Symmetrical Diamides Based on 2,6-Bis(methoxycarbonyl)pyridine: Syntheses and Metal Ion Binding Studies

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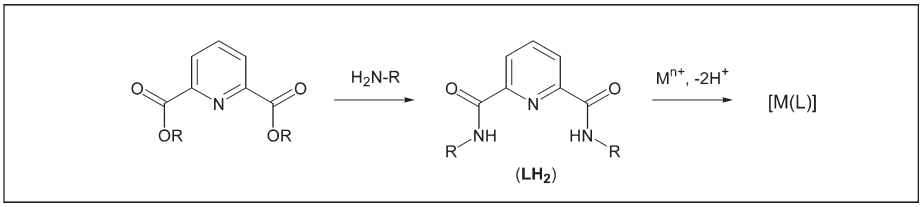

Symmetrically-armed molecules based on a 2,6-diamidopyridine core, 2,6-bis[*N*-(1′-piperidinylethyl)-carbamyl]pyridine (**1**), 2,6-bis[*N*-(1′-piperazinylethyl)carbamyl]pyridine (**2**), 2,6-bis[*N*-2′-(5″-nitropyridine)-1′-azapropyl)carbamyl]pyridine (**3**), 2,6-bis[*N*-(3′-hydroxypropyl)carbamyl]pyridine (**4**), 2,6-bis[*N*-(5′-hydroxy-3′-azapentyl)carbamyl]pyridine (**5**), 2,6-bis[*N*-2′-oxo-2′,3′-dihydropyrimidin-4′-yl)carbamyl]-pyridine (**6**) as well as the thioamide analogue 2,6-bis[(S-2′-pyridinyl)carbothiyl]pyridine (**7**) have been prepared and characterized. An X-ray crystal structure of **1** confirms its formation. These molecules are potentially multidentate ligands for metal ions, and complexation has been probed through spectroscopic characterization, particularly by electrospray ionization mass spectrometry, and isolation of some first-row transition metal complexes. The ligands, with potentially coordinating arms extending from each amide, dominantly form simple 1:1 M:L complexes. They show no tendency toward polynuclear helicate formation.

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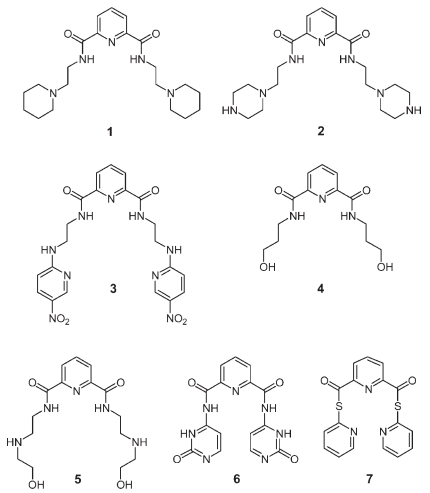
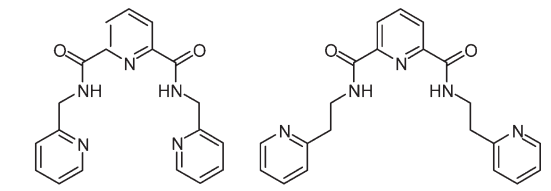
INTRODUCTION

Development of molecules that contain pyridine-2-carboxamido functionality within larger frameworks have been vigorously pursued in recent years [1–7]. Molecules with a —HN—OC—pyridine—CO—NH— core have found wide application, ranging from use in electroluminescent devices to oxidation catalysts. Recently, systems based on a 2,6-diamidopyridine core that support helicate metal complex formation have been developed [3,6,8], and represent a novel extension of this chemistry. This type of structure appears to arise in systems with aromatic nitrogen heterocycles terminating the two pendant arms, where favorable π-π stacking interactions support oligomer self-assembly. It is therefore of interest to develop and examine examples of symmetrical molecules with different potentially chelating arms, here 2,6-bis[*N*-(1′-piperidinylethyl)carbamyl]-pyridine (**1**), 2,6-bis[*N*-(1′-piperazinylethyl)carbamyl]-pyridine (**2**), 2,6-bis[*N*-(2′-(5″-nitropyridine)-1′-azapropyl)carbamyl]pyridine (**3**), 2,6-bi[*N*-(3′-hydroxypropyl) carbamyl]pyridine (**4**), and 2,6-bis[*N*-(5′-hydroxy-3′-azapentyl)carbamyl]pyridine (**5**). To extend the examination further, we have prepared two examples without methylene linkages in the arms, 2,6-bis[*N*-(2′-oxo-2′,3′-dihydropyrimidin-4′-yl)carbamyl]pyridine (**6**) and the thioamide analogue 2,6-bis[*S*-(2′-pyridyl)carbothiyl]pyridine (**7**).

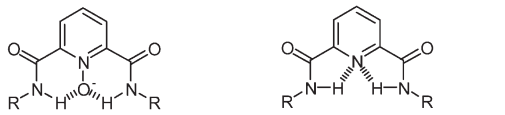


While 2,6-bis[*N*-(2′-pyridylmethyl)carbamyl]pyridine (**8**) has a strong tendency to form helical species on

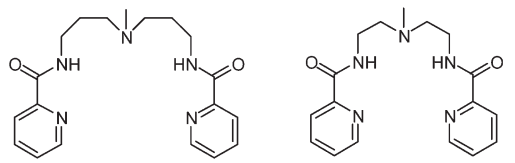
metal ion complexation [8], the longer-chain analogue **9** shows no tendency toward helicate formation [9], suggesting that forces that control helicate formation are subtle. Further, although **8** displays no chirality as a free ligand [10], adopting the *syn*, *syn* conformation resulting from intramolecular hydrogen bonding, a bisoxazoline analogue adopts a helical superstructure in the crystal even when a metal is absent [11]. Combining strands containing heteroatoms with a core subunit containing a heteroatom such as **10** or **11** can lead in a very simple way to structures where a helical conformation is stabilized by a network of intramolecular hydrogen bonds [12]. Whether this capacity for helicate formation, either as free or complexed species, also extends to systems with aliphatic side chains reported here was one factor driving this study. Complexation of the new molecules reported here is explored in part with a view to probing stoichometry and to explore the thesis that terminating saturated amine and alcohol groups, although capable of strong hydrogen bonding interactions, do not tend to support the formation of helicates because they have no π-π stacking ability.



