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Syntheses and studies of flexible amide ligands: a toolkit for studying metallo-supramolecular assemblies for anion binding

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ABSTRACT

The syntheses of seven flexible bidentate bis-pyridyl diamide and four monodentate pyridyl amide ligands containing central amide units are described. The bis-pyridyl ligands were prepared in one step from commercially available compounds in moderate to good yield. These compounds all possess external metal coordinating pyridyl groups and internal amide functionalities, with the potential to bind anions. Crystal structures of six of the bis-pyridyl diamide ligands are described. The four compounds with xylene cores *N*,*N*′-[1,3-phenylenebis(methylene)]bis-3-pyridinecarboxamide **1**, *N*,*N*′-[1,3-phenylenebis(methylene)]bis-4-pyridinecarboxamide **2**, *N*,*N*′-[1,4-phenylenebis(methylene)]bis-3-pyridinecarboxamide **3** and *N*,*N*′-[1,4-phenylenebis(methylene)]bis-4-pyridinecarboxamide **4** crystallize with extensive amide N–H···O=C hydrogen bonding between the diamide compounds, giving rise to two and three dimensional hydrogen bonded networks. *N*,*N*′-Bis(3-pyridylmethyl)benzene-1,3-dicarboxamide **5**, the only compound with the amide groups directly attached to a central benzene core, was not able to be crystallised. *N*,*N*′-2,6-Bis(3-pyridylmethyl)pyridine dicarboxamide **6** and *N*,*N*′-2,6-bis(4-pyridylmethyl)pyridine dicarboxamide **7** have a mismatch of hydrogen bond donor and acceptor regions preventing ready involvement of the amide NH groups in network formation. For comparison we also prepared compounds *N*,*N*′-2′-propyl-6-(3-pyridylmethyl)pyridine dicarboxamide **10** and *N*,*N*′-2′-propyl-6-(4-pyridylmethyl)pyridine dicarboxamide **11** with two amide groups but only the one external donor pyridyl moiety, and compounds *N*-6-[(3-pyridylmethylamino)carbonyl]-2-pyridinecarboxylic acid methyl ester **8** and *N*-6-[(4-pyridylmethylamino)-carbonyl]-2-pyridinecarboxylic acid methyl ester **9**, which have only the one amide.

1. Introduction

The field of anion binding has rapidly progressed over the last decade.[1–4] This birth of anion coordination chemistry[5] originated in the appreciation of the significant impact anions have in environmental, biological and medicinal arenas. This includes fertilizer run-off, toxic metallo-anion species and sulfate anion contamination of low-level nuclear wastes, for example. Strategies to selectively complex anions have been described for a large range of anions. These include using organic hosts with diverse hydrogen bonding donor groups[2,3] and/or π-acidic heteroarene scaffolds;[6–8] electrostatic interactions with cations;[1,9] and more recently, metallo-supramolecular assemblies[10] and coordination polymers.[11]

The use of a metallo-supramolecular species to bind anions introduces the attendant advantages of metallo-supramolecular chemistry. The anion binding and encapsulating assemblies of interest can be readily explored using a number of relatively simple ligands capable of interacting with anions; the structural complexity required to bind an anion is generated by the choice of metal ion used to assemble the metallo-supramolecular species (Fig. 1). Furthermore, labile transition metal centres allow these to be dynamic assemblies that respond to external stimuli, while the correct choice of metal centre can add additional scope in terms of optical or electrochemical responses to binding.

The use of ligands containing hydrogen bond donor groups to bind anions as part of a transition metal complex or metallo-supramolecular assembly is not a new strategy. Transition metal complexes with pendant hydrogen bond donor groups have been reported by several groups.[12–14] Similarly, metallo-supramolecular assemblies with internal hydrogen bonding domains have also been reported.[10,15–17] In an effort to generate simple metallo-supramolecular assemblies to bind anions we focused our attention on a series of simple relatively flexible mono- and bis-amido containing heterocyclic ligands. These flexible and

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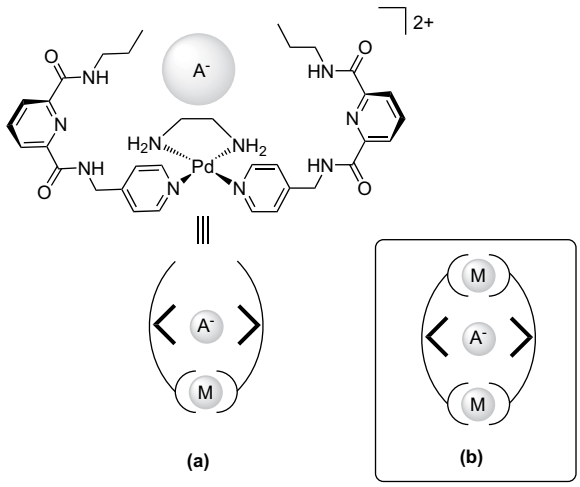

Figure 1. Schematic representations of the targeted metallo-supramolecular assemblies formed with (a) monodentate and (b) bidentate ligands.

accommodating assemblies should be capable of binding a range of anionic guests.

The ligands we have based our studies on are shown in Diagram 1. These include the ligands of primary interest (**1**–**7**), which possess two external pyridyl metal coordinating sites and two internal amido groups, compounds **8** and **9** with two amido groups but only the one external donor pyridyl moiety, and **10** and **11**, which have only the one amide. Herein we describe the syntheses of these compounds and the crystal structures of six of the bis-amido bridging ligands.

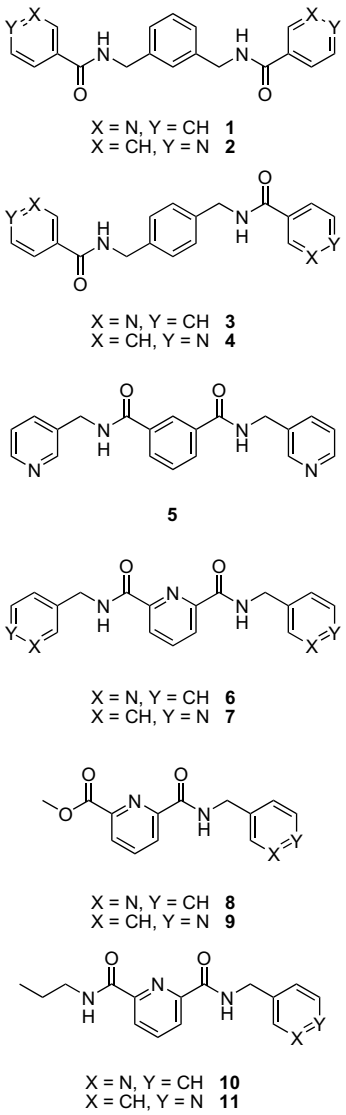

Diagram 1.

2. Results and discussion

2.1. Syntheses

In our strategy to use simple organic ligands to bind anions within metallo-supramolecular assemblies we required a relatively simple and direct route to our desired compounds. The choice of amide hydrogen bond donor groups was made for two primary reasons; amide hydrogen bond donors are commonly used to bind anions and they can be readily prepared on a large scale in high yielding reactions. One issue we wished to avoid was the low solubility of many amide derivatives; this prompted us to opt for additional flexibility through the use of xylyl, instead of benzene, spacers in **1**–**4** and the picolyl group in compound **5**. Furthermore, the additional length of the diamides would allow for the formation of slightly larger metallo-supramolecular structures capable of accommodating larger guest species within the resulting cavities. Oddly, very little attention has been paid to these particular flexible bis-amides. Compound **1** has been studied with regard to blood platelet aggregation,[18] while compounds **2**–**4** have not been reported before and the only description of compound **5** is as an anti-oxidant in lubricating grease.[19] The 4-pyridyl isomer of compound **5**, *N*,*N*′-bis(4-pyridylmethyl)benzene-1,3-dicarboxamide, **A** (Diagram 2) has attracted considerably more attention,[17, 20] while *N*,*N*′-bis(3-pyridylmethyl)benzene-1,4-dicarboxamide, **B** and *N*,*N*′-bis(4-pyridylmethyl)benzene-1,4-dicarboxamide, **C** have also been previously prepared and crystal structures of the bis-amides and their complexes reported.[21–23] Related compounds lacking the methylene spacer, and concomitant additional flexibility, have also been studied.[24] Flexible diamides with aliphatic cores have also attracted attention.[25]

Compounds **1**–**4** were prepared by reacting commercially available nicotinoyl or *iso*-nicotinoyl chlorides with the correct diamine. These were isolated in good yields (54–90%) by a simple work-up procedure, and characterized by NMR and IR spectroscopy, mass spectrometry and combustion analysis. In all cases, crystals of the resulting diamides were obtained that were suitable for structure determinations by X-ray crystallography. The fifth isomeric compound **5** was obtained by similar chemistry but with a reversal of the functional groups of the two reaction partners.

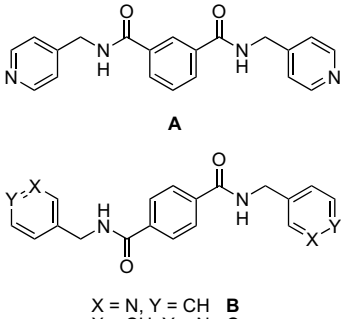

Diagram 2.

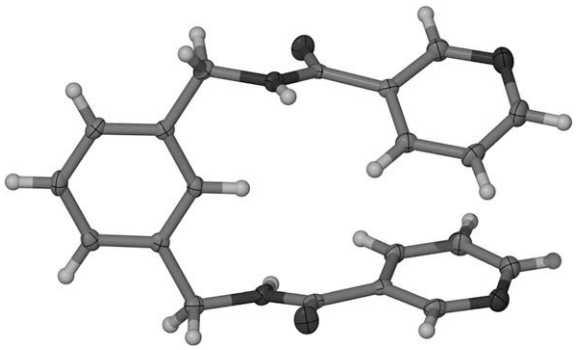

Figure 2. A perspective view of the 'U'-shaped conformation of compound **1**. Ellipsoids shown at 50% probability level and the deuterio-chloroform solvate not shown.

