylurea with nitrate, optimized with DFT at the B3LYP/6-31G* level.[42]

prevent these groups from self-association into the typical hydrogen-bonded chains, so they remain available for guest binding.

This review is organized around two major themes corresponding to the utilization of *N*,*N*′-disubstituted ureas and thioureas as either basic building blocks for the assembly of hydrogen-bonded networks and nanostructures, or as functional groups for guest binding in crystalline frameworks. The scope of this paper is limited to *N*,*N*′-disubstituted ureas and thioureas, which from now on may be simply referred to as ureas and thioureas. The unsubstituted homologues with their rich and fascinating inclusion chemistry are not included here, and the interested reader is referred to other reviews that cover them in detail.[8,14]

Ureas as building blocks for the assembly of crystalline frameworks

Since the early crystallographic characterizations of symmetrically disubstituted ureas[15] it was found that these groups tend to form one-dimensional hydrogen-bonded chains by employing their two NH proton donors and the C=O proton acceptor in bifurcated hydrogen bonds. This hydrogen-bonded motif was described later by Etter using graph set notations as C(4)[$R_2^1(6)$], where C(4) denotes a chain motif with 4 atoms in the repeat unit, and [$R_2^1(6)$] denotes a hydrogen-bonded ring motif consisting of 6 atoms, with 2 donors and 1 acceptor.[16] Etter noted that "the NH hydrogens prefer to adopt an *anti* relationship to the carbonyl group and to form three-center bonds to urea carbonyl groups". The resulting one-dimensional chains are persistent in many crystals, although they may be disrupted by the presence of strong hydrogen-bond acceptors. Adjacent urea groups in the chain prefer to be coplanar, with the NH protons approaching the carbonyl group in the plane defined by the oxygen lone pairs, except for the cases where bulky substituents prohibit the formation of short NH···O=C interactions, which determine the urea planes to twist relative to each other.

The urea hydrogen-bonded chains were ingeniously exploited by Lauher and Fowler in the design of two-dimensional layered networks. By using self-complementary carboxylic acid and urea groups, they synthesized a series of crystals connected orthogonally by hydrogen-bonded urea chains and carboxylic acid dimers (Fig. 2(a)).[17] Similarly, disubstitution of ureas with amide groups resulted in hydrogen-bonded networks consisting of orthogonal urea···urea and amide···amide hydrogen bonds. In this case, both the cyclic dimer and the one-dimensional catamer hydrogen bond motifs were observed for the amide groups (Fig. 2(b) and (c)).[18]

Hollingsworth *et al.* took a similar approach for the synthesis of layered hydrogen-bonded crystals. Fig. 2(d) depicts their reported structure of the *N*,*N*′-bis(5-cyanopentyl)-urea/urea cocrystal, which displays alternative hydrogen-bonded chains of substituted and unsubstituted ureas linked into layers by –NH···NC– hydrogen bonds.[19]

Taking advantage of the propensity of ureas to form hydrogen-bonded chains with urea···urea intermolecular spacing of about 4.6 Å, Lauher and Fowler used this motif to organize 1,3-diacetylenes for solid-state topochemical polymerization.[20] Thus, by co-crystallizing a urea–dicarboxylic

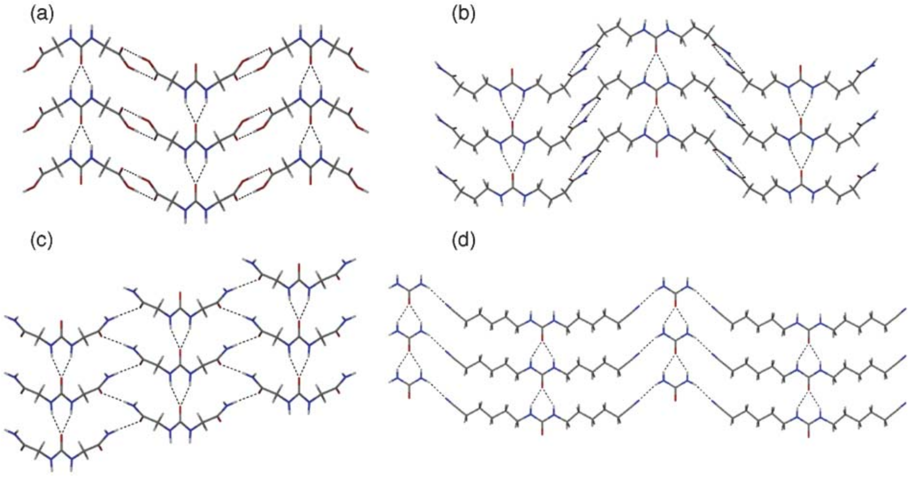


Fig. 2 Layered networks assembled from urea hydrogen-bonded chains by orthogonal hydrogen bonding of: (a) dicarboxylic acid dimers, (b) amide dimers, (c) amide catamers, (d) ureas to –CN groups.

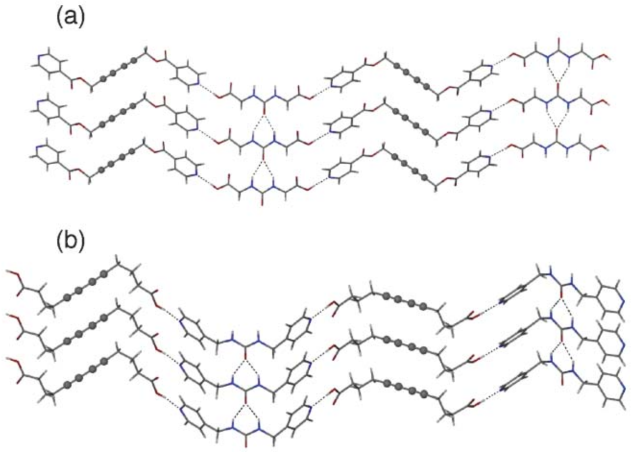


Fig. 3 Organization of 1,3-diacetylenes for solid-state polymerization by urea hydrogen-bonded chains.

acid derivative with a diacetylene functionalized with complementary pyridine groups, they obtained the anticipated layered network consisting of urea chains orthogonally connected by COOH···pyridine hydrogen bonds (Fig. 3). The diacetylene groups were thus aligned in stacks with a spacing of 4.71 Å and a tilt angle of 56.3°, which were within the necessary range for solid-state polymerization. Similarly, the 'inverted' cocrystal made of the corresponding bis-pyridine urea and diacetylene dicarboxylic acid derivative formed analogous hydrogen-bonded layers with the diacetylene functionalities aligned for solid-state polymerization (4.63 Å spacing, 61.0° tilt). Both cocrystals proved to be reactive in the solid state and could be readily polymerized, unlike crystals of the corresponding pure diacetylenes, which were inert.

The asymmetric ureas **1** and **2** were also found to self-assemble into one-dimensional chains *via* urea···urea hydrogen bonds.[21] The chains are further linked into layers by weaker I···O_2N– and CH···O_2N– interactions (Fig. 4). The two isostructural solids crystallized in the polar *Fdd*2 space group, and **1** showed nonlinear optical properties with a measured second harmonic generation signal that was 13 times stronger than that of simple urea.