8 **9**



10 **11**



12 **13**

RESULTS AND DISCUSSION

Synthesis of diamides. The new symmetrically armed compounds have been prepared using as the core reagent 2,6-bis(methoxy-carbonyl)pyridine, reacting with an amine. Conventional reflux in an organic solvent was not always successful, and a microwave reactor was used in some cases to drive the reaction to completion. For example, the synthesis of **2** was not achieved by refluxing in toluene, even for extended periods; the product obtained after 3 days reflux was assigned as a mixture of the diester precursor and the one-armed monoamide, from spectroscopy. However, solvent-free reaction conducted in a microwave proved successful. Possibly, reaction with an acid chloride rather than an ester may have been more successful conventionally, but the microwave technology supplied the answer to low reactivity without the need to change the key reagent; yields of up to 90% were achieved. Only with the synthesis of the thioamide 7, where a thiol rather than an amine is involved in the reaction, was the acid chloride approach necessarily adopted.

Compounds isolated were all microanalytically pure and readily characterized spectroscopically. For example, with diamide **1**, the NMR spectra are fully consistent with the structure assigned. The proton-decoupled ^{13}C spectrum displays nine peaks (five methylene, three aromatic and one amide carbon resonances), as expected for the symmetric diamide. The methylenes on the piperidine ring can be assigned unambiguously, with large signals at δ 54.1 and 25.0 ppm associated with the equivalent pairs of —***C***H_2—N— and adjacent —C—***C***H_2—C, respectively, and the remaining single central methylene found at 23.5 ppm. The two remaining methylenes of the aminoethyl chain are at 35.5 (—***C***H_2—N_{sec}) and 58.4 (—***C***H_2—NHCO—) ppm. By analogy to the spectra of the known diamide **8** and the diester precursor, the aromatic resonances can be assigned to the single ***C***H opposite the N group (138.0), the adjacent equivalent pair of ***C***H groups (124.0) and the equivalent pair of tertiary ***C*** (148.3), with the amide resonance at 163.4 ppm. Assignment in the ^1H NMR spectrum is facile from comparison with known analogues. Three resonances in the aromatic region display a ratio of 2:2:1, with the —NH—CO— resonance (a broadened triplet) at δ 9.17 ppm. Other resonances at 7.98 and 8.30 ppm are assigned to the protons of the single CH opposite the N group and the adjacent equivalent pair of CH groups, respectively. A set of resonances between δ 1.5 and 4.2 ppm arise from the 14 methylene protons, all of which are coupled, yielding a complex pattern that is not fully resolved. The set of methylenes in **1** give rise to strong resonances in the IR spectrum between 2760 and 2930 cm^{-1}. A strong —CO— resonance also occurs at 1658 cm^{-1}, with other —NHCO— bands at 1538 and 1444 cm^{-1}. The most characteristic pyridine resonances are those at 753 and 644 cm^{-1}. In the electrospray ionization mass spectrometry (ESI-MS), the species $\mathbf{1}\cdot H^+$ is observed at *m*/*z* 388 (calc. 388), with a minor peak due to the dihydrate at *m*/*z* 424. Details for other compounds prepared appear in summary form in the Experimental section.

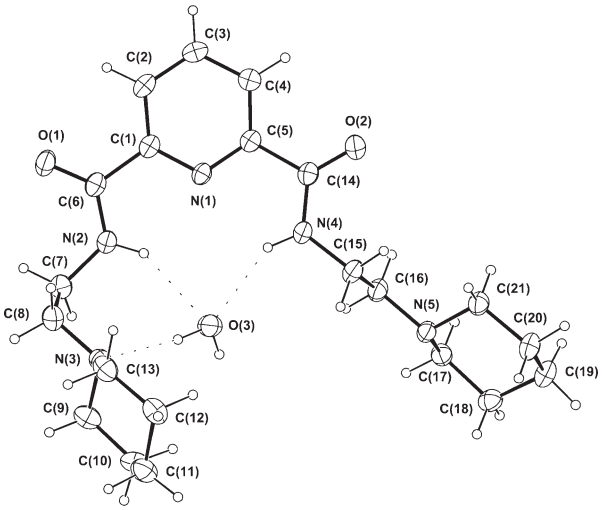


Figure 1. An ORTEP view of **1**, with 50% displacement ellipsoids.

An X-ray crystal structure analysis of **1** confirms the proposed connectivity in this molecule (Fig. 1), with distances and angle that are typical of these types of systems. The C—N distances to pyridine N (av. 1.339 Å), amide N (av. 1.335 Å to CO, av. 1.451 Å to CH_2), and tertiary amine (av. 1.469 Å) are consistent with the character of these groups. The pyridine ring is essentially planar, with the piperidine rings in chair conformations. The water molecule (O(3)) is structurally important, being strongly hydrogen-bonded to amide protons (HN(2) and HN(4)) and to the piperidine nitrogen (N(3)) of one of the two pendant arms. The N(2)H...O(3) and N(4)H...(O(3) distances are 1.331 and 1.450 Å, with the O(3)H....N(3) distance 1.473 Å. This water molecule is not only intramolecularly bonded to **1** but is also connected intermolecularly to an adjacent molecule, building a chain parallel to the *c*-axis. The arm that is not hydrogen-bonded (which includes N(5)) is displaced well away from the water molecule, with C—N_{tert} distances slightly longer (~10 pm) for the hydrogen-bonded compared with the nonbonded arm. Helicity seen in some aromatic-rich examples is not evident here.