Thus, phthaloyl chloride reacted with 3-pyridylmethylamine to give compound **5** in 65% isolated yield. The 4-pyridyl derivative of **5**, compound **A** has been prepared by other workers.[17,20]

The five ligands described above possess relatively flexible structures with little conformational control over the directionality of the amide NH hydrogen bond donors. The 2,6-pyridinediamide moiety has been employed by numerous groups to pre-organize the two amide NH donors.[26] We chose to incorporate this moiety into our compounds as pre-organized analogues of **1** and **2**. Other groups[27] have accessed the 2,6-pyridinediamide moiety from 2,6-dimethylpyridine dicarboxylate rather than the equivalent acid chloride. We opted for this route in the synthesis of compounds **6** and **7**, by analogy to the successful synthesis of the 2-pyridyl analogue.[28] Simply refluxing a suspension of 2,6-dimethylpyridine dicarboxylate with a greater than twofold excess of 3- or 4-aminomethylpyridine in toluene gave compounds **6** and **7** in 76% and 40%, respectively. These compounds were characterized by NMR and IR spectroscopy, mass spectrometry and combustion analysis, and both compounds yielded crystals suitable for structure determination by X-ray crystallography.

Having prepared a series of bidentate ligands with internally directed hydrogen bond donor groups, we set about preparing the related mono amide and model diamide derivatives. Compounds **8** and **9** were synthesized using conditions similar to those used to prepare the potentially bidentate compounds **6** and **7**. By altering the stoichiometry of the reaction **8** and **9** were obtained after column chromatography in 59 and 68% yield, respectively. These could then be reacted with an excess of propylamine to give compounds **10** and **11** in 68 and 58% isolated yields, respectively.

2.2. Structure determinations

*2.2.1. Structures of N,N′-[1,3-phenylenebis(methylene)]-bis-3-pyridinecarboxamide chloroform solvate, **1**·$CDCl_3$ and N,N′-[1,3-phenylenebis(methylene)]-bis-3-pyridinecarboxamide **2***

In the solid-state structures of diamides **1** and **2** the compounds adopt an almost identical solid-state conformation and the hydrogen bonded networks have an identical topology. Crystals of **1**·$CDCl_3$ were obtained by allowing a deuterated chloroform solution of the compound to slowly evaporate. Compound **1** crystallises in the monoclinic space $P2_1/c$ with four complete molecules of **1** and four deuterated chloroform solvate molecules in the unit cell. Compound **1** adopts a 'U'-shaped conformation in the solid state (Fig. 2), with the 3-pyridinecarboxamide groups almost mutually in plane and perpendicular to the central xylene group. One of the 3-pyridinecarboxamide moieties is inclined by ca. 14.5° from perpendicular while the other is significantly more twisted at ca. 35.4° from perpendicular, reducing the gap between the two arms of the compound but not sufficient to generate significant intramolecular π-stacking interactions.

While the compound adopts the generally desired 'U'-shape the amide hydrogen bond donors are orientated perpendicular to the xylene groups and not into the potential 'cavity' of the compound. Within the extended structure the compound **1** forms four N–H···O═C hydrogen bonds to three other molecules of **1**, with distances fairly typical of moderately strong hydrogen bonds.[29] Two of these hydrogen bonds are to a symmetry-related molecule of **1** leading to an N–H···O═C hydrogen bonded dimer with d=1.979 Å and D=2.769 Å. The other two N–H···O═C hydrogen bonds are to two other molecules of **1** with d=1.995 Å and D=2.768 Å. Thus, the overall packing of compound **1** consists of hydrogen bonded dimers that are hydrogen bonded to four other dimers to give 2-D hydrogen bonded sheets that extend within the *bc* plane of the unit cell (Fig. 3). Within each hydrogen bonded dimer of **1** the molecules are lying in opposite directions, allowing for additional weak C–H···π interactions between the pyridyl group of one molecule and the xylene moiety of a second.

If the $(\mathbf{1})_2$ dimers are considered as four-connecting nodes (i.e., the internal hydrogen bonds within the dimers are treated as topologically trivial) then the extended structure has a (4,4) network topology. The two dimensional hydrogen bonded sheets are packed into layers with the deuterated chloroform molecules sandwiched between the 4-connected 2-D sheets to complete the 3-D packing of **1**·$CDCl_3$.

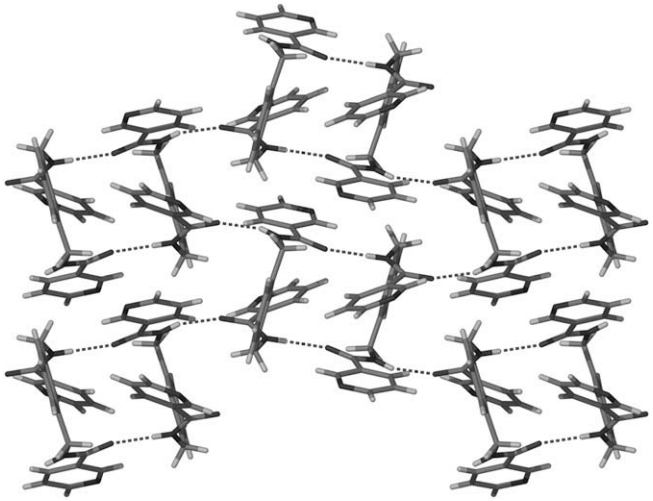

Figure 3. A perspective view of the extended hydrogen bonded sheet in the *bc* plane of **1**·$CDCl_3$ showing the hydrogen bonded dimers.

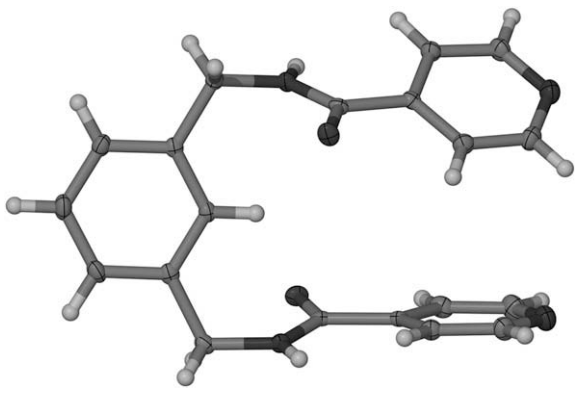

Figure 4. A perspective view of the 'U'-shaped conformation of **2**, which adopts a conformation very similar to compound **1** in the solid state. Ellipsoids shown at 50% probability level.

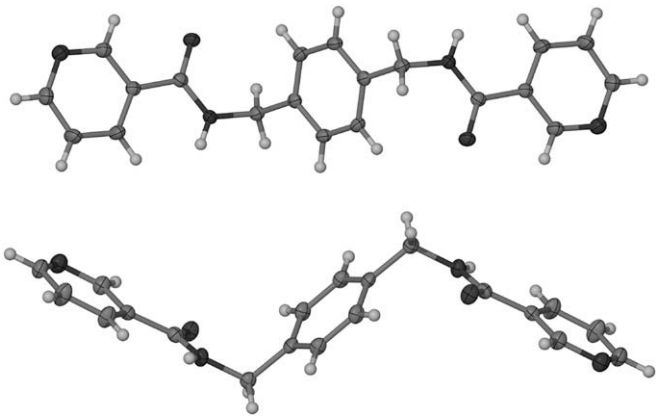

Figure 5. Two perspective views from the crystal structure of **3** showing the zigzag conformation of the compound in the solid state. Ellipsoids shown at 50% probability level. Symmetry operation used to generate complete molecules: $-x$, $-y$, $-z$.

Crystals of **2** were obtained from a methanol solution of **2** and copper(II) nitrate by slow evaporation. Compound **2** crystallised in the monoclinic space $P2_1/n$ with four complete molecules of **2** in the unit cell. Compound **2** adopts the same 'U'-shaped conformation (Fig. 4) as the isomeric ligand **1**, with the 4-pyridinecarboxamide groups almost mutually in plane and perpendicular to the central xylene group (twists of ca. 13.2° and 23.5° from perpendicular). Again, the hydrogen bond amide donors are not directed into the 'U'-shaped cavity of the ligand.

Compound **2** is hydrogen bonded into 4-connected sheets in an identical connectivity to the isomeric compound **1**, with subtle differences in the lengths of the amide hydrogen bonds. The sheets are oriented along the body diagonal of the unit cell. The crystals contain no solvate molecules and thus the sheets are closely-packed to complete the 3-D packing within the crystal.

The solid-state conformations for **1** and **2** are quite different to those observed for a complex of compound **A** reported in the literature. In a [2+2] dimetallomacrocycle reported by Diaz et al.[17] compound **A** adopts a planar, more open conformation with one amide NH and a second amide carbonyl group pointing into the macrocyclic structure. This change apparently arises from switching the positions of the methylene and carbonyl groups within the flexible arms of the diamides, although compound **A** is coordinated by a metal in the work of Diaz et al.

2.2.2. *Structure of N,N′-[1,4-phenylenebis(methylene)]-bis-3-pyridinecarboxamide* ***3***

Crystals of **3** were obtained by slow evaporation of a methanol–acetonitrile solution of the diamide and silver hexafluorophosphate. Compound **3** crystallises in the monoclinic space group $C2/c$ with half the ligand molecule, which lies on the twofold axis, in the asymmetric unit. The compound adopts a zigzag conformation with both 3-pyridinecarboxamide arms twisted about the sp^3-CH_2 linker at ca. 112.7° to the xylene core; one arm is directed above and the other below the plane of the central xylene ring, Figure 5. Bond lengths and angles are unremarkable for such a compound. The pyridyl donors are oriented in opposing directions as defined by a centre of symmetry passing through the centroid of the xylene ring.