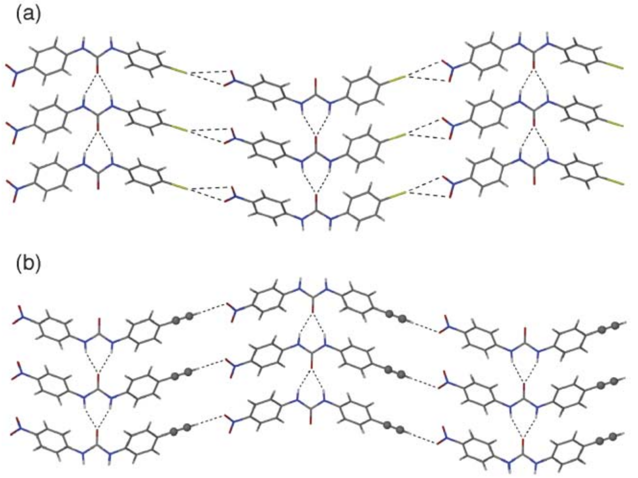


Fig. 4 Assembly of layered networks through urea···urea hydrogen bonding and I···O_2N– (a) and CH···O_2N– (b) interactions.

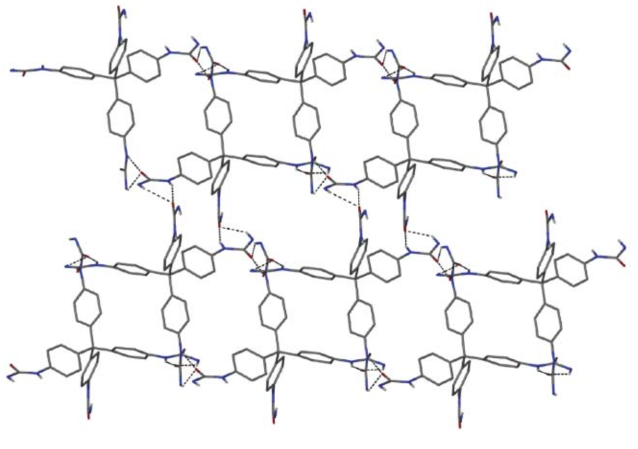
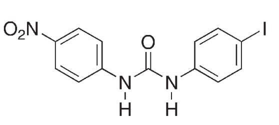


Fig. 5 Chiral three-dimensional framework assembled through urea···urea hydrogen bonds. The disordered *sec*-butyl substituents on ureas are not shown for clarity.



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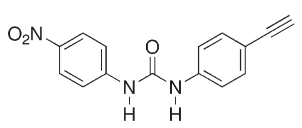

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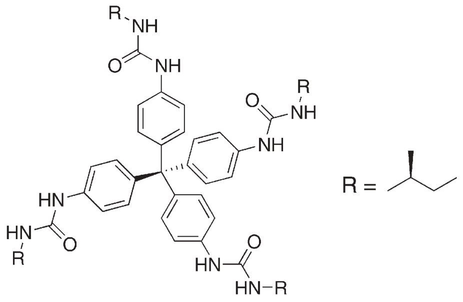
A three-dimensional framework assembled through urea···urea hydrogen-bonds was reported by Wuest and co-workers.[22] The tetrakis-urea tecton **3** substituted with chiral *sec*-butyl groups formed a tetragonal porous crystal (Fig. 5) that included two equivalents of the HCOOH solvent of crystallization. Such chiral porous hydrogen-bonded frameworks are of special interest due to their potential use in enantioselective separations and catalysis.



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Thioureas as building blocks for the assembly of crystalline frameworks

In contrast to ureas, thioureas have been far less explored as design elements in crystal engineering. Although the thiocarbonyl group is a weaker hydrogen-bond acceptor than the carbonyl one, this is compensated by the stronger acidity of the –NH donors in thioureas.[23] In fact, a comparative study of analogous urea and thiourea derivatives found the latter to have a larger dimerization constant in solution.[11d] One would therefore expect thioureas to be reliable supramolecular building blocks, comparable to urea analogs. However, upon close examination, thioureas show significant differences from ureas with respect to conformational behavior and hydrogen-bonding preference. Lauher and Fowler noted in their early study that although thioureas form hydrogen-bonded chains similar to those formed by analogous ureas, the thiourea groups are almost orthogonal to each other due to the sidewise approach of the NH donors to the thiocarbonyl acceptor.[17] As a result thiourea chains display a zigzag shape compared to the relatively straight chains formed by ureas. This was supported by our recent Cambridge Structural Database (CSD 5.28, November 06) survey of *N*,*N*′-dialkylureas and thioureas, which found mean angles between the C=X (X = O, S) vectors of 161(23) and 123(21)°, respectively.[24] In order to understand this difference, we examined theoretically the electrostatic potential surfaces of *N*,*N*′-dimethylurea and its thiourea analog, using DFT at the B3LYP/6-31G* level.[24] As depicted in Fig. 6, the most negative potential in urea is found around the axial position of the C=O bond, whereas in the thiourea analog the highest electron density is found on an equatorial torus around the S atom. As a result, ureas tend to hydrogen-bond into straight chains, with the urea groups approaching each other along their C=O vectors.[25] In contrast, thioureas approach each other obliquely in order to optimize the electrostatic interactions between the NH protons and the negative torus of the S atom.

Another significant difference between the two analogous classes of compounds is that while ureas are present predominantly in the *trans–trans* conformation[6] (defined based on the HNCS dihedral angle), thioureas typically exist in solution as mixtures of *trans–trans* and *trans–cis* rotamers.[26] The conformational flexibility of *N*,*N*′-dialkylthioureas was also confirmed by theoretical calculations in the gas phase, which found the two rotamers to be close in energy (typically within 1 kcal mol^{-1}), with the *trans–cis* isomer being slightly preferred.[9a,27] As a result, in addition to the zigzag chains formed by the *trans–trans* conformer, thioureas can also self-associate into dimers in the solid state, *via* two complementary NH···S hydrogen bonds formed between two thioureas in *trans–cis* conformation [$R_2^2(8)$ graph set] (Scheme 1). A CSD survey (November 03) found the dimer motif to be only slightly more preferred than the chain motif,[28] in accord with the observed conformational flexibility of thioureas in solution and the gas phase.[9a] This chain/dimer duality was also observed in a series of *meta*-substituted aromatic bis(thiourea) derivatives recently reported by Doxsee and co-workers.[9b]