The product **2** is anticipated to be spectroscopically somewhat similar to **1**, because the sole difference is the replacement of the methylene opposite the tertiary amine in the six-membered ring by an —NH— group, reducing the number of inequivalent carbons from nine to eight. Aromatic resonances occur at δ 124.4 (124.0 in **1**), 139.3 (138.0 in **1**), and 147.4 (C_{tert}, 148.3 in **1**), with the amide C at 164.9 ppm (163.4 in **1**). Methylenes in the aliphatic ring are unambiguously defined by their intensity, and occur at 43.3 and 51.5 ppm. Notably, the equivalent methylenes occur at 25.0 and 54.1 ppm in **1**, with the significant shift of one methylene here arising from transition for one equivalent pair from a —C—$\boldsymbol{C}H_2$—C— to a —C—$\boldsymbol{C}H_2$—N— environment, as required in the structure. Other methylenes in the chain linking to the amide have resonances at 35.5 and 56.1 ppm. Notable in the ^{1}H NMR is the absence of any resonance above 2.2 ppm, fully consistent with there being no —C—CH_2—C— entities. A complex pattern of peaks occur from 2.3 to 3.6 ppm for the methylene groups, with the two types of pyridine protons found at 7.95 and 8.08 ppm. In the ESI-MS, the species **2**·H^+ is dominant at *m*/*z* 390.

The synthesis of **3** is of interest because it has pyridine groups terminating the chains and thus provides an extension of the series from a compound with a one atom chain, **8**, and a two atom chain, **9**, to now a three atom chain, joining each terminal pyridine group to the amide. Other differences resulting from the commercial precursor used here are the 5-nitro group on the pyridine ring, characterized clearly by IR resonances at 1540 and 1334 cm^{-1}, and an aza group in the propyl chain. Strong amine bands occur at 3280, 3230, and 1590 cm^{-1} in the IR spectrum. The amide group is defined by resonances in the NMR spectra at 161.4 ppm (^{13}C), and 8.84 ppm (^{1}H), analogous to positions in other molecules synthesized. The presence of two magnetically distinctly types of pyridine ring is clear in the ^{13}C NMR, with a complex set of resonances, some overlapping, between 146.6 and 108.4 ppm. Methylene resonances occur at 43.0 and 48.5 ppm. The ^{1}H NMR spectrum displays aliphatic resonances between 2.5 and 3.1 ppm, and aromatic resonances between 6.5 and 8.2 ppm, with protons adjacent to the nitro group being shifted to higher field. In the ESI-MS, the dominant species is **3**·H^+ (*m*/*z* 496).

The aminoalcohol-based ligands **4** and **5** were prepared in good yield by conventional methods. Their spectroscopy has characteristics consistent with their formation. For **4**, the ^{13}C resonances of the aliphatic chains shows the three expected signals at 30.5 (central C—CH_2—C), 36.2 (—CH_2—N—) and 59.0 (—CH_2—OH) ppm, with three resonances from the single pyridine (124.3, 139.3, 147.6 (pyC_{tert}) ppm) and a single carbonyl resonance (165.3 ppm) as required for a symmetrically armed ligand. The alcohol has a characteristic strong IR resonance at 3425 cm^{-1}, apart from the compound showing typical amide bands. The analogue **5** is also spectroscopically consistent with the structure assigned.

The ligand **6**, based on cytosine, forms readily under microwave conditions despite there being possibly greater steric demands as a result of the reacting amine being attached directly to an aromatic ring. Two carbonyl resonances are found in the ^{13}C NMR near 160 ppm, due to the amide and pendant ring carbonyl

groups, as well as a set of six aromatic resonances due to the carbons in the cytosine and pyridine rings.

The final example, **7** is a thioamide; as such, it was appropriate to prepare it by reaction of an acid chloride rather than a diester, due to the different reactivity of the thiol group. This is a very rapid and clean reaction, with the product isolated in high yield. The —CO—S— functionality leads to a shift in the carbonyl resonance in the ^{13}C NMR to near 190 ppm; the presence of aromatic resonances, five from the pendant pyridine and three from the core pyridine, is consistent with the presence of two equivalent chains.

Transition metal complexes. Complexation behavior was probed spectroscopically (particularly by ESI-MS), with only selected examples prepared and isolated as solids. The type of complexes formed by the 2,6-diamidopyridines is influenced by the type of pendant chains present, and the donor groups therein. With Cu(II), all of **1**–**6** apparently form only simple 1:1 complexes in solution from ESI-MS, with several examples isolated as blue-purple solids. For **1**–**5**, the relatively long chains from the amide to the terminal donors suggest sufficient flexibility that would allow the donor groups terminating these arms to bind in addition to the planar $—^{-}N—OC—$pyridine$—CO—N^{-}—$ unit; the two pendant arms donors may thus promote the favored five-coordination. Others symmetric N_5-diamide compounds such as **12** and **13** have been described [13], prepared by a different route. The copper(II) complex of **12** reportedly binds copper(II) ion as a 1:1 M:L species to form a pentadentate mononuclear copper(II) ion. This complex is one of a number of mononuclear copper(II) complexes that contain dicarboxamido ligation in CuN_5 chromophores [9,14], and support the assignment of similar geometries for the present complexes. Unfortunately, crystals suitable for X-ray structure have not been obtained. However, ESI-MS clearly supports simple ML structures and not higher order polymetallic systems. For example, **2** in the presence of $Cu(OAc)_2$ exhibits no peaks that can be assigned to polymetallic species, but a signal at *m*/*z* 479, 481 arises from $[Cu(\mathbf{2})(OAc)]^+$. The ligands **1** and **2** not only have flexible two-carbon chains linking the amide groups to the terminal group, but the terminal group in each case is an aliphatic amine in a nonaromatic ring, unable to stabilize polynuclear assemblies through π-stacking of terminal groups, and are not expected to form helicates.

The way the pendant chains can influence coordination outcomes has been illustrated with **8** and **9**; whereas **8** shows a strong tendency toward helicate formation on complexation, the analogue with a longer methylene chain, **9**, is not known to form helicates [8]. It is not surprising, therefore, that the even longer chain analogue **3** studied here also does not form helicates, from spectroscopic and ESI-MS evidence. For **4** and **5**, with pendant chains terminated by alcohol groups, we also observe no evidence of helicates despite the potential for alcohol groups to be involved in strong hydrogen bonding interactions that could stabilize more complex assemblies. The general observation of only simple 1:1 complexes forming with aliphatic amines or alcohols as arms indirectly supports a key role for π-stacking in helicate assembly.