Each molecule of **3** participates in four hydrogen bonds to four symmetry-related molecules of **3** and thus, each ligand can be considered a 4-connecting node. This leads to a (4,4) hydrogen bonded network, Figure 6, with a zigzag structure when viewed perpendicular to the plane of the sheet. As the atoms involved in hydrogen bonding are not at the ends of the molecule, this results in protrusions of the 3-pyridine rings above and below the sheets. Association of the layers completes the 3-D packing of the crystal.

Crystals of an isomer of **3** *N,N′*-bis(3-pyridylmethyl)benzene-1,4-dicarboxamide dihydrate were reported by Ge et al.[22] In that structure the diamide **B** adopts a similar conformation to the one reported for **3** here; both compounds adopt the *anti* configuration. In the structure of compound **B** the two water solvate molecules mediate hydrogen bonding interaction between the molecules of the diamide. The same diamide was also used to prepare two isostructural coordination polymers with copper(II) and zinc(II) dinitrate.[21] In those structures compound **B** adopted a different conformation, highlighting the generally flexible nature of the ligands.

2.2.3. *Structures of N,N′-[1,4-phenylenebis(methylene)]-bis-4-pyridinecarboxamide:* ***4***·*1/3(*CD_3COCD_3*) and* ***4***·*2(*H_2O*)*

Standing of an acetone-d_6 solution of **4** provided needle-shaped crystals suitable for X-ray crystallography. Compound **4** crystallises in the rhombohedral space group *R*-3 with a hexagonal arrangement of six molecules of the ligand around channels of disordered acetone solvent. The asymmetric unit consists of half a ligand molecule and a highly disordered, and partially occupied, acetone solvate molecule lying on a special position. The complete ligand is generated by a centre of symmetry and **4** adopts an almost identical conformation to **3** but with slight twisting of the pyridyl rings relative to the plane of the amide bonds (torsion angle of 31.6° relative to the equivalent torsion angle for **3** of 4.9°). Each molecule of **4** is involved in four hydrogen bonds; two bonds to two different symmetry-related molecules resulting in a hydrogen bonded 1-D tape (Fig. 7).

The packing of **4** in the high-symmetry rhombohedral space group consists of rosettes of six 1-D hydrogen bonded tapes of **4**

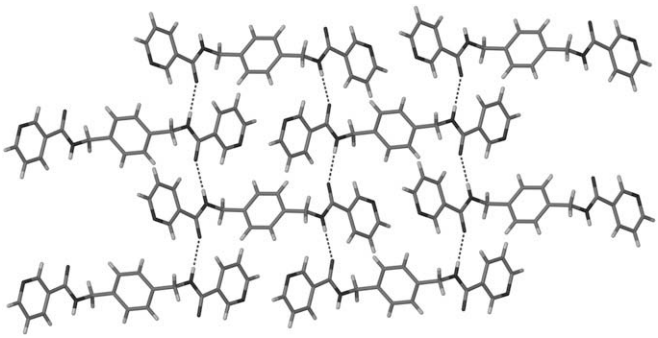

Figure 6. A perspective view of the four-connected 2-D hydrogen bonded network in the structure of **3**.

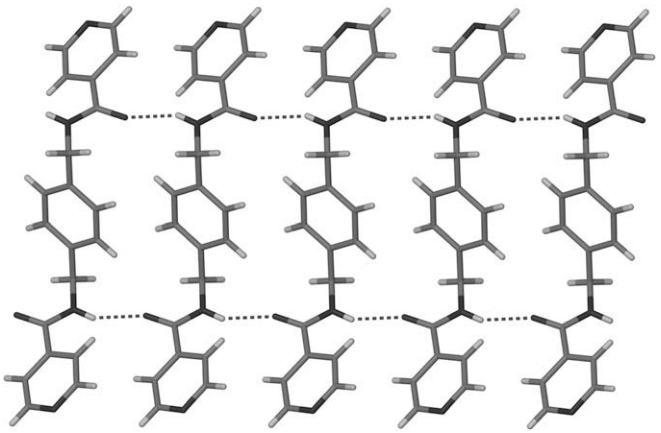

Figure 7. View of the hydrogen bonded tapes of **4** extending along the *c*-axis of the unit cell.

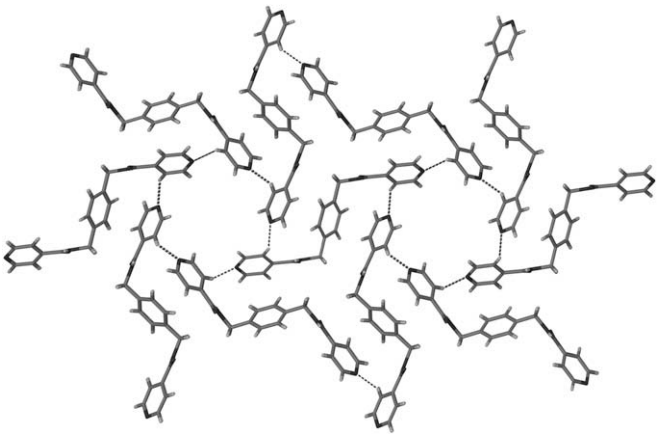

Figure 8. A perspective view of the packing of **4**·1/3(CD_3COCD_3) viewed down the *c*-axis of the unit cell, showing the rosettes of six 1-D hydrogen bonded tapes of **4** arranged around the channels of highly disordered acetone molecules (not shown).

arranged around the channels of disordered acetone molecules, Figure 8. These rosette arrangements are stabilized by very weak C–H···N_{py} interactions (d=2.55 Å) between adjacent molecules of **4**.

As an interesting comparison, a second sample of crystals of compound **4** was obtained by slow evaporation of an acetonitrile–methanol solution of **4** and silver trifluoroacetate. The compound is a 3-D hydrogen bonded network structure, which crystallises in the monoclinic space group $P2_1/n$. The compound crystallises as its dihydrate, which appears to be a common formulation for similar diamides.[22,23] The water solvate molecules mediate the hydrogen bonding between the molecules of **4**. This leads to hydrogen bonded one dimensional tapes with molecules of **4** connected by two water molecules to a further molecule of **4** (Fig. 9) extending along the *a*-axis of the unit cell. The water molecules act as three connecting nodes forming three hydrogen bonds with three different molecules of **4**. Within the tapes the OH···O=C hydrogen bond distance is 2.123 Å, while the NH···O_{water} hydrogen bond distance is 2.061 Å. The water solvate molecules are involved in a third hydrogen bond as a donor to a pyridine nitrogen atom of a nearby tape (OH···N_{py} d=1.962 Å). This leads to a 3-D hydrogen bonded network whereby each tape is hydrogen bonded, through water solvate molecules, to four other tapes, Figure 10.

2.2.4. *Structure of N,N′-2,6-bis(3-pyridylmethyl)pyridine dicarboxamide hydrate,* ***6***·H_2O

Compound **6** was crystallised by slow evaporation of a dichloromethane solution of the compound. Compound **6** crystallises in the triclinic space group *P*-1, with two complete molecules of **6** and a hydrogen bonded water molecule in the asymmetric unit (Fig. 11). The two molecules of **6** in the asymmetric unit have very similar conformations, with the only differences being subtle discrepancies in bond lengths and angles (particularly in the intramolecular hydrogen bonding patterns) and an altered intermolecular hydrogen bonding pattern. A solvate water molecule acts as a hydrogen bond donor to one molecule of **6** through a pyridyl ring nitrogen atom and an amide carbonyl oxygen atom (on a symmetry equivalent molecule). The solvate water molecule also acts as a hydrogen bond acceptor for a C_{py}–H (d=2.387 Å) provided by the other molecule of **6** in the asymmetric unit. Intramolecular hydrogen bonding (d=2.250–2.369 Å) pre-organizes the NH functionality of the ligand into a central pocket, hopefully capable of binding anions. This is the exact opposite of the behaviour of compounds **1** and **2**, based around the 1,3-xylene core, whereby steric repulsions appear to force the amide functional groups out of the plane of the xylene core. It also appears there may also be weak C–H···O=C interactions (d=2.456 and 2.471 Å) between the two molecules in the asymmetric unit.

Both of the molecules form hydrogen bonded dimers in the solid state (Fig. 12). The hydrogen bonding motifs are the same for both dimers but there are subtle differences in the hydrogen bond lengths. The intermolecular NH···N_{py} hydrogen bonding distances within the dimers range from 2.16 to 2.42 Å. One of the dimers has an asymmetric hydrogen bonding arrangement with two shorter and two longer hydrogen bonds, while the second dimeric assembly has a hydrogen bonding pattern with near equivalent hydrogen bond lengths. The extensive hydrogen bonding interactions

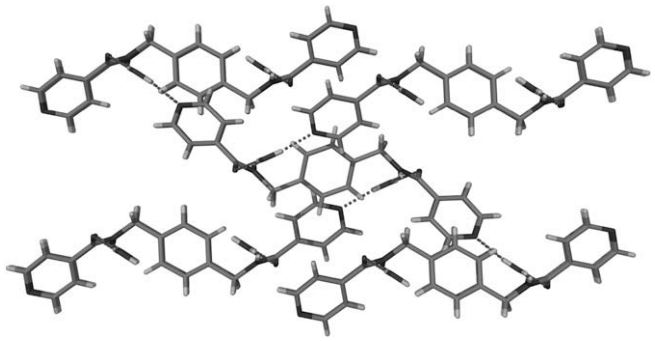

Figure 10. A view of the 3-D hydrogen bonded network structure in the crystal structure of **4**·2(H_2O) when viewed down the *a*-axis. Each 1-D tape is hydrogen bonded to four other tapes through the water solvate molecules.