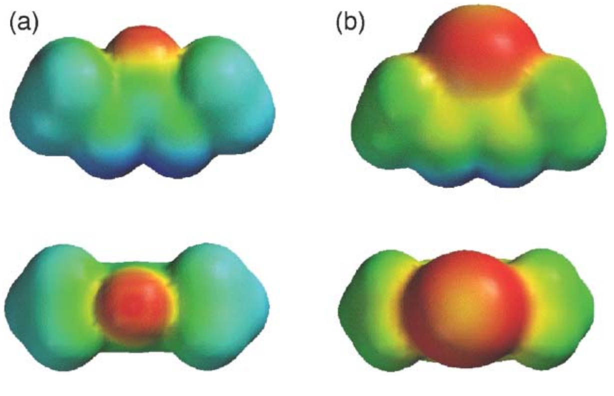
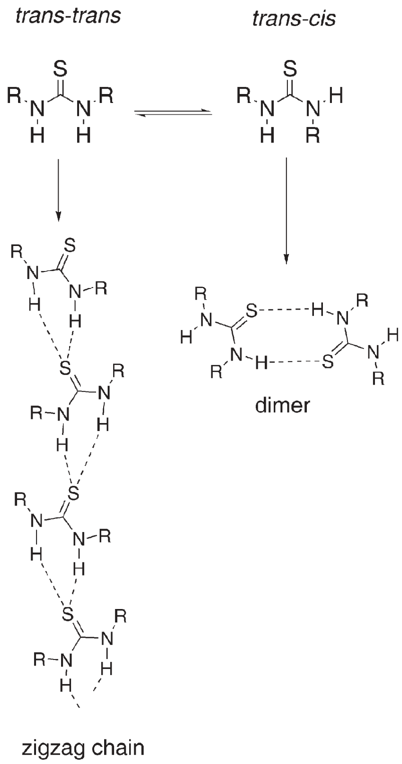


Fig. 6 Electrostatic potential maps for *N*,*N*′-dimethyl-urea (a) and -thiourea (b) calculated with DFT at the B3LYP/6-31G* level.[24] Red = negative potential, blue = positive potential.



Scheme 1 Hydrogen-bonding motifs typically observed for disubstituted thioureas in the solid state.

We recently demonstrated that the formation of one motif over the other in crystalline *N*,*N*′-dialkylthioureas can be controlled by the bulkiness of the two alkyl substituents.[9a] Fig. 7 depicts the hydrogen-bonded dimers observed in crystal structures of symmetrical diethyl-, diisopropyl-, dicyclohexyl- and dibenzyl-thioureas. Despite the significant variation in the organic substituents, all dimers form similar layered networks by further hydrogen bonding between the S atoms and the *trans* H atoms. In direct contrast, bis(*tert*-butyl)thiourea adopts the *trans–trans* conformation in the solid state and thereby self-associates into hydrogen-bonded chains (Fig. 8), despite the fact that the *trans–cis* conformation is more stable in the gas phase. Molecular modeling indicated that the *trans* NH hydrogen in the *trans–cis* rotamer of this thiourea is inaccessible for hydrogen bonding, which apparently tipped the balance towards the less stable *trans–trans* rotamer and its corresponding chain motif.

In order to fine-tune the steric bulkiness around the NH group, we synthesized the asymmetrical thioureas **4–6**, where the *t*-Bu substituent was kept constant, but the second substituent was varied from Me, to allyl, and benzyl. While DFT calculations indicated that for all three thioureas the *trans–cis* rotamer should be slightly preferred, single-crystal X-ray studies showed that only **4** formed the dimer motif, while **5** and **6** were present in the *trans–trans* conformation and

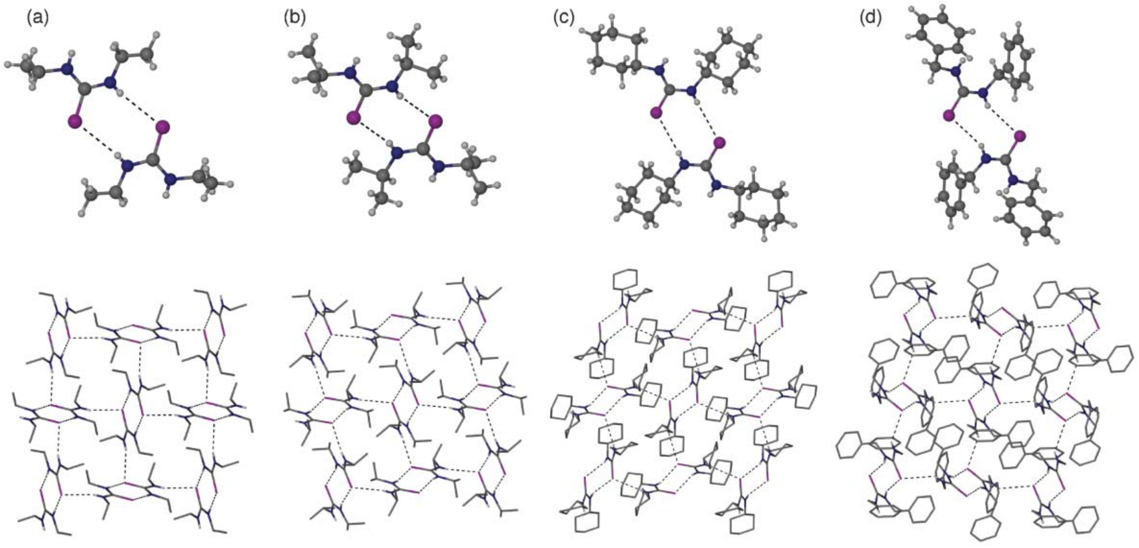
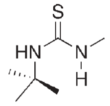


Fig. 7 Hydrogen-bonding in crystals of diethyl- (a), diisopropyl- (b), dicyclohexyl- (c) and dibenzyl-thiourea (d), showing thiourea dimers (top) further linked into layers (bottom).

consequently formed the chain motif (Fig. 9). Close examination of the space-filling models showed that the Me group in **4** is not sufficiently bulky to completely hinder the trans NH hydrogen, unlike the larger allyl and benzyl groups, which completely blocked the access to the S acceptor in **5** and **6**.[9a]



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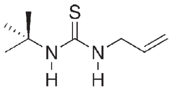

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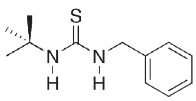

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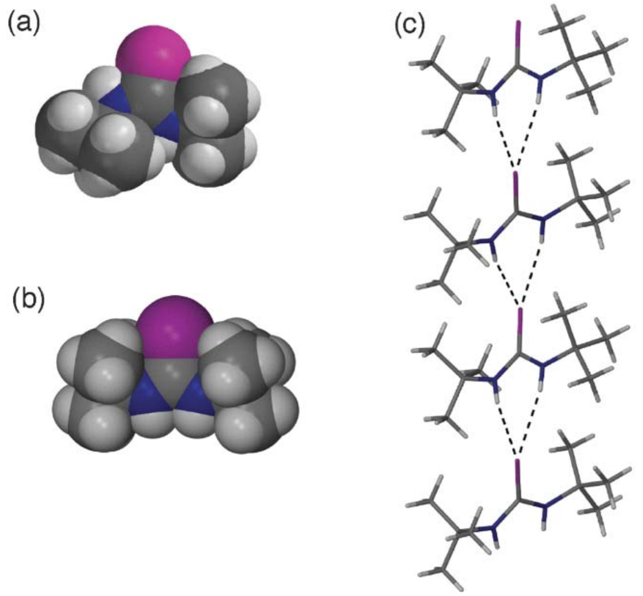
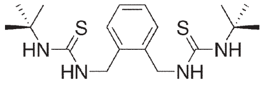


Fig. 8 Molecular and crystal structure of bis(*tert*-butyl)thiourea. (a) Molecular model of the lower energy *trans–cis* isomer, showing the steric hindrance of the *trans* NH. (b) Observed *trans–trans* rotamer in the crystal. (c) Hydrogen-bonded chain in the crystal.