For **6** and **7**, where no methylene spacer groups separate the amide groups from the pendant rings, there is again no evidence for oligomeric complexes forming. For the copper(II) complex of **6**, binding of at least the central pyridine N and the two amido N is expected, but this has not been explored in any detail at this stage. For **7**, there is limited evidence that complexation was achieved, consistent with the thioamide being a poor donor, disrupting binding by other groups. However, an apparent Zn(II) complex precipitated readily, suggesting that complexation is possible. Although the nature of this species is uncertain, the limited studies show no real evidence for other than simple 1:1 speciation, and hence further examination was not pursued.

Complexation of diamides with nickel(II) usually yield species that are light brown and thus presumably low-spin square-planar d^8 species, also assigned as simple 1:1 monomers from ESI-MS. There is no clear evidence of helicate formation with these ligands and this metal; in solution, ESI-MS shows no peaks assignable to polynuclear species. For example, spectra of mixtures of **1** or **2** with nickel(II) acetate are dominated by peaks due to $Ni(L\text{-}H)^+$ (*m*/*z* 445 and 447 for **1** and **2**, respectively). With **4**, where alone an N_3O_2 donor set is offered, an orange diamagnetic solid was isolated, its magnetic and spectroscopic properties confirming it as a monomeric square-planar species, presumably with one pendant arm unbound. Cobalt(III) complexes of **1** and **3** were prepared to probe the mode of binding of these systems to an inert metal ion strongly favoring octahedral coordination. Simple 1:1 complexes with ligand bound symmetrically to the metal ion are supported, from spectroscopic characterization and comparison with analogues [15], with either *mer*-CoN_3X_3 geometry with pendant amines or as a CoN_5X complex involving binding of all five nitrogen donors found. Complexation of inert octahedral Co(III) by these ligand systems is fully consistent with expected behavior, and the chemistry does not warrant further extension.

CONCLUSION

Synthesis of symmetrically armed diamides based on the 2,6-diamidopyridine core with a range of new

pendants has been established, with microwave synthesis promoting formation of desired products. Consistent with earlier studies, 2,6-diamidopyridines with pendant chains including at least two methylene groups do not undergo helicate formation irrespective of the type of donor group terminating the chains. For aliphatic-terminated molecules like **1** and **2**, loss of the ability of the pendants to participate in π-stacking, found to stabilize helicates with **8**, further restricts the likelihood of helicate formation. It is notable that all known polynuclear helicates of this class of ligand have high levels of aromaticity, and the failure of saturated ligand systems examined here to helicate indirectly supports a role for aromatic groups as structure makers. A more extensive examination of the coordination of these new ligand systems is not warranted, as complexation has been defined adequately here as dominated by simple 1:1 M:L species. Because none of the variety of diamide ligand systems prepared here, irrespective of the type of pendant groups involved, showed a propensity toward helicate formation, the view that stabilization of helicates is not routinely promoted simply because of the presence of the —NHCO—py—CONH— core is supported; this means that the character of the pendant groups is particularly important, as otherwise conventional coordination chemistry results.

EXPERIMENTAL

NMR spectra were recorded on solutions of ligand and complexes, usually in $CDCl_3$ or D_2O, using a Bruker DPX300 spectrometer, whereas FTIR spectra were recorded on a Bio-Rad Win-IR spectrometer with compounds dispersed in KBr disks. UV–Vis spectra were recorded using a Hitachi 150-20 UV–Vis spectrophotometer. ESI-MS were recorded for aqueous or methanolic 10^{-4} *M* solutions, using a Micromass VG Platform II single quadrupole mass spectrometer; experimental peak values are identified by the *m*/*z* ratio of the most abundant peak. Microanalysis was performed by the Microanalytical Unit, A.N.U., Canberra. 2,6-Bis(methoxycarbonyl)pyridine was made as reported in [8].

Diamide syntheses. ***2,6-Bis[N-(1′-piperidinylethyl)carbamyl]pyridine (1).*** 2,6-Bis(methoxycarbonyl)pyridine (5 g, 25.5 mmol) was suspended in toluene (300 mL) and a solution of the 1-(2′-aminoethyl)-piperidine (7.5 g, 58.5 mmol) was added slowly to the stirring solution. The solution was stirred and heated (∼100°C) for 30 min, then refluxed for 24 h. The heat source was removed, the condenser replaced by a $CaCl_2$ drying tube, and stirring continued for another 2 days. Evaporation of solvent yielded a brown oily product. This was twice taken up with diethyl ether and re-evaporated, resulting in a brown sticky solid, which was washed well with water three times and crystallized on standing (1.8 g, 20%). ^{13}C NMR ($CDCl_3$): δ 23.5, 25.1 (—C—**C**H_2—C), 35.7, 54.0, 58.0 (—CH_2—N), 123.9, 137.9 (pyCH), 148.4 (pyC_{tert}), 163.3 (CO) ppm; ^{1}H NMR ($CDCl_3$): δ 1.5–4.2 (m, 28H, —CH_2—), 7.98 (t, 1H, pyH), 8.30 (d, 2H, pyH), 9.17 (t, 2H, —NHCO—); IR: 3470 (OH_2), 3317, 1657, 1538, 1444 (NHCO), 1119, 753, 682 (py) cm^{-1}; ESI-MS (H_2O): *m*/*z* 388 (**1**) H^+). *Anal.* Calcd for $C_{21}H_{33}N_5O_2{\cdot}H_2O$: C, 62.2; H, 8.7; N, 17.5. Found: C, 62.1; H, 8.7; N, 17.2.