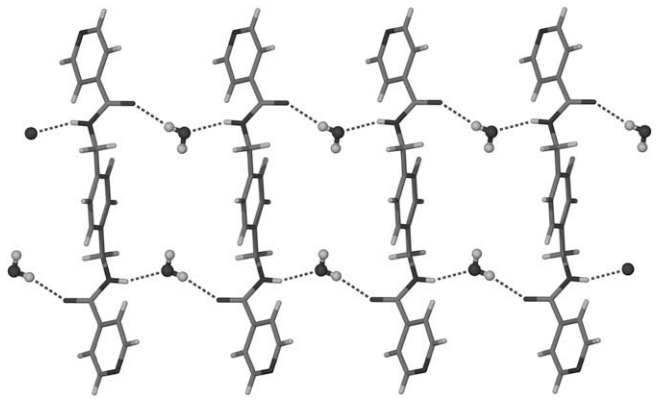

Figure 9. View of the water solvate-mediated hydrogen bonded tapes of **4** extending along the *a*-axis of the unit cell of the structure of **4**·2(H_2O).

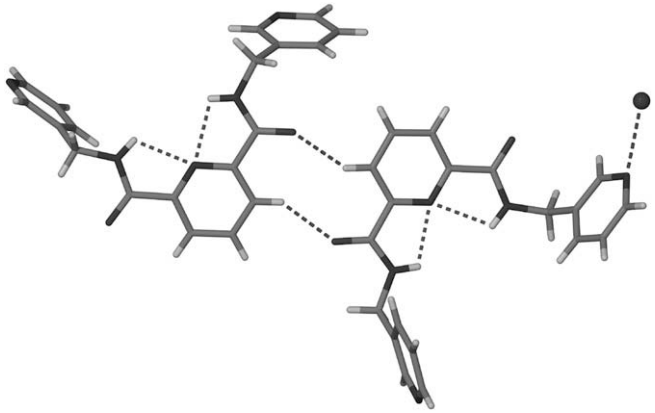

Figure 11. A view of the asymmetric unit of **6**·H_2O, showing the pre-organizing intramolecular hydrogen bonding interactions and the intermolecular hydrogen bonding by one molecule of **6** to a solvate water molecule.

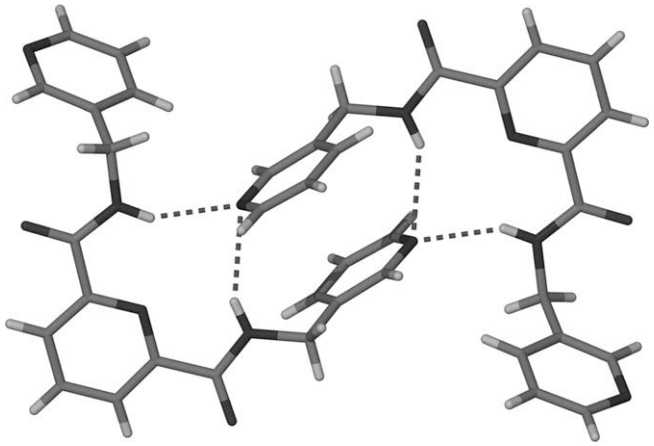

Figure 12. One of the two hydrogen bonded dimers of **6**, with only the intermolecular hydrogen bonding shown. Symmetry operation used to generate dimer: $-x-1, -y, 1-z$.

between **6** and the solvate water molecule lead to an intricate and complicated hydrogen bonded network within the crystal.

2.2.5. *Structure of N,N′-2,6-bis(4-pyridylmethyl)pyridine dicarboxamide dihydrate,* ***7***·*2(H$_2$O)*

Compound **7** also crystallises in the triclinic space group *P*-1, but with only one molecule of the diamide in the asymmetric unit (Fig. 13). One solvate water molecule acts as a hydrogen bond acceptor for the amide N–H donors of **7** (NH···O, d=2.099 and 2.114 Å). The solvate water molecule also acts as a hydrogen bond donor (OH···N$_{py}$ d=1.994 Å) to another symmetry-related molecule of **7**. This results in hydrogen bonded dimers {(**7**)$_2$(H$_2$O)$_2$} within the crystal structure (Fig. 14). Again, intramolecular hydrogen bonding (d=2.264–2.290 Å) pre-organizes the NH functionalities of the diamide into a central pocket, hopefully capable of binding anions. A second solvate water molecule is hydrogen bonded to the carbonyl group of **7** (OH···OC d=1.897 Å).

Within the crystal structure of **7**·2(H$_2$O) the hydrogen bonded dimers {(**7**)$_2$(H$_2$O)$_2$} are packed in chains through hydrogen bonding OH···O=C mediated by the second solvate water molecule. The resulting chains are then associated with adjacent chains through the two water solvate molecules to give a hydrogen bonded 2-D network. The hydrogen bonding leads to an overlapping of the hydrogen bonded chains within the 2-D network but no π-stacking interactions are apparent between the central pyridine rings of adjacent molecules of **7**. The water molecule hydrogen bonded within the cavity of the diamide accepts two hydrogen bonds and is the donor in two other hydrogen bonds, while the other water solvate molecule is three connecting (donor of two, acceptor for one). The crystal packing is completed by weaker CH···π and π-stacking interactions between the 2-D hydrogen bonded sheets.

Within the seven diamide structures reported, a number of different hydrogen bond motifs and diamide conformations have been observed. Regarding this latter feature, in our investigation of coordination complexes of these ligands[30] we have observed that these flexible diamides maintain similar conformations in the resulting coordination polymers and discrete metallo-macrocyclic structures. Thus, while the diamides have a number of degrees of flexibility within their structures there are preferred conformations for the various cores of the diamides that appear to restrict the conformations.

On the former point of hydrogen bond motifs, the seven structures show several different hydrogen bonding patterns that have been observed for other diamide ligands reported in the literature (Fig. 15). Within the structures of **1**·CDCl$_3$ and **2**, diamide hydrogen bonding motifs (a) and (b) are observed; within the dimeric units mode (b) occurs and the connections between dimeric units utilise mode (a). Diamide **3** utilizes mode (a), while the structure of **4**·1/3(CD$_3$COCD$_3$) utilizes mode (b). Mode (b) is observed in the dihydrate of compound **4** but the hydrogen bonds are mediated by water solvate molecules. The crystal structures of compounds **6** and **7** have a primary amide hydrogen bonding donor motif as shown for structure (c), where the two donors hydrogen bond to a non-amide acceptor.

Preliminary investigations of the reactions of compounds **1**–**5** with transition metal salts have given solid-state structures in which the pyridyl donors coordinate the metal cation to form 1-D and 2-D coordination polymers and the amide N–H and C=O groups are then involved in extending these structures to 2-D and 3-D networks, respectively, through hydrogen bonding.[30] The compounds most suitable for generating complexes capable of anion binding into a cavity formed within a metallo-supramolecular assembly appear to be compounds **6** and **7** with the pre-organized pocket. Recent studies into the coordination chemistry of **6**

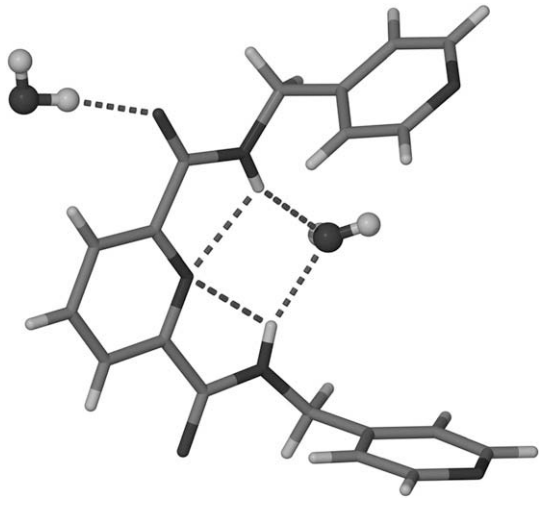

Figure 13. A perspective view of the asymmetric unit of **7**·2(H$_2$O), showing the intramolecular hydrogen bonding that pre-organizes the amide NH binding pocket and the two hydrogen bonded water solvate molecules.

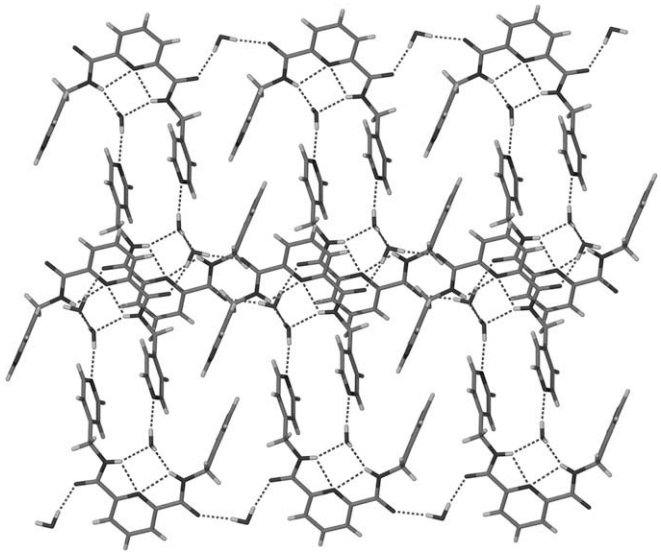

Figure 14. A view of the 2-D hydrogen bonded sheets in the crystal structure of **7**·2(H$_2$O).