This study thus demonstrated that by fine-tuning the bulkiness of the organic substituents on thiourea one can predictably switch between the dimer and the chain motifs. This unequivocal example of steric control over hydrogen bonding in the solid state opens new ways to manipulate crystal structures, by allowing one to significantly increase the incidence of particular synthons that otherwise may be improbable. An immediate practical consequence of this basic concept was the design of more elaborate architectures from thioureas **7–9**, where the hydrogen-bonded chains were connected into ribbons or layers by organic linkers (Fig. 10).



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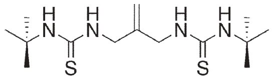

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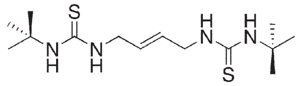

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A different way to control the conformation of thioureas and thus their solid-state structures was demonstrated by Palmore and co-workers. By employing cyclic thiourea derivatives they locked the conformation of the thiourea group into the *cis–cis* form, which otherwise is significantly higher in energy than the *trans–cis* or *trans–trans* isomers.[29] As a result, one-dimensional tapes could be assembled in the solid state (Fig. 11), which may be considered extended analogs of the dimers.[30]

Assembly of crystalline nanostructures from ureas and thioureas

The predictable self-association of ureas into one-dimensional chains has been exploited for the assembly of nanotubular materials by employing the macrocyclic urea derivatives **10–13**.

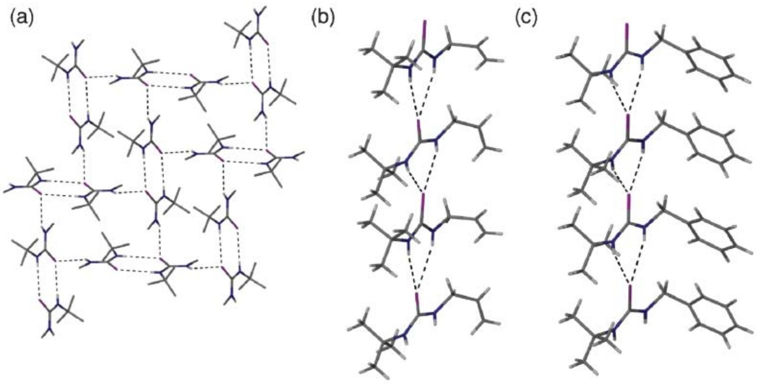


Fig. 9 Crystal structures of **4–6** showing hydrogen-bonded layers of dimers in **4** (a) and hydrogen-bonded chains in **5** (b) and **6** (c).

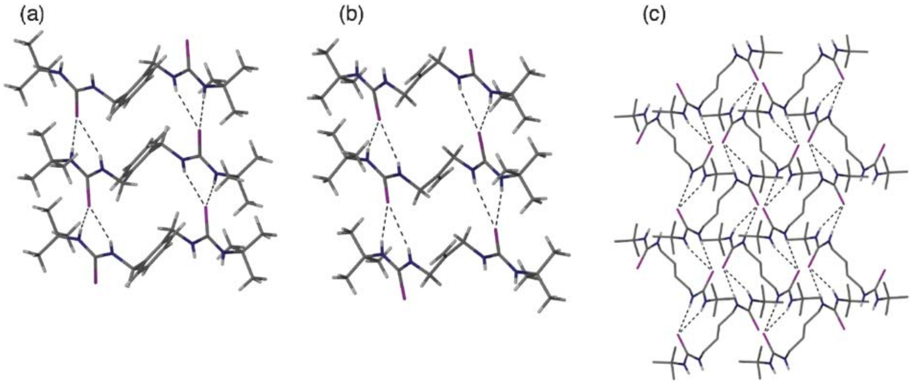
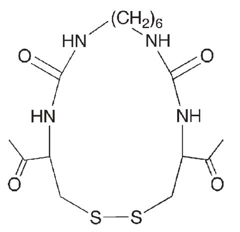


Fig. 10 Crystal structures of **7–9** showing hydrogen bonded-ribbons in **7** (a) and **8** (b), and layers in **9** (c).



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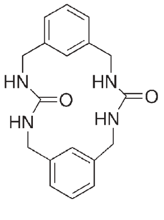

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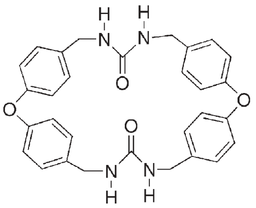

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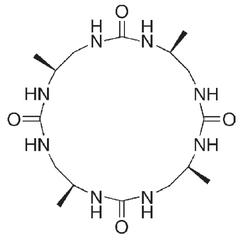

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The first example demonstrating this approach involved the cystine-based cyclic bis-urea **10**, which self-assembled in the crystalline state into extended nanotubes containing antiparallel urea hydrogen-bonded chains (Fig. 12(a)).[31] A similar nanotube was synthesized from the macrocyclic bis-urea **11**, although the internal diameter of the tube was too small to include any guest (Fig. 12(b)).[32] The larger macrocyclic analogue **12** formed similar crystalline hydrogen-bonded nanotubes (Fig. 12(c)) that showed zeolitic properties such as reversible guest inclusion and stereoselective photodimerization of enones. For example, these nanotubes can reversibly include acetic acid guest molecules with retention of the overall structure and crystallinity, and are thermally stable up to 180 °C.[33] These remarkable properties can be attributed to the strong and directional urea hydrogen-bonded chains, which align and hold the macrocycles for nanotube formation and stability. The same nanotubular material was recently employed as a host for the stereoselective photodimerization of 2-cyclohexenone.[34] The head-to-tail dimer was almost exclusively obtained, in direct contrast to photodimerizations of the same enone in other confined media such as zeolites, which typically yield the head-to-head dimer.

Chiral square-shaped nanotubes filled with disordered water molecules are formed by the cyclotetraurea **13** substituted with enantiopure alanine residues.[35] The chirality of the alanine aminoacid is transferred to the nanotube, which is highly polar with all urea groups aligned in the same direction (Fig. 12(d)).

A different approach towards tubular nanostructures sustained by urea hydrogen-bonded chains was demonstrated by Barboiu *et al.* Urea-functionalized crown ether **14** stacks into extended tubes in the crystalline state, held together by urea···urea hydrogen bonding and π-stacking interactions (Fig. 13).[36] Similar tubular nanostructures assembled from the analogous ureido–crown ether **15** derivatized with –$Si(OEt)_3$ groups were incorporated into organic–inorganic hybrid membranes *via* sol–gel chemistry, and these membranes were

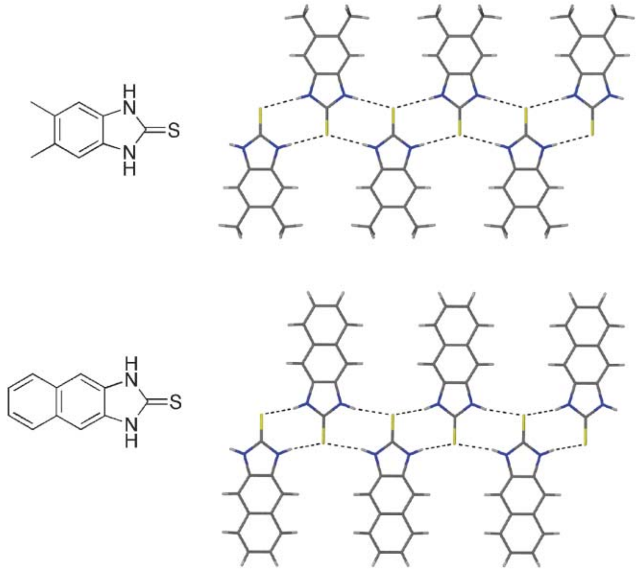
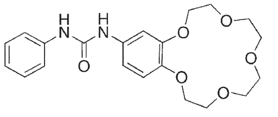


Fig. 11 Hydrogen-bonded tapes in crystals of cyclic thioureas.

demonstrated to function as ion-driven ATP pumps.[37] The ureido–benzo-18-crown-6 macrocycle **16**, on the other hand, was found to display a different tubular nanostructure in the solid state, with the crown rings alternating about the urea hydrogen-bonded chains (Fig. 13).[38] These columnar structures showed ion-channel behavior when assembled in lipid bilayer membranes.