2,6-Bis[N-(1′-piperazinylethyl)carbamyl]pyridine (2). Reaction as for **1** was unsuccessful, but using a microwave reactor (Panasonic Dimension 4, Genius NN-C 2000W) proved successful. The diester (1 g, 5.1 mmol) and 1-(2′-aminoethyl)-piperazine (1.44 g, 11.1 mmol) were mixed in a small flask fitted with a microcondenser. The mixture was placed in the microwave for 180 s on high power, and a brown oily product resulted. After standing at room temperature overnight, diethyl ether (20 mL) was added. Further standing for ∼24 h resulted in an oily solid, which was washed with water (50 mL) three times, yielding a light brown solid on drying (1.04 g, 80%). ^{13}C NMR ($CDCl_3$): δ 35.5, 43.3, 51.4, 56.1 (—CH_2—N), 124.4, 139.3 (pyCH), 147.4 (pyC_{tert}), 164.9 (—NHCO—) ppm; ^{1}H NMR ($CDCl_3$): δ 2.3–3.6 (m, 24H, —CH_2—), 4.6 (br m, 2H, —NH—), 7.95 (t, 1H, pyH), 8.08 (d, 2H, pyH), 9.12 (br t, 2H, —NHCO—) ppm; IR: 3475 (OH_2), 3290, 1627 (—NH—), 1608, 1540, 1444 (NHCO), 1080, 763, 690 (py) cm^{-1}; ESI-MS (H_2O): *m*/*z* 390 (**2**·H^+). *Anal.* Calcd for $C_{20}H_{34}N_7O_2 \cdot 1.25H_2O$: C, 56.2; H, 8.8, N, 22.9. Found: C, 55.9; H, 8.8; N, 22.9.

2,6-Bis[N-2′-(5″-nitropyridine)-1′-azapropyl)carbamyl]pyridine (3). 2-(3′-Amino-1′-azapropyl)-5-nitropyridine (2.04 g, 16 mmol) and 2,6-bis(methoxycarbonyl)pyridine (2.0 g, 8 mmol) were mixed in a small flask fitted with a condenser and microwaved for 25 min at medium power. The resulted brown oil was left at room temperature overnight after diethyl ether (30 mL) was added, and the pale yellow solid that formed was washed with water (3 × 50 mL), collected, washed with small amounts of ethanol then diethyl ether in turn, and dried in a desiccator (3.7 g, 74%). ^{13}C NMR ($CDCl_3$): δ 43.0, 48.5 (—CH_2—), 108.4, 124.2, 131.8, 134.2, 134.4 (pyC), 139.4, 146.6, (pyC_{tert}), 161.3 (CO) ppm; ^{1}H NMR ($CDCl_3$): δ 2.5–3.1 (m, 8H, —CH_2), 6.5–8.1 (m, 9H, overlapping pyH), 8.83 (br t, 2H, —NHCO—) ppm; IR: 3470 (OH_2), 1608, 1458 (—NHCO), 1545, 1333 (—NO_2), 1108, 1037, 823, 763, 688 (py) cm^{-1}; ESI-MS (H_2O): *m*/*z* 496 (**3**·H^+). *Anal.* Calcd for $C_{21}H_{21}N_9O_6{\cdot}2H_2O$: C, 47.5; H, 4.8; N, 23.7. Found: C, 47.5; H, 5.1; N, 23.5.

2,6-Bis[N-(3′-hydroxypropyl)carbamyl]pyridine (4). A solution of 2,6-bis(methoxycarbonyl)pyridine (0.975 g, 5 mmol) in toluene (30 mL) was stirred and heated (60°C), and a solution of 3-amino-1-propanol (0.976 g, 13 mmol) in toluene (11 mL) was added slowly. The mixture was heated to ∼100°C using an oil bath and stirred for 1 h, then refluxed for 22 h; some white solid commenced forming after refluxing ∼6 h. Heating was discontinued and slow cooling allowed as the mixture was stirred for a further 24 h at room temperature. During this time, white solid continued to form; this was collected, washed in turn with diethyl ether (3 × 5 mL) and a little chloroform, and air dried (1.36 g, 98%). ^{13}C NMR (D_2O): δ 30.5 (—C—**C**H_2—C), 36.2 (—CH_2—N), 59.0 (—CH_2—O), 124.3, 139.3 (pyCH), 147.7 (pyC_{tert}), 165.3 (CO) ppm; ^{1}H NMR (D_2O): δ 1.89 (m, 4H, —C—CH_2—C), 3.50 (t, 4H, —CH_2—O), 3.69 (t, 4H, —CH_2—N), 8.12 (m, 3H, overlapped pyH); IR: 3425 (OH), 3286, 1659, 1543 (NHCO), 1110, 1072, 1034, 941, 848, 748, 679 (py) cm^{-1}. *Anal.* Calcd for $C_{13}H_{19}N_3O_4{\cdot}{}^1/_4H_2O$: C, 54.6; H, 6.7; N, 14.7. Found: C, 54.6; H, 6.2; N, 14.7.

2,6-Bis[N-(5′-hydroxy-3′-azapentyl)carbamyl]pyridine (5). A solution of 2,6-bis(methoxycarbonyl)pyridine (1.953 g, 10

mmol) in toluene (15 mL) was stirred and heated (85°C), and a solution of 2-(2′-aminoethylamino)ethan-1-ol (2.185 g, 21 mmol) in toluene (5 mL) was added slowly. The mixture was heated to ~100°C and stirred for 0.5 h, then refluxed for 24 h; a yellow oily product commenced forming after ~1 h. The heat was turned off and slow cooling allowed as the mixture was stirred for a further 24 h at room temperature. During this time more product formed; this was collected, washed with a little diethyl ether, redissolved in chloroform (20 mL) and extracted with water (3 ×15 mL). The aqueous phase was collected, and the water was removed by rotary evaporation, resulting in a light yellow oily product (2.4 g, 71 %). ^{13}C NMR (D_2O): δ 39.2, 47.7, 50.2 (—CH_2—N), 60.6 (—CH_2—O), 125.1, 139.9 (pyCH), 148.0 (pyC_{tert}), 165.8 (CO) ppm; ^{1}H NMR (D_2O): δ 2.88 (t, 4H, —CH_2—N), 2.94 (t, 4H, —CH_2—N), 3.61 (t, 4H, —CH_2—N), 3.78 (t, 4H, —CH_2—O), 8.10 (m, 3H, overlapped pyH) ppm; IR: 3480 (OH_2), 3325 (OH), 1651, 1543 (NHCO), 1126, 1057, 918, 849, 748, 671 (py) cm^{-1}. *Anal*. Calcd for $C_{15}H_{25}N_5O_4{\cdot}2H_2O$: C, 47.9; H, 7.8; N, 18.7. Found: C, 47.5; H, 7.8; N, 19.1.