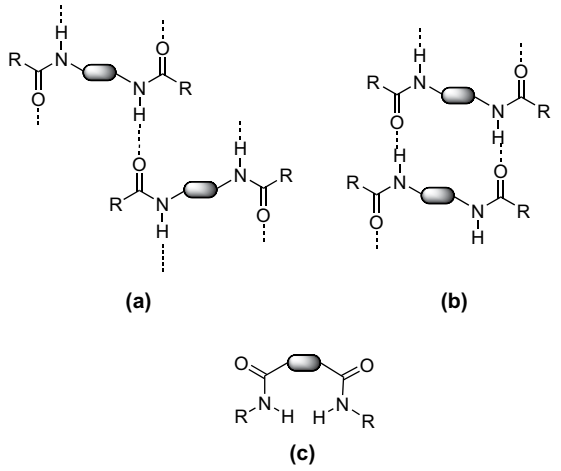

Figure 15. The simplified versions of the primary hydrogen bonding motifs observed in the crystal structures reported in this work. The different conformations of the various diamides are neglected.

and **7** have revealed a number of discrete metallo-macrocyclic structures and coordination polymers whereby the amide N–H donor groups are hydrogen bonded to anions within these structures.[30] The formation of these types of structures (involving hydrogen bonded anions) may be a consequence of the mismatch of hydrogen bond donor acceptor and donor groups that limits the ability to form the types of hydrogen bonded networks observed for diamides like **1**–**5**.

We examined the behaviour of compounds **6** and **7** in solution to investigate if self-association could be mediated by hydrogen bonding involving the central 2,6-pyridine dicarboxamide moiety. In the crystal structure of **6**·H_2O the diamide forms a hydrogen bonded dimer (Fig. 12). Electrospray mass spectrometry (ES-MS) of **6** conducted in chloroform solution reveals peaks for $[\mathbf{6}+H]^+$ (348.2, 100%), $[(\mathbf{6})_2+H]^+$ (694.6, 55%) and $[(\mathbf{6})_3+H]^+$ (1041.6, 37%). Formation of the dimeric ion $[(\mathbf{6})_2+H]^+$ could be due to formation of a dimer like that observed in the crystal structure, although other possibilities exist. The trimer may involve hydrogen bonding by a third molecule of **6** to a amide oxygen atom of the dimer $[(\mathbf{6})_2+H]^+$ to give the species observed by ES-MS. ES-MS in methanol led to the observation of three dominant species $[\mathbf{6}+H]^+$ (348.2, 50%), $[\mathbf{6}+Na]^+$ (370.1, 30%) and $[(\mathbf{6})_2+Na]^+$ (716.8, 100%), while the previously observed protonated dimer $[(\mathbf{6})_2+H]^+$ (694.6, 6%) was in low abundance and trimer $[(\mathbf{6})_3+H]^+$ was not observed. The sodium salt of the trimer $[(\mathbf{6})_3+Na]^+$ (1063.7, 10%) could also be detected. Similar observations were made for compound **7**. ES-MS in chloroform led to the ionization of only two species: $[\mathbf{7}+H]^+$ (348.2, 100%) and $[(\mathbf{7})_2+H]^+$ (694.6, 34%). In methanol three main species were observed, $[\mathbf{7}+H]^+$ (348.2, 100%), $[\mathbf{7}+Na]^+$ (370.1, 17%) and $[(\mathbf{7})_2+Na]^+$ (716.8, 35%). The protonated dimer was also detected with a low relative abundance. Compounds **6** and **7** did not ionize very well in DMSO. The major peaks observed were due to formation of $[(\mathbf{6})_2+Na]^+$ and $[(\mathbf{7})_2+Na]^+$.

We also examined the behaviour of **6** and **7** in solution by NMR spectroscopy. Dilution experiments on both **6** and **7** in DMSO-d_6, where stable hydrogen bonded aggregates would be unlikely to be observed, showed very little change in the spectra as the concentration was lowered from ca. 0.5 M to 0.01 M. In contrast, over the same regime of concentration the ^{1}H NMR spectra of both **6** and **7** in $CDCl_3$ showed quite dramatic changes with concentration (Fig. 16). Significant downfield shifts for the NH protons were observed in both cases as the concentration was increased. This indicated hydrogen bonded aggregates were being formed in solution. Upfield shifts were also observed, particularly for the

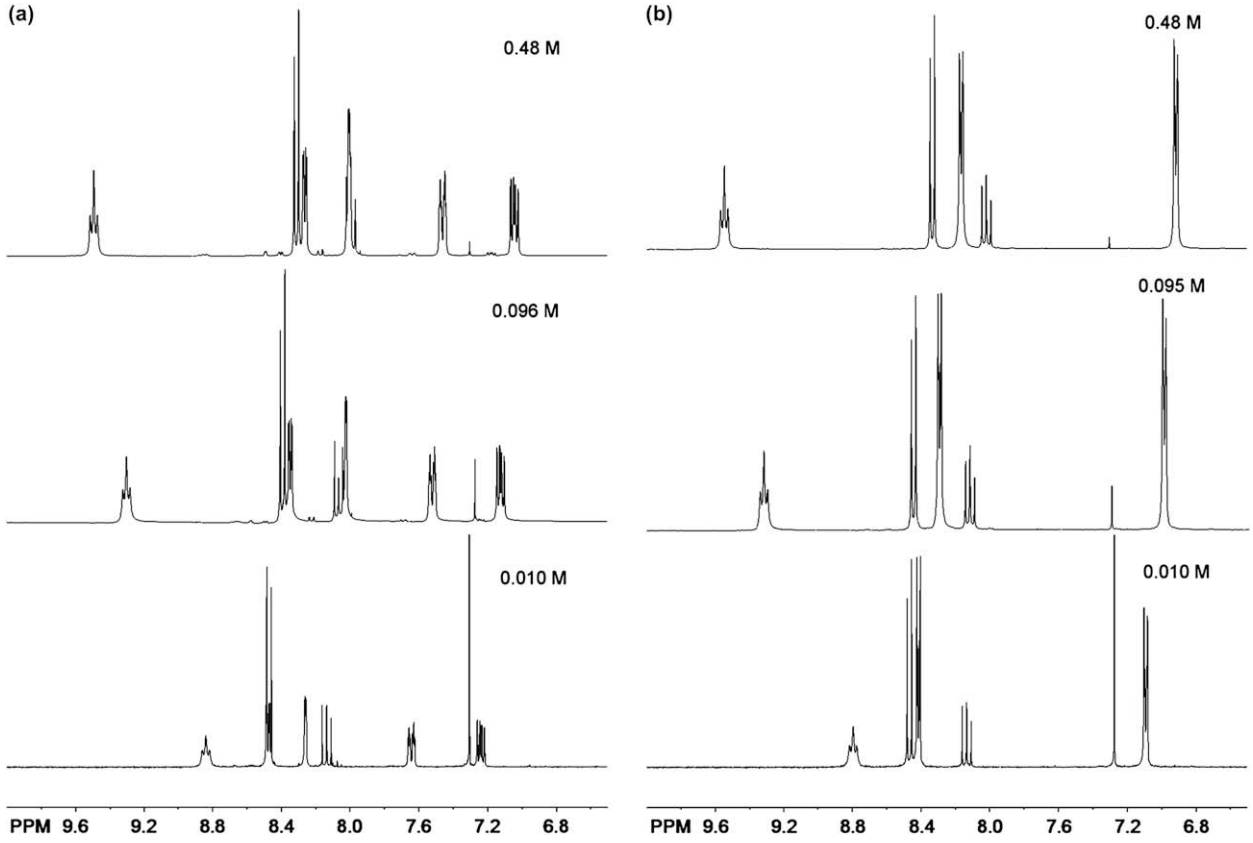

Figure 16. The aromatic regions of the ^{1}H NMR spectra of **6** (a) and **7** (b) in $CDCl_3$.

pyridyl protons on the external pyridine rings but also for the H3 and H5 protons on the central 2,6-pyridine dicarboxamide core. These changes are consistent with the formation of a hydrogen bonded dimer in which adjacent aromatic rings (see Fig. 12) result in shielding of the pyridyl protons on **6** (and **7** in solution).

3. Conclusions

In summary, seven bis-pyridyl ligands were prepared in one step from commercially available compounds in moderate to good yields. Crystal structures of six of the diamide compounds are reported, revealing information about the structures and conformations of these diamides. While these structures only provide information regarding the solid state, they provide some insight into the type of compound more likely to give the required simultaneous cation and anion binding in solution. In this regard, compounds **1**–**5** all display hydrogen bonded 1-D tapes and 2-D sheet structures that utilise all the N–H donors in forming the resulting network structure. This would appear to limit their applicability for simultaneous cation and, in particular, anion binding. These extended network structures form through complementary hydrogen bonding interactions whereby each molecule displays two regions with hydrogen bond donors and two with hydrogen bond acceptors. This contrasts with the type of solid-state structures observed with compounds **6** and **7**. In these structures the preorganised amide N–H hydrogen atoms are involved in hydrogen bonding only to water solvate molecules (**6**) or the external pyridine donor in the case of **7**. In the case of these two compounds, each molecule displays only one region with hydrogen bond donors and two with hydrogen bond acceptors. This arrangement limits the potential for the types of hydrogen bonded network observed for **1**–**5** and suggests that these compounds will be more suitable for interacting with both cations and anions as part of discrete metallo-supramolecular assemblies and coordination polymers.

Unfortunately, the ease of crystallization of the hydrogen bonded network structures of compounds **1**–**5** reported here, and in other studies by us,[30] indicates that hydrogen bonded networks of the nature described for diamides but involving discrete coordination complexes and infinite coordination polymers will be ever present issues. As noted, some of the crystal structures reported here were obtained from solutions containing transition metal salts indicating a preference for forming hydrogen bonded networks over metal complexes under the conditions employed to crystallize these particular compounds.

4. Experimental

4.1. General experimental

Melting points were recorded on an Electrothermal melting point apparatus. Infrared spectra were collected on a Perkin Elmer BX FTIR spectrometer as KBr disks. The Campbell Microanalytical Laboratory at the University of Otago performed elemental analyses. Electrospray (ES) mass spectra were recorded using a Finnigan LCQ mass spectrometer. Other mass spectral analyses were carried out on a Shimadzu LCMS-QP8000α using an APCI ionization technique. NMR spectra were recorded on either a Varian Unity Inova 300 MHz, 500 MHz or Bruker 300 MHz NMR spectrometer at 23 °C using a 5 mm probe. ^{1}H NMR spectra recorded in $CDCl_3$ were referenced relative to the internal standard Me_4Si; ^{1}H NMR spectra recorded in DMSO-d_6 were referenced to the solvent peak: 2.6 ppm. When required, 2-D COSY and NOESY experiments were performed using standard pulse sequences. Unless otherwise stated, the values given for chemical shifts are to the centre of a multiplet.