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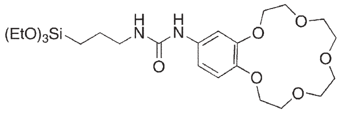

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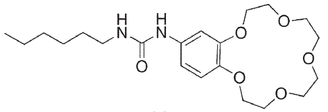

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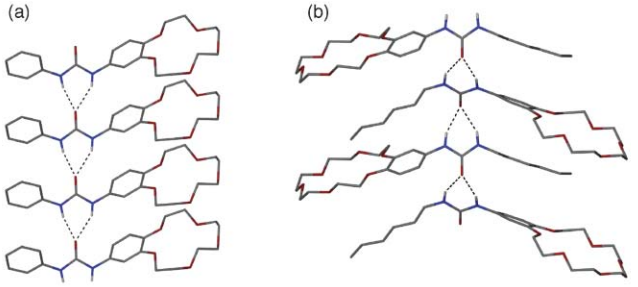
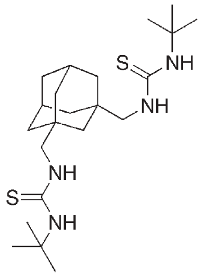


Fig. 13 Hydrogen-bonded tubular structures self-assembled from **14** (a) and **16** (b).

Recent work in our group led to the discovery that the bis-thiourea **17** self-assembles into nanosized columnar aggregates of thiourea octamers in the solid state (Fig. 14).[24] While substitution with *t*-Bu end groups ensured that the thiourea groups adopted the *trans–trans* conformation required for association into hydrogen-bonded chains, the single-crystal X-ray structural determination revealed that instead of the typical open-ended zigzag chains, the thiourea groups in **17** self-assembled into centrosymmetric cyclic octamers. The octamers consist of four thiourea groups from two molecules of **17** positioned transversally across the octamers, and four additional thiourea groups from four different molecules, which covalently bridge the octamers into one-dimensional columnar aggregates. The columns are filled with adamantane linkers and *t*-Bu groups, and have an external diameter of about 2 nm. We rationalized the formation of this unique columnar architecture based on the softness of the thiourea···thiourea hydrogen bonds and conformational flexibility of the linker, coupled with the optimal shape and



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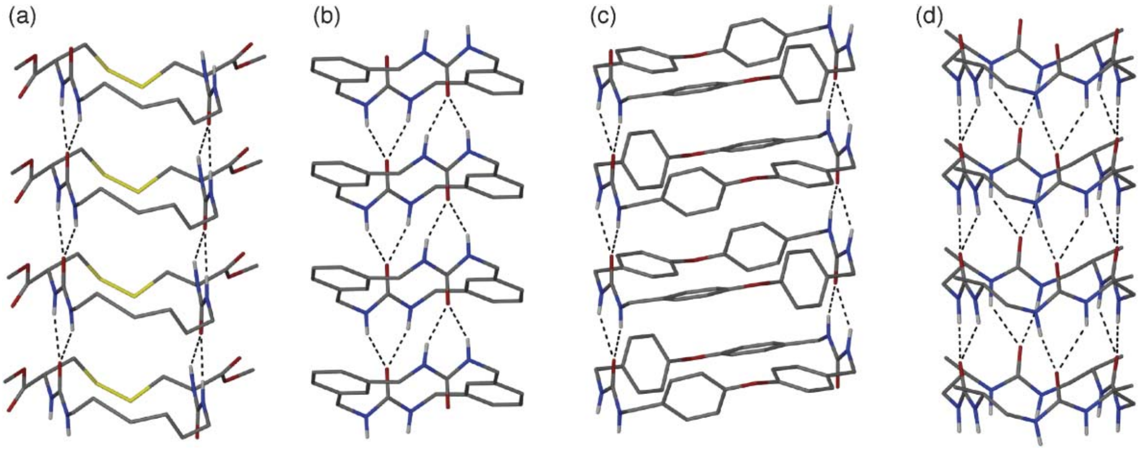


Fig. 12 Hydrogen-bonded nanotubes self-assembled from urea macrocycles.

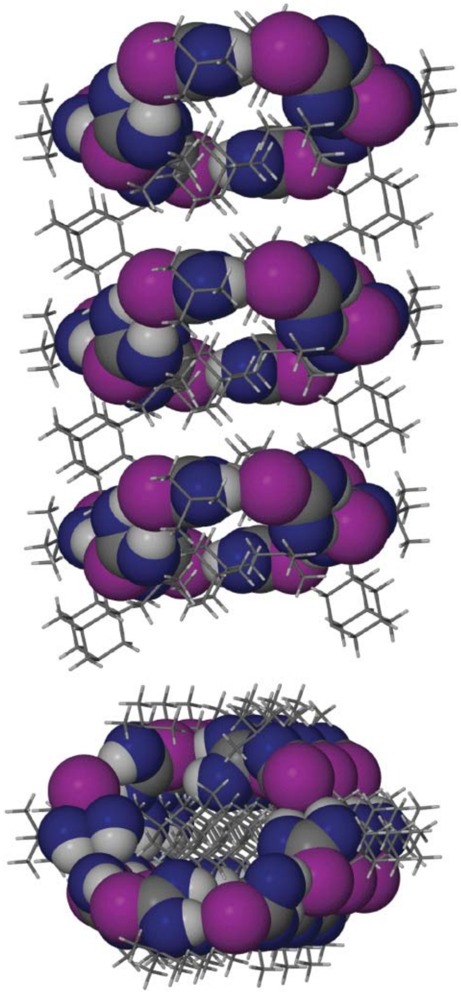
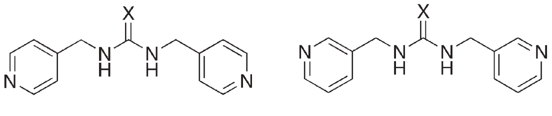


Fig. 14 Hydrogen-bonded nanocolumn assembled from bis-thiourea **17**.

volume of the adamantane and *t*-Bu groups that filled the internal volume of the columns efficiently.