2,6-Bis[N-(2′-oxo-2′,3′-dihydropyrimidin-4′-yl)carbamyl]-pyridine (6). Cytosine (1.14 g, 8 mmol) and 2,6-bis(methoxycarbonyl)pyridine (1.0 g, 4 mmol) were mixed in a small flask fitted with a condenser and microwaved for 20 min at low power. On cooling to room temperature, a glistening white precipitate formed and was collected. Spectroscopy identified this as a mixture of the desired product and some unreacted cytosine. Selective dissolution of the product in hot acetone (~100 mL) and filtration effected separation. The solution was taken to dryness, the product collected, washed with small amounts of diethyl ether, and dried in a desiccator (0.9 g, 65%). ^{13}C NMR (D_2O): δ 93.6, 128.7, 142.6, 144.9 (pyC, pyrimC), 146.0, 148.4 (pyC_{tert}, pyrimC_{tert}), 159.7, 164.6 (CO) ppm; ^{1}H NMR (D_2O): δ 6.20 (m, 4H, pyrimH), 7.76 (m, 3H, overlapped pyH), 8.50 (br m, 2H, —NHCO—) ppm; IR: 1670 (C=N), 1653, 1455 (NHCO), 1110, 1037, 825, 765 (py) cm^{-1}; ESI-MS (MeOH): *m/z* 363 (**6**·H$^+$). *Anal*. Calcd for $C_{15}H_{11}N_7O_4$: C, 51.0; H, 3.2; N, 27.7. Found: C, 50.8; H, 3.3; N, 27.5.

2,6-Bis[S-(2′-pyridyl)carbothiyl]pyridine (7). A mixture of pyridine-2-thiol (2.18 g, 19.6 mmol) and triethylamine (1.98 g, 19.6 mmol) dissolved in dichloromethane (50 mL) was added dropwise over ~10 min to a solution of 2,6-bis(chlorocarbonyl)-pyridine (2.0 g, 9.8 mmol) in dichloromethane (50 mL) stirring in an icebath. The reaction was rapid and was halted after 20 min, when the insoluble white hydrochloride salt of triethylamine was removed *via* gravity filtration. The resultant filtrate was taken to dryness under reduced pressure to yield a crude orange solid. This was mixed with ethyl acetate (40 mL) and the suspended product collected by vacuum filtration. Washing the solid with several fractions of diethyl ether gave a pale orange solid on drying (3.0 g, 86%). ^{13}C NMR ($CDCl_3$): δ 123.7, 124.6, 130.6, 137.2, 139.2, 146.4 (pyC), 150.6, 152.1 (pyC_{tert}), 190.9 (CO) ppm; ^{1}H NMR ($CDCl_3$): δ 7.3–8.1 (m, 9H, overlapped pyH), 8.65 (m, 2H, NpyH) ppm; IR: 3490 (OH_2), 1607, 1459 (CO), 1109, 1041, 822, 765 (py) cm^{-1}; ESI-MS (MeOH): *m/z* 353 (**7**·H$^+$) *Anal*. Calcd for $C_{17}H_{11}N_3O_2S_2{\cdot}{}^1/_3H_2O$: C, 56.8; H, 3.3; N, 11.7. Found: C, 56.9; H, 3.6; N, 11.4.

Metal complex syntheses. ***Aqua(hydrogen 2,6-bis[N-(1′-piperidinylethyl)carbamido]pyridine)dichlorocobalt(III), [Co((1)-H)Cl$_2$(OH$_2$)].*** To a solution of **1** (1.63 g, 4 mmol) in methanol (50 mL) was added a solution of $CoCl_2{\cdot}6H_2O$ (0.95 g, 4.2 mmol) in water (50 mL). The resulted dark brown solution was stirred and heated (60°C) for 4 h. After stirring at room temperature overnight, HCl (10*M*, 1 mL) was added to the solution, and stirring was continued for ~24 h. The solution was diluted to 1 L with water and sorbed onto a column of Dowex 50W × 2 cation exchange resin. The column was washed with 1*M* HCl to remove any unreacted $Co(II)_{aq}$. The major product was removed by elution with 5*M* HCl, and was rotary evaporated to a small volume then set aside for crystallization. After a few weeks standing, anation yielded a neutral green powder (brown-yellow in aqueous solution) that was collected, washed with ethanol, ether, and dried in a desiccator (1.1 g, 56%). ^{13}C NMR (D_2O): δ 20.4, 22.1 (C—**C**H_2—C), 33.7, 53.1, 55.2 (—**C**H_2—N), 124.8, 139.5, 147.1 (py**C**), 166.0 (N**C**O) ppm; ^{1}H NMR (D_2O): δ 1.7–3.8 (m, 28H, —CH_2—), 7.9 (br t, 1H, pyH), 8.18 (br d, 2H, pyH) ppm; IR: 3450 (OH_2), 1675, 1648 (CO), 1541, 1455, 1418 (NCO), 1120, 755, 676 (py) cm^{-1}; UV–Vis (OH_2): λ_{max} (ε_{max}) 518 nm (61 M^{-1} cm^{-1}), 332 (807). *Anal*. Calcd for $C_{21}H_{34}N_5O_3Cl_2Co$: C, 47.1; H, 6.6; N, 13.1%. Found: C, 47.0; H, 7.1; N, 13.0.