Unless otherwise stated, reagents were obtained from commercial sources and used as received. Solvents were dried by literature procedures and freshly distilled as required. 2,6-Dimethylpyridine dicarboxylate was prepared by a literature method.[31]

4.2. Syntheses

*4.2.1. General procedure for the synthesis of **1**–**4***

Commercially available acid chloride hydrochloride salts (20 mmol) were suspended in dichloromethane (20 mL) in a round bottomed flask fitted with a pressure equalizing dropper funnel. The dropping funnel was charged with dichloromethane (20 mL), the diamine (10.0 mmol) and triethylamine (3.0 mL, 21.6 mmol), which was then added dropwise to the suspension. The reaction mixture was stirred at room temperature for 24–36 h before the resulting suspension was poured into saturated sodium bicarbonate solution (300 mL) and extracted with dichloromethane (3×200 mL). The combined extracts were dried over $MgSO_4$ and the dichloromethane removed. The resulting residue was purified as described.

*4.2.2. N,N′-[1,3-Phenylenebis(methylene)]bis-3-pyridinecarboxamide, **1***

Following the general procedure a pink-brown oil was obtained. This was triturated with hot diethyl ether, collected by filtration, washed with diethyl ether to give the diamide **1** as a white solid (2.70 g, 78%). Mp 141–142 °C; Found: C, 69.3; H, 5.4; N 16.1. $C_{20}H_{18}N_4O_2$ requires C, 69.3; H, 5.25; N 16.2%; max(KBr disk)/cm^{-1} 3356, N–H *str.* (asym.); 3062, N–H *str.* (sym.); 1633, C=O *str.*; 1594, C=C *str.*; 1571, N–H *bend* and 1538, N–H *bend* (*1*°); ^{1}H (500 MHz; acetone-d_6; Me_4Si) δ=4.61 (4H, d, ^3J=5.8 Hz, ϕ-*CH*$_2$NH), 7.28–7.29 (3H, m, H4, H5, H6), 7.41 (1H, s, H2), 7.45 (2H, dd, ^3J=4.8, 7.9 Hz, pyH5), 8.23 (2H, dt, ^3J=7.9 Hz, pyH4), 8.43 (2H, br s, NH), 8.69 (2H, d, ^3J=4.8 Hz, pyH6) and 9.09 (2H, d, ^2J=1.7 Hz, pyH2); ^{13}C (125 MHz; acetone-d_6; Me_4Si) δ=43.9, 124.2, 127.2, 127.6, 129.4, 131.2, 135.6, 140.5, 149.4, 152.8 and 165.9; *m*/*z* (APCI) 347 (MH^+, 100%). Crystals of **1**·$CHCl_3$ were obtained from a concentrated chloroform solution on standing.

*4.2.3. N,N′-[1,3-Phenylenebis(methylene)]bis-4-pyridinecarboxamide, **2***

Following the general procedure described, but using dichloromethane–methanol (98:2, 3×200 mL) to extract the product from the aqueous bicarbonate solution, a white solid was obtained. This was suspended in diethyl ether, collected by filtration, washed with diethyl ether to give the diamide **2** as a white solid (2.05 g, 59%). Mp 177–178 °C; Found: C, 68.7; H, 5.2; N 15.9. $C_{20}H_{18}N_4O_2 \cdot {}^1\!/_4\ H_2O$ requires C, 68.45; H, 5.3; N 16.0%; max(KBr disk)/cm^{-1} 3307, N–H *str.* (asym.); 3062, N–H *str.* (sym.); 1646, C=O *str.*; 1601, C=C *str.* and 1547, N–H *bend*; ^{1}H (500 MHz; acetone-d_6; Me_4Si) δ=4.60 (4H, d, ^3J=5.9 Hz, ϕ-*CH*$_2$NH), 7.27–7.29 (3H, m, H4, H5, H6), 7.39 (1H, s, H2), 7.78 (4H, d, ^3J=4.5 Hz, pyH3, pyH5), 8.51 (2H, br s, NH) and 8.70 (4H, d, ^3J=7.6 Hz, pyH2, pyH6); ^{13}C (125 MHz; acetone-d_6; Me_4Si) δ=43.8, 122.0, 127.2, 127.5, 129.4, 140.4, 142.6, 151.3 and 165.8; *m*/*z* (APCI) 347 (MH^+, 100%). Crystals of **2** were obtained from slow evaporation of a methanol solution of **2** and copper nitrate.

*4.2.4. N,N′-[1,4-Phenylenebis(methylene)]bis-3-pyridinecarboxamide, **3***

Following the general procedure described, a white solid was obtained after quenching the reaction with aqueous bicarbonate solution. This was collected by filtration, washed with dichloromethane, ethanol and diethyl ether and dried under suction to give **3** (1.35 g, 39%). The filtrate was poured into a separating funnel, the chlorinated layer separated and the aqueous layer extracted with dichloromethane–methanol (95:5, 3×200 mL). The combined extracts were dried over $MgSO_4$ and the solvent removed to give

a white solid. The solid was suspended in dichloromethane (ca. 10 mL), collected by filtration, washed with diethyl ether to give further diamide **3** as a white solid (540 mg, 16%, combined yield 1.89 g, 55%). Mp 203.5–205.5 °C; Found: C, 67.5; H, 5.2; N 15.5. $C_{20}H_{18}N_4O_2 \cdot {}^1/_2\ H_2O$ requires C, 67.6; H, 5.4; N 15.8%; max(KBr disk)/cm^{-1} 3332, N–H *str.* (asym.); 3060, N–H *str.* (sym.); 1639, C=O *str.*; 1592, C=C *str.* and 1542, N–H *bend*; ^{1}H (500 MHz; acetone-d_6; Me_4Si) δ=4.60 (4H, d, ^3J=5.8 Hz, ϕ-CH_2NH), 7.36 (4H, s, H2, H3, H5, H6), 7.47 (2H, dd, ^3J=4.8, 7.9 Hz, pyH5), 8.25 (2H, dt, ^3J=7.9 Hz, pyH4), 8.40 (2H, br s, NH), 8.69 (2H, d, ^3J=4.8 Hz, pyH6) and 9.10 (2H, d, ^2J=1.8 Hz, pyH2); ^{13}C (125 MHz; acetone-d_6; Me_4Si) δ=43.8, 124.2, 128.7, 131.2, 135.6, 139.1, 149.4, 152.8 and 165.8; *m*/*z* (APCI) 347 (MH^+, 100%). Crystals of **3** were obtained from a methanol–acetonitrile solution of **3** and silver hexafluorophosphate by slow evaporation.

4.2.5. *N,N′-[1,4-Phenylenebis(methylene)]bis-4-pyridinecarboxamide,* ***4***

Following the general procedure described (on a smaller scale: isonicotinoyl chloride hydrochloride 8.43 mmol; 1,4-xylenediamine 4.15 mmol), a white solid was obtained after quenching the reaction with aqueous bicarbonate solution. This was collected by filtration, washed with dichloromethane, ethanol and diethyl ether and dried under suction to give **4** (783 mg, 54%). The filtrate was poured into a separating funnel, the chlorinated layer separated and the aqueous layer extracted with dichloromethane–methanol (9:1, 4×100 mL). The combined extracts were dried over $MgSO_4$ and the solvent removed to give further **4** as an oily solid. This was suspended in dichloromethane (ca. 10 mL) to give a white solid, collected by filtration, washed with diethyl ether to give further diamide **4** (527 mg, 37%; combined yield 1.31 g, 91%). Mp 197–199 °C; Found: C, 67.0; H, 5.3; N 15.6. $C_{20}H_{18}N_4O_2 \cdot 2/3H_2O$ requires C, 67.0; H, 5.45; N 15.6%; max(KBr disk)/cm^{-1} 3287, N–H *str.* (asym.); 3062, N–H *str.* (sym.); 1640, C=O *str.*; 1600, C=C *str.* and 1540, N–H *bend*; ^{1}H (500 MHz; acetone-d_6; Me_4Si) δ=4.59 (4H, d, ^3J=5.7 Hz, ϕ-CH_2NH), 7.35 (4H, s, H2, H3, H5, H6), 7.80 (4H, d, ^3J=4.5 Hz, pyH3, pyH5), 8.48 (2H, br s, NH) and 8.71 (4H, d, ^3J=4.5 Hz, pyH2, pyH6); ^{13}C (125 MHz; acetone-d_6; Me_4Si) δ=43.2, 121.4, 128.1, 138.4, 142.0, 150.7 and 165.2; *m*/*z* (APCI) 385 (MK^+, 100%), 369 (MNa^+, 22), 347 (MH^+, 90). Crystals of **4**·1/3(CD_3COCD_3) were obtained from a concentrated acetone-d_6 solution of **4** by slow evaporation, while crystals of **4**·2(H_2O) were obtained from a solution of **4** and silver trifluoroacetate dissolved in methanol and acetonitrile.