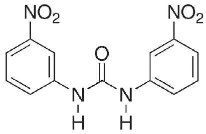
Ureas and thioureas as anion-binding groups in crystalline frameworks

As described in the previous sections, ureas and thioureas are reliable building blocks for the assembly of crystalline materials due to their persistent formation of hydrogen-bonded chains. On the other hand, the same groups have long been known to bind various anions in solution *via* hydrogen bonding by their two NH donors.[11] Ureas and thioureas are particularly complementary to oxoanions, as they can form chelate hydrogen bonding to their O–X–O edge. This led to the question whether ureas and thioureas could be utilized as functional groups for anion binding and recognition in crystalline frameworks. However, this would require the disruption of the hydrogen-bonded chains, which at first appeared a daunting task, considering the prevalence of this motif in the solid state. Indeed, bis(pyridyl)ureas **18** and **20**, and their thiourea analogs **19** and **21** showed inconsistent anion complexation when incorporated in coordination polymers due to the competing self-association and solvent binding processes.[39,40]



X = O (**18**), S (**19**)   X = O (**20**), S (**21**)

In our quest to design improved ureas and thioureas with stronger hydrogen-bond donor abilities and lower self-association tendencies for more predictable anion binding and recognition in the solid state we found inspiration in the seminal study of Etter, who in the late 1980s demostrated that diaryl urea substituted with electron-withdrawing groups have a decreased tendency to self-associate into hydrogen-bonded chains.[41] The most dramatic example is *N*,*N'*-bis(*m*-nitrophenyl)urea (**22**), which showed an unusual ability to bind various molecules containing hydrogen-bond acceptors such as ethers, ketones, DMSO and triphenylphosphine oxide.



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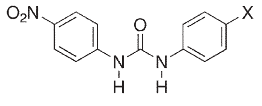
The bis(*p*-nitrophenyl)urea isomer and the mononitrated 1-(*m*-nitrophenyl)-3-phenylurea showed a similar, although weaker tendency, as only the stronger hydrogen bond acceptors such as DMSO or triphenylphosphine oxide could be co-crystalized with these compounds. Etter attributed these findings to the formation of intramolecular CH···O hydrogen bonds between the *ortho* H atoms and the carbonyl group, promoted by the increased acidity of these hydrogens due to the proximal electron-withdrawing NO_2 substituents. As a result, the C=O group is less available to accept hydrogen bonds from urea NH donors, thus disrupting the formation of the chain motif. This hypothesis was supported by the observed planar conformation of **22**, adopted to optimize the intramolecular CH···O hydrogen bonds, compared to the much larger dihedral angles between urea and Ph groups typically found in diarylureas. This observation is consistent with our high-level quantum chemical calculations (MP2/aug-cc-pVDZ) on monoarylurea models that showed the NO_2 substitution increases the rotation barrier around the N-aryl bond from 2.4 kcal mol^{-1} in phenylurea to 3.2 kcal mol^{-1} in *m*-nitrophenylurea.[42]

Nangia and co-workers reached a similar conclusion from their study of asymmetrical diarylureas **23–27**, which were found not to form the hydrogen-bonded chain motif, but instead to bind the solvent of crystallization or the NO_2 substituent.[21] Another structural study by Abad *et al.* on a series of fluorinated *N*-(2-chloropyridin-4-yl)-*N'*-phenylureas (**28**) also found the absence of the chain motif in this series of compounds, apparently caused by the formation of intramolecular CH···O hydrogen bonds, which decreased the ability of the carbonyl group to engage in intermolecular hydrogen bonding to the NH groups.[43] As an alternative, the pyridine substituents interacted with ureas, despite

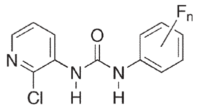
Table 1 Hydrogen bonding parameters and binding energies for nitrate complexation by various R–NH–C(=O)–NH–R ureas, calculated with DFT at the B3LYP/6-31G* level[42]

R	$d(\mathrm{H\cdots O})/\text{Å}$	$\Delta E/\mathrm{kcal\ mol^{-1}}$
Me	1.888	−30.8
Ph	1.817	−43.4
m-NO_2Ph (**22**)	1.779	−56.6
m-pyridyl (**29**)	1.801	−49.8
m-CNPh (**30**)	1.781	−55.7

their weaker hydrogen-bond accepting abilities compared to the carbonyl group.



X = F (**23**), Cl (**24**), Br (**25**), NMe$_2$ (**26**), Ac (**27**)



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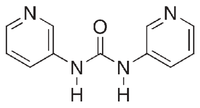
The *N*,*N*′-bis(*m*-pyridyl)urea (**29**) studied independently by Nangia's group[44] and us[42] showed a similar behavior, suggesting that pyridine rings have sufficient electron-withdrawing capabilities to promote intramolecular CH⋯O hydrogen bond formation and thus suppress the formation of the chain motif. This inspired us to employ this urea derivative, as well as the *N*,*N*′-bis(*m*-cyanophenyl)urea **30** in the synthesis of functional metal-organic frameworks (MOFs), *via* metal coordination by the pyridine or CN groups, with the urea groups acting as binding and recognition elements for anions.[42]



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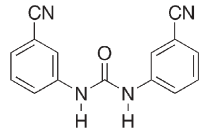

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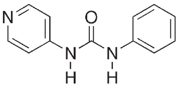
The strong affinities of these ureas to oxoanions was confirmed by our theoretical calculations of nitrate complexation, which found binding energies significantly larger than those of the *N*,*N*′-dimethyl or -diphenyl analogs, and comparable with that of **22** (Table 1).[42]

There was also experimental precedent for anion binding by coordination complexes of the mono(*m*-pyridyl)ureas **31** and **32** reported by the groups of Barboiu[45] and Steed,[46] respectively, or of the quinoline-urea **33** reported by Bondy, Gale and Loeb (Fig. 15).[47]

Steed and co-workers also reported nitrate binding in the solid state by a silver macrocycle obtained from ligand **34** containing the (*m*-pyridyl)urea group,[7d] and coordination of the same anion by a one-dimensional coordination polymer synthesized from ligand **35**.[48]

Our structural study of the MOFs obtained from **29** and **30** by coordination of various Zn, Cu and Ag transition metal salts confirmed that these urea-functionalized ligands are versatile anion binders in the solid state, forming chelate hydrogen bonds to various oxoanions with a wide range of basicities, such as SO_4^{2-}, NO_3^-, $CH_3SO_3^-$, $CF_3SO_3^-$ and ClO_4^- (Fig. 16).[42] In a parallel study, Das and Dastidar reported similar anion binding in MOFs made from **29**.[49] The observations of anion binding by the urea groups in these MOFs were generally correlated with the absence of urea hydrogen-bonded chains and the presence of intramolecular CH⋯O hydrogen bonding.