Aqua(2,6-bis[N-(2′-(5′′-nitropyridine)-1′-azapropyl)carbamido]pyridine)cobalt(III) chloride, [Co((3)-2H)(OH$_2$)]Cl. A solution of **3** (0.5 g, 4 mmol) in methanol (100 mL) was mixed with $CoCl_2{\cdot}6H_2O$ (0.95 g, 4 mmol) in water (100 mL) and pH adjusted to ~7. The brown solution was stirred overnight, and then 10*M* hydrochloric acid (1 mL) was added to the solution, which was stirred at room temperature for ~24 h, then diluted to 1 L with water and sorbed onto a column of Dowex 50W × 2 cation exchange resin. The column was washed with water, then eluted with 1*M* HCl to remove any unreacted $Co(II)_{aq}$. The product was removed with 3*M* HCl and concentrated on a rotary evaporator to a small volume, then set aside for crystallization. After a few weeks, red-brown microcrystals were collected, washed with a small amount of absolute ethanol then diethyl ether in turn, and dried in a desiccator (1.7 g, 71%). IR: 1604 (NH), 1475, 1420, 1365 (NCO), 1505, 1373 (—NO_2), 1154, 1077, 822, 766 (py) cm^{-1}; UV–Vis (OH_2): λ_{max} (ε_{max}) 584 nm (48 M^{-1} cm^{-1}); (1*M* HCl) 508 nm (ε 28), 348 (118); ESI-MS: *m/z* 588 ([ML(OH_2)]$^+{\cdot}OH_2$). *Anal*. Calcd for $C_{21}H_{19}N_9ClCoO_7{\cdot}1^3/_4H_2O$: C, 39.8; H, 3.6; N, 19.8. Found: C, 40.0; H, 3.7; N, 19.7.

(2,6-Bis[N-(2′-(5′-nitropyridine)-1′-azapropyl)carbamido]-pyridine)copper(II), [Cu((3)-2H)]. Solutions of **3** (0.05 g, 0.09 mmol) in methanol (50 mL) and copper chloride (0.01 g, 0.09 mmol) in water (5 mL) were mixed in a flask, pH adjusted (~7) and then warmed (60°C) for 2 h with stirring, giving a clear blue solution. This was rotary evaporated dry, redissolved in methanol (25 mL), filtered, and stood in a flask (lightly stoppered with cotton wool) in a fume cupboard. After a week some blue crystals were collected by filtration, washed with a small amount of ethanol then diethyl ether in turn, and air dried (0.025 g, 41%). IR: 1590, 1417 (NCO), 1546, 1375 (NO_2), 1151, 1033, 820, 767 (py) cm^{-1}; UV–Vis (OH_2): λ_{max} (ε_{max}) 687 nm (131 M^{-1} cm^{-1}). *Anal*. Calcd for $C_{21}H_{19}CuN_9O_6{\cdot}2^1/_2H_2O$: C, 41.9, H, 4.1, N, 20.9. Found: C, 41.9, H, 4.3, N, 20.8.

(2,6-Bis[N-(3′-hydroxypropyl)carbamido]pyridine)copper(II), [Cu((4)-2H)]. To a stirring solution of **4** (0.143 g, 0.5 mmol) and NaOH (0.052 g, 1.3 mmol) in methanol (10 mL) was slowly added a solution of $Cu(ClO_4)_2{\cdot}6H_2O$ (0.185 g, 0.5 mmol) in methanol (2 mL). The immediately formed purple

solution was stirred at room temperature for 30 min, and then stood in a sealed jar in a diethyl ether atmosphere. Purple microcrystals formed after several days, and were collected and air dried; these were a sesqui(hydrate hydrogen perchlorate) salt (0.153 g, 59%). IR: 3379 (OH), 1651 (CO), 1574 (NCO), 1142, 1088, 987, 841, 756, 687 (py), 1119, 632 (ClO_4^-) cm^{-1}; UV–Vis (OH_2): λ_{max} (ε_{max}) 576 nm (142 M^{-1} cm^{-1}). *Anal*. Calcd for $C_{13}H_{17}CuN_3O_4 \cdot 1^1/_2H_2O \cdot 1^1/_2HClO_4$: C, 30.0; H, 4.2; N, 8.0. Found: C, 29.9; H, 4.5; N, 7.8.

(2,6-Bis[N-(3′-hydroxypropyl)carbamido]pyridine)nickel(II), [Ni(4-2H)]. To a stirring solution of **4** (0.428 g, 1.5 mmol) and NaOH (0.120 g, 3 mmol) in methanol (25 mL) was slowly added a solution of $Ni(ClO_4)_2 \cdot 6H_2O$ (0.549 g, 1.5 mmol) in methanol (5 mL), and the pH was raised to ~10 with methanolic NaOH solution. The resulting orange-red solution was heated for 2 h at 60°C, and then allowed to cool and filtered to remove some green solid. The orange-red filtrate was rotary evaporated to dryness, washed with diethyl ether (2 × 20 mL), then was redissolved in a small volume of methanol (~10 mL) and crystals grown in a diethyl ether atmosphere. Some orange crystals formed after several days, and were collected, washed with a little diethyl ether and air dried; they crystallized as a diamagnetic monohydrogen perchlorate salt (0.34 g, 68%). ^{1}H NMR (D_2O): δ 1.92 (m, 4H, CH_2), 3.53 (t, 4H, CH_2), 3.73 (t, 4H, CH_2), 8.14 (m, 3H, pyH); ^{13}C NMR (D_2O): δ 30.5 (CH_2), 36.2 (—CH_2—N), 59.0 (—CH_2—O), 124.2, 139.2 (pyCH), 147.4 (pyC_{tert}), 165.0 (CO) ppm; IR: 3333 (OH), 1651, 1543 (NCO), 1149, 1088, 995, 849, 748, 687 (py) 1119, 630 (ClO_4^-) cm^{-1}; UV–Vis (OH_2): λ_{max} (ε_{max}) 365 nm (72 M^{-1} cm^{-1}). *Anal*. Calcd for $C_{13}H_{17}NiN_3O_4 \cdot HClO_4$: C, 35.6; H, 4.2; N, 9.6. Found: C, 35.9; H, 4.6; N, 9.2.

(2,6-Bis[N-(5′-hydroxy-3′-azapentyl)carbamido]pyridine)-copper(II), [Cu((5)-2H)]. To a stirring solution of **5** (0.190 g, 0.5 mmol) and NaOH (0.050 g, 1.25 mmol) in methanol (10 mL) was slowly added a solution of $Cu(ClO_4)_2 \cdot 6H_2O$ (0.185 g, 0.5 mmol) in methanol (2 mL). The immediately formed blue solution was stirred at room temperature for 30 min, and then stood in a sealed jar in a diethyl ether bath. Blue solid formed after several days, and was collected and air dried; it crystallized as a sesqui(hydrate hydrogen perchlorate) salt (0.155 g, 52%). IR: 3425 (OH), 1651, 1574 (NCO), 1142, 1119, 1088, 841, 764, 687 (py), 1068, 633 (ClO_4^-) cm^{-1}; UV–Vis (OH_2): λ_{max} (ε_{max}) 598 nm (113 M^{-1} cm^{-1}). *Anal*. Calcd for $C_{15}H_{23}CuN_5O_4 \cdot 1^1/_2H_2O$ $1^1/_2HClO_4$: C, 31.2; H, 4.8; N, 12.1. Found: C, 31.3; H, 4.5; N, 11.8.