4.2.6. *N,N′-Bis(3-pyridylmethyl)benzene-1,3-dicarboxamide,* ***5***

In a similar approach to the syntheses of **1**–**4**, phthaloyl chloride (2.03 g, 10.1 mmol) was dissolved in dichloromethane (20 mL). 3-Pyridylmethylamine (2.1 mL, 20.6 mmol) and triethylamine (2.9 mL, 20.9 mmol) dissolved in dichloromethane (20 mL) were added slowly and the resulting solution stirred for 48 h to give the diamine **5** as a white solid (2.29 g, 65%) following work-up in the usual manner. Mp 148–149 °C; Found: C, 69.35; H, 5.3; N 16.5. $C_{20}H_{18}N_4O_2$ requires C, 69.3; H, 5.25; N 16.2%; max(KBr disk)/cm^{-1} 3268, N–H *str.* (asym.); 3055, N–H *str.* (sym.); 1665, C=O *str.*; 1631, C=C *str.*; 1579, N–H *bend* and 1541, N–H *bend* (*1*°); ^{1}H (500 MHz; acetone-d_6; Me_4Si) δ=4.64 (4H, d, ^3J=5.7 Hz, pyCH_2NH), 7.31 (2H, dd, ^3J=4.8, 7.7 Hz, pyH5), 7.56 (1H, t, ^3J=7.8 Hz, H5), 7.78 (2H, dt, ^3J=7.8 Hz, pyH4), 8.07 (2H, d, ^3J=7.8 Hz, H4, H6), 8.42 (1H, t, H2), 8.46 (2H, d, ^3J=4.7 Hz, pyH6), 8.50 (2H, br s, NH) and 8.62 (2H, d, pyH2); ^{13}C (125 MHz; acetone-d_6; Me_4Si) δ=41.8, 124.2, 127.0, 129.5, 130.8, 135.8, 135.9, 136.1, 149.3, 150.3 and 166.9; *m*/*z* (APCI) 347 (MH^+, 100%).

4.2.7. *N,N′-2,6-Bis(3-pyridylmethyl)pyridine dicarboxamide* ***6***

2,6-Dimethylpyridine dicarboxylate (489 mg, 2.50 mmol) and a slight excess of 3-aminomethylpyridine (0.56 mL, 5.49 mmol) were refluxed under nitrogen in toluene (20 mL) for 18 h. The solution was cooled to room temperature and the solvent removed on the rotary evaporator. The oily residue was dissolved in dichloromethane (75 mL), washed with saturated $NaHCO_3$ solution (2×50 mL), dried over $MgSO_4$ and taken to dryness. This gave a pale yellow oil that solidified on standing. The solid was suspended in hot diethyl ether (10 mL), collected by filtration, washed with a further quantity of diethyl ether (10 mL) and dried in vacuo to give **6** as a white solid (659 mg, 76%). Mp 164–166 °C; Found: C, 64.4; H, 5.1; N 19.5. $C_{19}H_{17}N_5O_2 \cdot {}^1/_2\ H_2O$ requires C, 64.0; H, 5.1; N 19.65%; max(KBr disk)/cm^{-1} 3259, N–H *str.* (asym.); 3090, N–H *str.* (sym.); 1677, C=O *str.* and 1532, N–H *bend* (*1*°); ^{1}H (500 MHz; $CDCl_3$; Me_4Si) δ=4.47 (4H, d, ^3J=6.2 Hz, pyCH_2NH), 7.18 (2H, dd, ^3J=4.8, 7.7 Hz, pyH5′), 7.58 (2H, d, ^3J=7.8 Hz, pyH4′), 8.09 (1H, t, ^3J=7.8 Hz, pyH4), 8.19 (2H, d, pyH2′), 8.43 (4H, m, pyH3, pyH5, pyH6′) and 8.86 (1H, t, ^3J=6.0 Hz, NH); (500 MHz; acetone-d_6; Me_4Si) δ=4.62 (4H, d, ^3J=6.1 Hz, ϕ-CH_2NH), 7.30 (2H, dd, ^3J=4.8, 7.8 Hz, pyH5′), 7.71 (2H, dt, ^3J=7.8, pyH4′), 8.24 (1H, t, ^3J=6.9 Hz, pyH4), 8.36 (2H, d, ^3J=6.9 Hz, pyH3, pyH5), 8.46 (2H, d, ^3J=4.8 Hz, pyH6′), 8.66 (2H, d, pyH2′) and 9.23 (2H, br s, NH); ^{13}C (125 MHz; $CDCl_3$; Me_4Si) δ=40.7, 123.8, 125.5, 134.3, 136.0, 139.2, 148.7, 148.8, 148.9 and 163.9; *m*/*z* (APCI) 348 (MH^+, 100%). Crystals were obtained by slow evaporation of a dichloromethane solution of **6**.

4.2.8. *N,N′-2,6-Bis(4-pyridylmethyl)pyridine dicarboxamide* ***7***

In a similar approach to the synthesis of **6**, 2,6-dimethylpyridine dicarboxylate (780 mg, 4.00 mmol) and a slight excess of 4-aminomethylpyridine (1.12 mL, 11.0 mmol) were refluxed under nitrogen in toluene (30 mL) for 120 h. The solution was cooled to room temperature and the solvent removed on the rotary evaporator. The oily residue was dissolved in dichloromethane (100 mL), washed with saturated $NaHCO_3$ solution (2×50 mL), dried over $MgSO_4$ and taken to dryness. This gave a pale yellow oil that was triturated with hot ethyl acetate, collected by filtration, washed with diethyl ether (10 mL) and dried in vacuo to give **6** as a cream solid (549 mg, 40%). Mp 142–3 °C; Found: C, 65.7; H, 4.9; N 20.2. $C_{19}H_{17}N_5O_2$ requires C, 65.7; H, 4.9; N 20.2%; max(KBr disk)/cm^{-1} 3260, N–H *str.* (asym.); 1761, C=O *str.* and 1533, N–H *bend* (*1*°); ^{1}H (300 MHz; $CDCl_3$; Me_4Si) δ=4.54 (4H, d, ^3J 6.3 Hz, pyCH_2NH), 7.03 (4H, d, ^3J 5.9 Hz, H3′, H5′), 8.13 (1H, t, ^3J 8.0 Hz, H4), 8.36 (4H, d, ^3J 6.0 Hz, H2′, H6′), 8.46 (2H, d, ^3J 6.0 Hz, H3, H5), 9.00 (2H, t, ^3J 6.3 Hz, NH); ^{13}C (125 MHz; $CDCl_3$; Me_4Si) δ=42.1, 122.4, 125.6, 139.3, 147.6, 148.5, 149.6 and 164.0; *m*/*z* (ES-MS) 348.4 (MH^+, 100%). Crystals were obtained by slow evaporation of an ethyl acetate solution of **7**.

4.2.9. *N-6-[(3-Pyridylmethylamino)carbonyl]-2-pyridinecarboxylic acid methyl ester* ***8***

A suspension of 2,6-dimethylpyridine dicarboxylate (1.96 g, 10.0 mmol) and 3-aminomethylpyridine (1.00 mL, 10.0 mmol) was refluxed in toluene (40 mL) for 24 h. The toluene was removed in vacuo, the residue was redissolved in dichloromethane (100 mL), washed with dilute hydrochloric acid (0.2 M, 2×50 mL) and the dichloromethane layer discarded. The aqueous extract was neutralized with sodium bicarbonate, extracted with dichloromethane (3×50 mL), dried over sodium sulfate and the solvent removed in vacuo. The resulting residue was purified by flash column chromatography on silica gel eluting with 1:9 methanol–CH_2Cl_2 to give **8** as an oil. Triturating the oil with hot diethyl ether gave a cream solid (1.62 g, 59%). Mp 87 °C; Found: C, 62.0; H, 4.9; N 15.5. $C_{14}H_{13}N_3O_3$ requires C, 62.0; H, 4.8; N 15.5%; max(KBr disk)/cm^{-1} 3505 O–H *str.*; 3283, N–H *str.* (asym.); 1731, 1661, C=O *str.* and 1533, N–H *bend* (*1*°); ^{1}H (300 MHz; $CDCl_3$; Me_4Si) δ=4.00 (3H, s, OCH_3), 4.72 (2H, d, ^3J=6.3 Hz, pyCH_2NH), 7.27 (1H, m, pyH5′, overlapped with $CHCl_3$), 7.73 (1H, d, ^3J=7.8 Hz, pyH4′), 8.04 (1H, t, ^3J=7.8 Hz, pyH4), 8.25 (1H, d, ^3J=7.8 Hz, pyH3 or pyH5), 8.43 (1H, d, ^3J=7.8 Hz, pyH3 or pyH5), 8.55 (2H, m, pyH6′, NH) and 8.65 (1H, s, pyH2′); ^{13}C

(125 MHz; acetone-d_6; Me_4Si) δ=40.9, 52.9, 123.5, 125.5, 127.4, 133.7, 135.6, 138.6, 146.5, 148.9, 149.2, 149.7, 163.6 and 164.8; *m*/*z* (ES-MS) 272.1 (MH^+, 72%).

4.2.10. *N*-6-[(4-Pyridylmethylamino)carbonyl]-2-pyridinecarboxylic acid methyl ester **9**

A suspension of 2,6-dimethylpyridine dicarboxylate (3.92 g, 20.0 mmol) and 4-aminomethylpyridine (2.00 mL, 20.0 mmol) was refluxed in toluene (80 mL) for 36 h. The toluene was removed in vacuo, the residue was redissolved in dichloromethane (100 mL), washed with dilute hydrochloric acid (0.2 M, 2×100 mL) and the dichloromethane layer discarded. The aqueous extract was neutralized with sodium bicarbonate, extracted with dichloromethane (3×100 mL), dried over sodium sulfate and the solvent removed in vacuo. The resulting residue was purified by flash column chromatography on silica gel eluting with 1:9 methanol–CH_2Cl_2 to give **9** as an oil, which solidified on standing. The solid was sonicated in diethyl ether, collected by filtration and dried to give a cream solid (3.71 g, 68%). Mp 129–30 °C; Found: C, 62.0; H, 4.9; N 15.5. $C_{14}H_{13}N_3O_3$ requires C, 62.1; H, 4.9; N 15.6%; max(KBr disk)/cm^{-1} 3284, N–H *str.* (asym.); 1712, 1673, C=O *str.*; 1600, N–H *bend* and 1561, N–H *bend* (*1*°); ^1H (300 MHz; $CDCl_3$; Me_4Si) δ=4.01 (3H, s, OCH_3), 4.72 (2H, d, ^3J=6.5 Hz, pyCH_2NH), 7.28 (overlapped with residual $CHCl_3$, 2H, m, pyH3′, pyH5′), 8.05 (1H, t, ^3J=7.8 Hz, pyH4), 8.27 (1H, d, ^3J=7.8 Hz, pyH5), 8.43 (1H, d, ^3J=7.8 Hz, pyH3) and 8.57 (3H, m, pyH2′, pyH6′, NH); ^{13}C (125 MHz; $CDCl_3$; Me_4Si) δ=42.3, 53.0, 122.3, 125.6, 127.6, 138.7, 146.6, 147.1, 149.6, 150.0, 150.1 and 163.8; *m*/*z* (APCI) 272 (MH^+, 100%).