In contrast to anion binding by ureas, there is a limited number of analogous studies involving thioureas as anion binding groups in coordination frameworks. Ligands **19** and **21** have been employed in the synthesis of coordination polymers, but their flexible conformation and tendency to self-associate limits their utility as anion binders.[40] More structural and theoretical studies addressing the conformational and hydrogen-bonding preferences of thioureas are needed before



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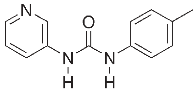

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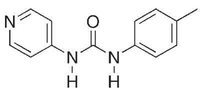

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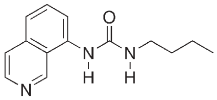

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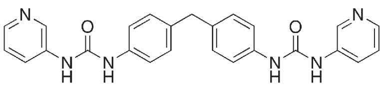

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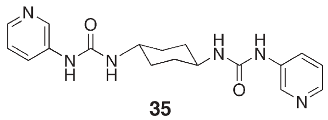

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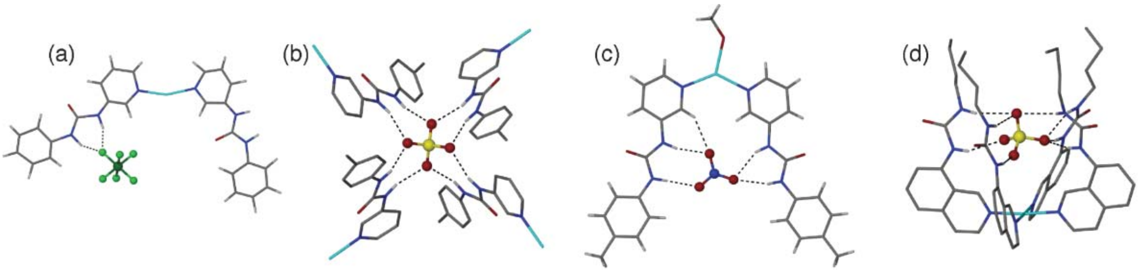


Fig. 15 Anion binding by metal–organic complexes of ligands **31–33**: (a) PF_6^- binding by **31**, (b) SO_4^{2-} binding by **32a**, (c) NO_3^- binding by **32a**, (d) SO_4^{2-} binding by **33**.

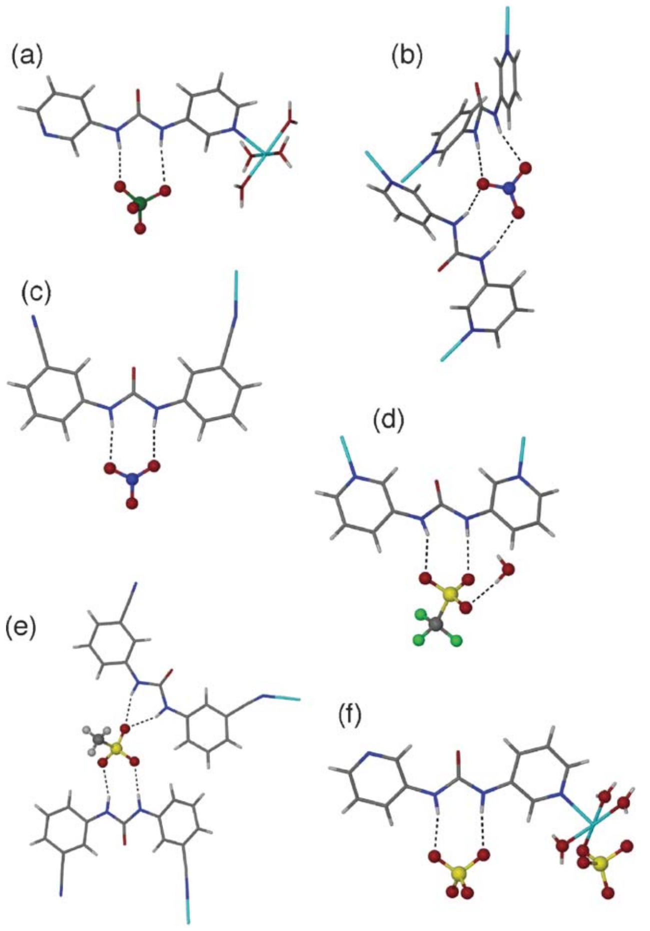


Fig. 16 Oxoanion binding in MOFs functionalized with urea groups: (a) perchlorate binding by **29**, (b) nitrate binding by **29**, (c) nitrate binding by **30**, (d) triflate binding by **29**, (e) methanesulfonate binding by **30**, (f) sulfate binding by **29**.

these groups can be predictably employed as anion recognition elements in crystalline frameworks.

Anion separation by urea-functionalized metal–organic frameworks

Encouraged by the consistent anion binding by **29** and **30** within coordination frameworks, we have recently begun exploring the possibility of anion separation by competitive crystallization of MOFs[12] containing these ligands. We focused initially on the simple mono-urea ligand **29** to probe the intrinsic anion selectivity of the urea group in crystalline solids, with the intention to subsequently move toward more complex poly-urea ligands with shape complementarity for oxoanions. Addition of one equivalent of **29** in EtOH to an aqueous solution containing one equivalent of $Zn(NO_3)_2$ and one equivalent of each NaCl, NaBr, NaI, $NaClO_4$ and Na_2SO_4 resulted in selective crystallization of the halides as solid solutions with the composition $Zn(\mathbf{29})Cl_xBr_yI_z$ ($x + y + z = 2$), and total exclusion of the oxoanions.[50] Single-crystal and powder X-ray studies indicated that all zinc halides formed one-dimensional coordination chains with **29**, with the chains further linked into layers by urea···X and urea···urea (for X = Br^- and I^-) hydrogen bonds (Fig. 17). The initially precipitated solid solution from the competition experiment was found to have predominantly the $Zn(\mathbf{29})Cl_2$ structure, which contained mostly Cl^-, and smaller amounts of Br^- and I^-. This selectivity could be rationalized based on the stronger interaction of the more basic chloride with the urea and Zn^{2+} acidic centers. However, this metastable phase converted in time into the more dense, thermodynamically preferred $Zn(\mathbf{29})Br_2$ phase (also as a solid solution), in which the Br^- was found to predominate. As depicted in Fig. 17(b), this structure contains two different halide sites, with only one of them hydrogen-bonded by urea, which explains the lower discrimination among halides observed in this phase.

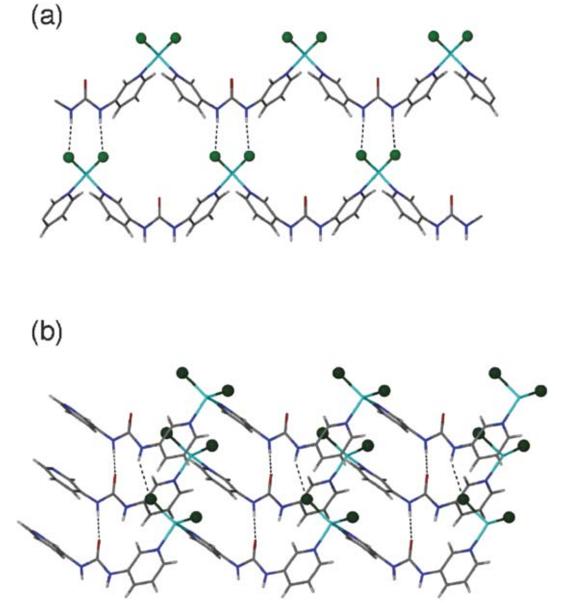
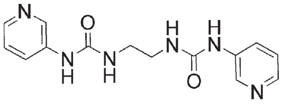


Fig. 17 Halide binding in Zn coordination polymers containing ligand **29**: (a) Crystal structure of $[Zn(\mathbf{29})Cl_2]$ coordination polymer, (b) Crystal structure of $[Zn(\mathbf{29})Br_2]$ (isostructural to $[Zn(\mathbf{29})I_2]$) coordination polymer.