(2,6-Bis[N-(2′-oxo-2′,3′-dihydropyrimidin-4′-yl)carbamido]-pyridine)copper(II), [Cu((6)-2H)]. A solution of **6** (0.35 g, 1 mmol) in water was stirred at room temperature. A solution of $Cu(ClO_4)_2 \cdot 6H_2O$ (0.37 g, 1 mmol) was added. The resulting blue solution was allowed to evaporate slowly over the course of several weeks, yielding light blue crystals that were collected *via* filtration and air dried; it crystallized as a hydrogen perchlorate trihydrate salt (0.28 g, 55%). IR: 1670 (C=N), 1610, 1540, 1445 (NCO), 1110, 825, 765, 690 (py), 1070, 630 (ClO_4^-) cm^{-1}; UV–Vis (OH_2): λ_{max} (ε_{max}) 570 nm (120 M^{-1} cm^{-1}). *Anal*. Calcd for $C_{15}H_9N_7O_4Cu \cdot 3H_2O \cdot HClO_4$: C, 31.5; H, 3.0; N, 17.1. Found: C, 31.7; H, 2.85; N, 16.8.

(2,6-Bis[S-(2′-pyridyl)carbothiyl]pyridine)zinc(II) acetate monohydrate, [Zn(7)](CH$_3$COO)$_2$·H$_2$O. To a stirred ethanolic solution of **7** (0.2 g, 0.57 mmol) was added dropwise an aqueous solution containing zinc acetate monohydrate (0.11 g, 0.57 mmol). During the addition, a thick white precipitate formed, and this was collected by vacuum filtration, washed in turn with water and ethanol portions, and air dried (0.20 g, 83%). ^{13}C NMR (d_6-DMSO): δ 34.4 (CH_3), 115.3, 119.1, 128.0 131.3, 137.3, 138.8 (pyC), 144.3, 147.9 (pyC_{tert}), 169.2 (COO), 188.0 (CO) ppm; ^{1}H NMR (d_6-DMSO): δ 2.35 (s, 3H, CH_3), 6.83 (t, 2H, pyH), 7.07 (t, 2H, pyH), 7.24 (d, 2H, pyH), 7.42 (t, 1H, pyH), 7.62 (br s, 2H, pyH), 7.85 (m, 2H, pyH); IR: 1612, 1540, 1451 (CO), 1595 (COO^-), 1060, 820, 765, 680 (py) cm^{-1}. *Anal*. Calcd for $C_{21}H_{17}N_3O_6S_2Zn \cdot H_2O$: C, 56.3; H, 3.4; N, 11.6. Found: C, 56.9; H, 3.6; N, 11.4.

X-ray crystallography. A pale yellow prismatic crystal of **1**, crystallized by diethyl ether diffusion into a methanol solution in a sealed vessel, was mounted and quenched in a cold nitrogen gas stream from an Oxford Cryosystems Cryostream. A Bruker SMART 1000 CCD diffractometer using graphite monochromated MoKα radiation was used for data collection. Cell constants were obtained from a least squares refinement against 1014 reflections located between 5 and 56° 2θ. Data were collected at 150(2) Kelvin with ω scans to 57° 2θ. The data integration and reduction were undertaken with SAINT and XPREP [16], and subsequent computations were carried out with the teXsan [17], WinGX [18], and XTAL [19] graphical user interfaces. The intensities of 161 standard reflections recollected at the end of the experiment did not change significantly during the data collection. A Gaussian absorption correction [16,20] was applied to the data.

The structure was solved in the space group *C*2/c(#15) by direct methods with SIR97 [21], and extended and refined with SHELXL-97 [22]. The nonhydrogen atoms were modeled with anisotropic displacement parameters and a general riding atom model was used for H atoms. Amine and water sites were located and modeled with isotropic displacement parameters. The crystallographic data (excluding structure factors) for the structure are available from the Cambridge Crystallographic Data Centre as supplementary publication no. CCDC671132. Copies may be obtained from CCDC, Union Road, Cambridge CB2 1EZ, UK (deposit@ccdc.cam.ac.uk).

Crystal data. Formula $C_{21}H_{35}N_5O_3$, MW 405.54, monoclinic, space group *C*2/c(#15), *a* 31.825(5) Å, *b* 10.7930(16) Å, *c* 13.972(2) Å, β 114.147(4)°, *V* 4379.3(11) Å^3, D_c 1.230 g cm^{-3}, *Z* 8. Crystal size 0.382 × 0.261 × 0.184 mm^3, color yellow, crystal habit prisms. Temperature 150(2) K, λ(MoKα) 0.71073 Å, μ(MoKα) 0.084 mm^{-1}, $T(\text{Gaussian})_{min,max}$ 0.975, 0.989; $2\theta_{max}$ 56.64°, *hkl* range −41 41, −14 13, −18 18. *N* 21092, N_{ind} 5237 (R_{merge} 0.0372), N_{obs} 3821 ($I > 2\sigma(I)$), N_{var} 278. Residual* *R*1(*F*), *wR*2(F^2) 0.0354, 0.0836. GoF(all) 1.264. Residual extrema −0.203, 0.209 e$^-$Å^{-3} [*$R1 = \Sigma||F_o|-|F_c||/\Sigma|F_o|$ for $F_o > 2\sigma(F_o)$; $wR2 = (\Sigma w(F_o^2-F_c^2)^2/\Sigma(wF_c^2)^2)^{1/2}$, all reflections, $w = 1/[\sigma^2(F_o^2) + (0.03P)^2]$, where $P = (F_o^2 + 2F_c^2)/3$].

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