4.2.11. *N,N′*-2′-Propyl-6-(3-pyridylmethyl)pyridine dicarboxamide, **10**

A solution of **8** (271 mg, 1.00 mmol) and propylamine (0.41 mL, 5.0 mmol) was heated in toluene (10 mL) at 45 °C for 96 h. After 24 h further propylamine (0.41 mL, 5.0 mmol) was added. The solution was evaporated to dryness to give a residue that was dissolved in dichloromethane (50 mL), washed with water (50 mL), brine (50 mL), dried over sodium sulfate and the chlorinated solvent removed on the rotary evaporator. The oily solid was triturated with hot diethyl ether, the resulting cream solid collected by filtration, washed with further diethyl ether and dried in vacuo to give **8** (202 mg, 68%). Mp 118–20 °C; Found: C, 63.3; H, 6.1; N 18.5. $C_{16}H_{18}N_4O_2 \cdot {}^1/_4\ H_2O$ requires C, 63.4; H, 6.2; N 18.5%; max(KBr disk)/cm^{-1} 3308, N–H *str.* (asym.); 2962, 2933, C–H *str.*; 1677, C=O *str.*; 1603, C=C *str.*; 1532, N–H *bend*; ^1H (300 MHz; $CDCl_3$; Me_4Si) δ=0.94 (3H, t, ^3J=7.4 Hz, CH_3), 1.62 (overlapped with water, 2H, $CH_2CH_2CH_3$), 3.41 (2H, q, ^3J=6.3, 7.9 Hz, CH_2CH_2NH), 4.71 (2H, d, ^3J=6.3 Hz, pyCH_2NH), 7.29 (overlapped with residual $CHCl_3$, 1H, pyH5′), 7.74 (1H, d, ^3J=7.8 Hz, pyH4′), 7.83 (1H, br s, CH_2CH_2NH), 8.06 (1H, t, ^3J=7.9 Hz, pyH4), 8.24 (1H, br s, pyCH_2NH), 8.39 (2H, m, pyH3, pyH5), 8.55 (2H, m, pyH2, pyH6); ^{13}C (125 MHz; $CDCl_3$; Me_4Si) δ=11.4, 22.9, 40.8, 41.2, 123.8, 125.1, 125.3, 134.1, 135.9, 139.1, 148.3, 148.9, 149.0, 149.2, 163.5 and 163.9; *m*/*z* (ES-MS) 299.2 (MH^+, 92%), 321.1 (MNa^+, 14%).

4.2.12. *N,N′*-2′-Propyl-6-(4-pyridylmethyl)pyridine dicarboxamide, **11**

A solution of **9** (271 mg, 1.00 mmol) and propylamine (0.41 mL, 5.0 mmol) in toluene was heated at 45 °C for 96 h. After 24 h further propylamine (0.41 mL, 5.0 mmol) was added. The solution was evaporated to dryness to give a residue that was dissolved in dichloromethane (50 mL), washed with water (50 mL), brine (50 mL), dried over sodium sulfate and the chlorinated solvent removed on the rotary evaporator. Purification by flash column chromatography on silica gel eluting with 1:9 methanol–dichloromethane gave an oil. Triturating the oil with hot diethyl ether gave **11** as a cream solid (173 mg, 58%). Mp 122–3 °C;

Table 1
Selected details of data collections and structure refinements

	1·$CDCl_3$	**2**	**3**	**4**·1/3(CD_3COCD_3)	**4**·2(H_2O)	(**6**)$_2$·H_2O	**7**·2(H_2O)
Formula	$C_{21}H_{19}N_4O_2Cl_3$	$C_{20}H_{18}N_4O_2$	$C_{20}H_{18}N_4O_2$	$C_{21}H_{20}N_4O_{2.33}$	$C_{20}H_{22}N_4O_4$	$C_{38}H_{36}N_{10}O_5$	$C_{19}H_{21}N_5O_4$
M_r	465.75	346.38	346.38	365.74	382.42	712.77	383.41
Crystal size [mm]	0.28×0.16×0.01	0.44×0.34×0.09	0.14×0.13×0.02	0.57×0.10×0.04	0.39×0.36×0.07	0.50×0.18×0.10	0.37×0.28×0.20
Crystal system	Monoclinic	Monoclinic	Monoclinic	Rhombohedral	Monoclinic	Triclinic	Triclinic
Space group	$P2_1/c$	$P2_1/n$	$C2/c$	R-3	$P2_1/n$	P-1	P-1
a [Å]	13.9605(14)	14.1257(14)	18.927(2)	30.3830(10)	7.207(4)	9.6258(14)	9.353(3)
b [Å]	8.4423(8)	7.8617(8)	9.9021(11)		9.247(5)	12.9603(19)	10.466(2)
c [Å]	18.8676(18)	15.8007(15)	9.5588(10)	5.1056(3)	14.107(7)	14.756(2)	10.821(2)
α [°]						89.048(8)	95.734(5)
β [°]	103.885(4)	98.955(4)	117.295(4)		101.15(2)	72.082(8)	102.105(5)
γ [°]						88.131(8)	113.250(5)
V [Å^3]	2158.7(4)	1733.3(3)	1592.0(3)	4081.7(3)	922.3(8)	1750.6(4)	931.7(3)
Z	4	4	4	8	2	2	2
ρ_{calcd} [g cm^{-3}]	1.433	1.327	1.445	1.339	1.377	1.352	1.367
μ [cm^{-1}]	0.450	0.089	0.097	0.090	0.098	0.093	0.099
F000	960	728	728	1734	404	748	404
θ range [°]	2.22–25.00	1.80–27.50	2.39–26.54	2.32–30.18	2.65–26.50	1.45–27.66	2.16–36.57
Unique data, R_{int}	3749 [0.0492]	3958 [0.0233]	1647 [0.0403]	2676 [0.0361]	1889 [0.0392]	7942 [0.0615]	8717 [0.0265]
Obsd data [I>2σ(I)]	2959	3429	1233	2085	1489	6105	7334
No. parameters	271	235	118	133	135	478	265
R_1 [obsd data]	0.0334	0.0357	0.0406	0.0518	0.0348	0.1225	0.0487
wR_2 [all data]	0.0776	0.1328	0.1021	0.1291	0.0906	0.3597	0.1400
GOF	1.034	1.097	1.041	1.051	1.091	1.067	1.064

Found: C, 64.4; H, 6.3; N 18.8. $C_{16}H_{18}N_4O_2$ requires C, 64.4; H, 6.1; N 18.8%; max(KBr disk)/cm^{-1} 3505 O–H *str.*; 3288, N–H *str.* (asym.); 2956, 2932, C–H *str.*; 1665, C=O *str.*; 1533, N–H *bend*; ^{1}H (300 MHz; $CDCl_3$; Me_4Si) δ=0.96 (3H, t, ^3J=7.3 Hz, CH_3), 1.63 (overlapped with water, 2H, $CH_2CH_2CH_3$), 3.42 (2H, q, ^3J=6.3, 8.0 Hz, CH_2CH_2NH), 4.72 (2H, d, ^3J=6.4 Hz, pyCH_2NH), 7.24 (1H, d, ^3J=5.9 Hz, pyH3′, pyH5′), 7.88 (1H, br s, CH_2CH_2NH), 8.08 (1H, t, ^3J=7.8 Hz, pyH4), 8.25 (1H, br s, pyCH_2N*H*), 8.41 (2H, m, pyH3, pyH5), 8.55 (2H, d, ^3J=5.9 Hz, pyH2, pyH6); ^{13}C (125 MHz; $CDCl_3$; Me_4Si) δ=11.4, 22.9, 41.3, 42.2, 122.3, 125.2, 125.5, 139.1, 147.5, 148.2, 149.2, 149.8, 163.4 and 164.0; *m*/*z* (ES-MS) 299.0 (MH^+, 30%), 321.7 (MNa^+, 14%).

4.3. X-ray crystallography

Crystals were mounted under oil on a glass fibre and X-ray diffraction data collected at 90(2) K with Mo Kα radiation (λ=0.71073 Å) using a Bruker-AXS Single Crystal Diffraction System fitted with an Apex II CCD detector. Data sets were corrected for absorption using a multi-scan method, and structures were solved by direct methods using SHELXS-97[32] and refined by full-matrix least squares on F^2 by SHELXL-97,[33] interfaced through the program X-Seed.[34] In general, all non-hydrogen atoms were refined anisotropically and hydrogen atoms were included as invariants at geometrically estimated positions, unless specified otherwise in additional details below. Details of data collections and structure refinements are given in Table 1. CCDC-705849 to 705855 contain the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

Additional notes on refinement for ***4***$\cdot 1/3(CD_3COCD_3)$. The acetone-d_6 solvate molecule within the channels of the structure lies on a special position.

Additional notes on refinement for $(\mathbf{6})_2\cdot H_2O$. The hydrogen atoms on the water solvate molecule could not be located in the difference map. A residual electron density peak (1.47 e Å^3) lies adjacent to one of the hydrogen atoms of a pyridine ring.

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