Looking to improve oxoanion selectivity in MOFs, we turned our attention to the more elaborate poly(urea) ligands **36** and **37**. We reasoned that functionalization of MOFs with multiple urea groups that can encapsulate the anion by complementary hydrogen bonds would effectively isolate the anion and prevent it from interactions with less discriminatory metal centers and solvent molecules.



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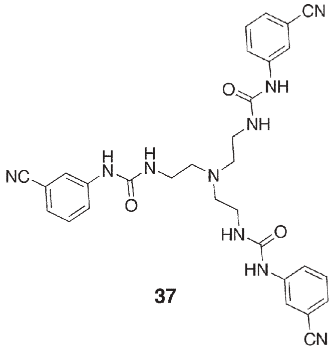

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The bis(urea) ligand **36** was found to form a two-dimensional rhomboid-grid network with $NiSO_4$, with each

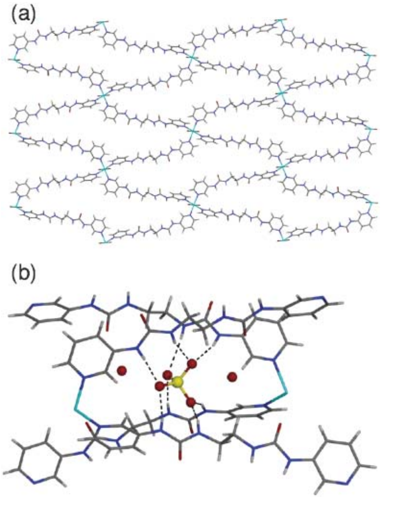

Fig. 18 Crystal structure of the coordination network of Ni^{2+} with **36**. (a) Nickel coordination layer displaying the rhomboid-grid architecture. (b) Sulfate intercalation between coordination layers *via* hydrogen bonding from four urea groups.

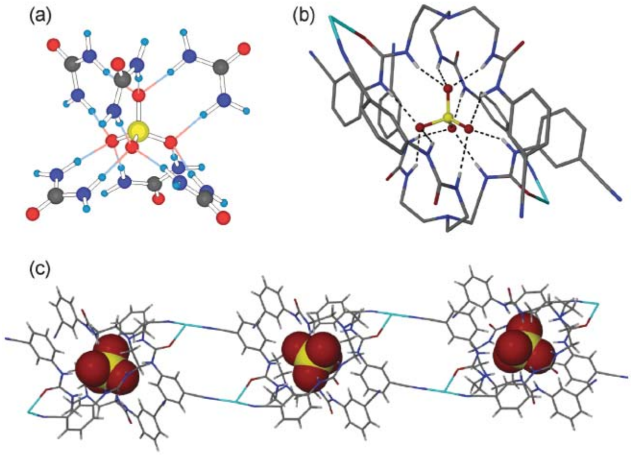

Fig. 19 Encapsulation of sulfate in a silver coordination polymer of **37**. (a) Molecular model showing the optimal sulfate binding by 12 hydrogen bonds from six urea groups. (b) Observed sulfate encapsulation in $Ag_2(\mathbf{37})_2$ coordination cages in the solid state. (c) Self-assembly of cages into polymeric chains.

Ni^{2+} center coordinated octahedrally by four equatorial pyridine groups and two axial water molecules (Fig. 18).[51] The sulfate anions are intercalated between layers and are chelated by four urea groups, two from each layer, in a total of eight hydrogen bonds. This coordination framework only forms with sulfate but not with other common anions, including F^-, Cl^-, Br^-, I^-, NO_3^- or ClO_4^-, indicating that the strong and complementary hydrogen bonds between SO_4^{2-} and urea groups are critical for the stability of the framework. This allowed us to exclusively separate sulfate from different aqueous anionic mixtures, including a 20-fold excess nitrate solution.

Although the complementarity for sulfate in the previously described MOF was significant, it was not ideal, as indicated by the inclusion of two water molecules in the crystal to complete the sulfate coordination by additional hydrogen bonding. Molecular modeling by Hay suggested that sulfate ideally accommodates six urea groups, each binding to one of the six O–S–O edges of this tetrahedral oxoanion, in a total of 12 hydrogen bonds.[11a] We found that the tris(urea) ligand **37** is suitable for this purpose, as indicated by molecular modeling showing that SO_4^{2-} can accommodate two such ligands by involving all 6 available urea groups. The crystal structure of the MOF synthesized from **37** and Ag_2SO_4 is depicted in Fig. 19, and shows that indeed, sulfate is encapsulated by two ligands *via* 12 hydrogen bonds from the urea groups. On the other hand, other anions of different shapes and basicities, such as BF_4^-, NO_3^-, $CH_3SO_3^-$ or AcO^- did not form MOFs with **37** due to their negligible interactions with this ligand, as indicated by solution NMR experiments.[52]

Summary and prospects

With their strong and predictable hydrogen-bonding, *N*,*N*′-disubstituted ureas are robust and versatile groups that can be rationally employed for the synthesis of crystalline solids with various architectures, from one-dimensional chains and nanotubes, to layers and three-dimensional frameworks. The conformationally more flexible thioureas, on the other hand, are somewhat less reliable design elements for crystal engineering, although strategies to control the supramolecular association of these groups in the solid state have begun to emerge. A particularly effective approach along this line is to use steric control to manipulate the hydrogen bonding of thioureas in the crystalline state.

Besides being useful building blocks for the assembly of hydrogen-bonded solids, ureas and thioureas can also act as functional groups for binding anionic or neutral species within crystalline frameworks. This type of functionality, however, requires that the self-association of these groups be suppressed, which can be achieved by strategic substitution with electron-withdrawing groups. Successful implementation of this strategy was demonstrated by the synthesis of metal–organic frameworks functionalized with urea groups for anion binding, which showed good anion separation selectivities.

The two types of urea functionalities, that of network builder on one hand, and of anion-binding group on the other, may not be always clearly differentiated. Actually, anion binding by ureas can in itself be exploited for framework assembly. A recent example from Gale's group, where carboxylate binding by an *ortho*-phenylene-bis urea was exploited for the deliberate assembly of a crystalline hydrogen-bonded tape, clearly demonstrates this concept.[53]

Thioureas have so far not been explored to their full potential as functional groups in crystalline frameworks. Given their stronger hydrogen-bonding donor ability compared to ureas, thioureas may prove particularly effective binding groups in the solid state, once sufficient control over their supramolecular chemistry is established. Recently, thioureas have been found to act as effective anion receptors or to catalyze various organic reactions with remarkable efficiencies and selectivities in solution.[54] If these abilities can be successfully transferred to crystalline solids with predetermined structures it may lead to a whole new generation of functional materials with unprecedented properties; that is, crystal engineering *par excellence!*

Acknowledgements

I would like to thank my coworkers and collaborators, particularly Peter Bonnesen, Slava Bryantsev, Nancy Engle, Maryna Gorbunova, Tammy Haverlock, Ben Hay, Bruce Moyer, and Vincent Sellin, who made invaluable contributions to the work leading to this review. This research was sponsored by the Division of Chemical Sciences, Geosciences, and Biosciences, Office of Basic Energy Sciences, U.S. Department of Energy, under contract number DE-AC05-00OR22725 with Oak Ridge National Laboratory managed by UT-Battelle, LLC.

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