SYNTHESIS AND PROPERTIES OF OLIGOCARBOXAMIDE MOLECULAR STRANDS CONTAINING 1,8-NAPHTHYRIDINE AND PYRIDINE GROUPS

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Abstract – Oligocarboxamide molecular strands based on carboxamide between 1,8-naphthyridine and pyridine, pyridine and pyridine, 1,8-naphthyridine and benzene, and pyridine and benzene have been prepared. They have afforded various inclusion complexes with organic solvents. Structural features of the inclusion complexes determined by X-Ray crystal structure analyses are described.

Supramolecular chemistry has developed as the chemistry of the entities generated via intermolecular noncovalent interactions.[1] Supramolecules, well-defined oligomolecular species, result from the specific intermolecular association of a few components.[2] In particular, helicity codons based on specially designed sequences of heterocyclic units enforce the self-organization multiturn helical entities.[3] A new family of oligocarboxamide strand (**1**) (Scheme 1) derived from 2,6-diaminopyridine and 2,6-pyridinedicarboxylic acid has recently been reported.[4-7] This compound not only self-organizes into a single helical monomer, but it reversibly assembles, giving rise to a double-helical dimer. A new type of oligomeric strand (**2**) (Scheme 1) composed of alternating pyrimidine and 1,8-naphthyridine heterocycles has also been reported.[8] Compound (**2**) also self-organizes into a helical monomer. Compound (**1**) can include H_2O in the helical internal space. Compound (**2**) can include a cesium ion in the helical internal space. Oligocarboxamide molecular strands containing 1,8-naphthyridine and pyridine groups are expected to include other molecules. We now report preparation of the strands containing 1,8-naphthyridine-pyridine ring (**3a**, **b**), pyridine rings (**3c-e**, **4**), 1,8-naphthyridine and benzene ring (**5a**, **b**), and pyridine and benzene ring (**5c-e**) with carboxamide linkage (Scheme 2), as well as the ability of these molecules to form inclusion complexes.

1

2

Scheme 1

3

a: R^1=$OC_{10}H_{21}$, R^2=t-BuO, X=1,8-naphthyridine group
b: R^1=H, R^2=t-BuO, X=1,8-naphthyridine group
c: R^1=$OC_{10}H_{21}$, R^2=t-BuO, X=pyridine group
d: R^1=H, R^2=t-BuO, X=pyridine group
e: R^1=$OC_{10}H_{21}$, R^2=$C_6H_5CH_2O$, X=pyridine group

4

1,8-naphthyridine group:

pyridine group:

5

a: *m*-, X=1,8-naphthyridine group
b: *p*-, X=1,8-naphthyridine group
c: *o*-, X=pyridine group
d: *m*-, X=pyridine group
**e**: *p*-, X=pyridine group
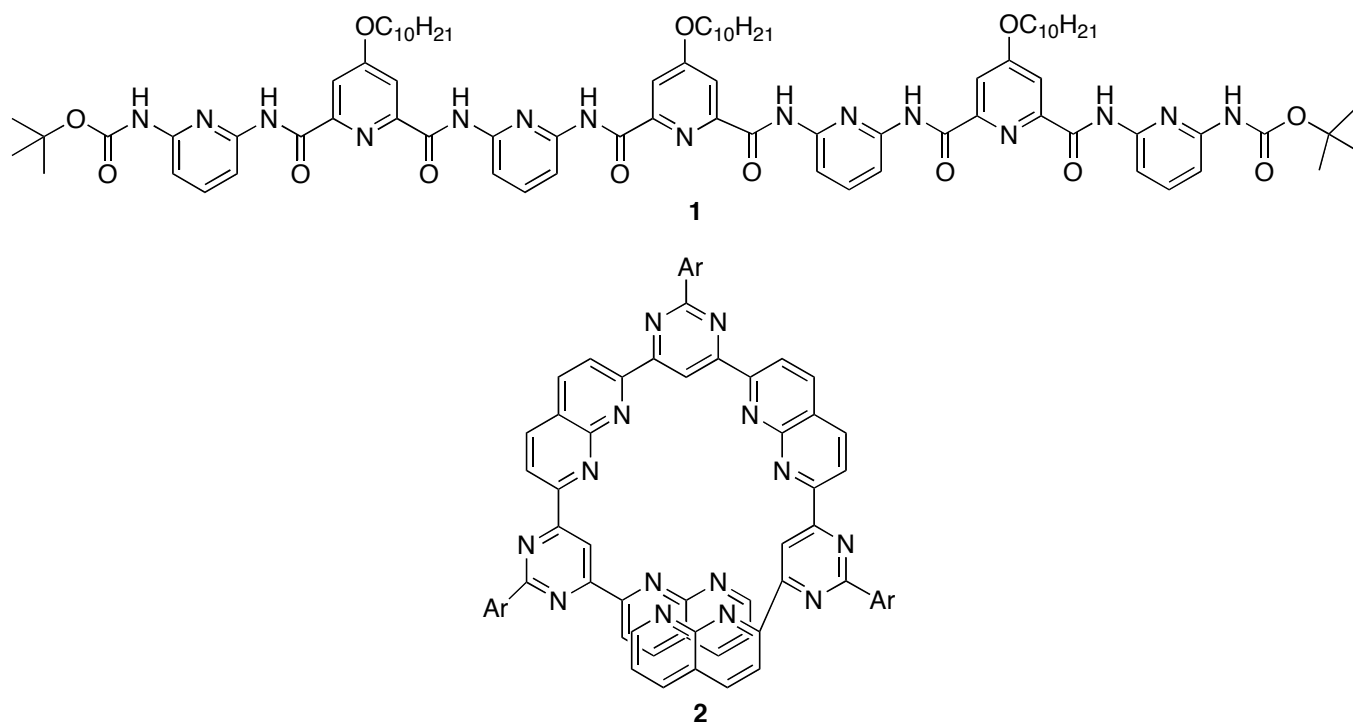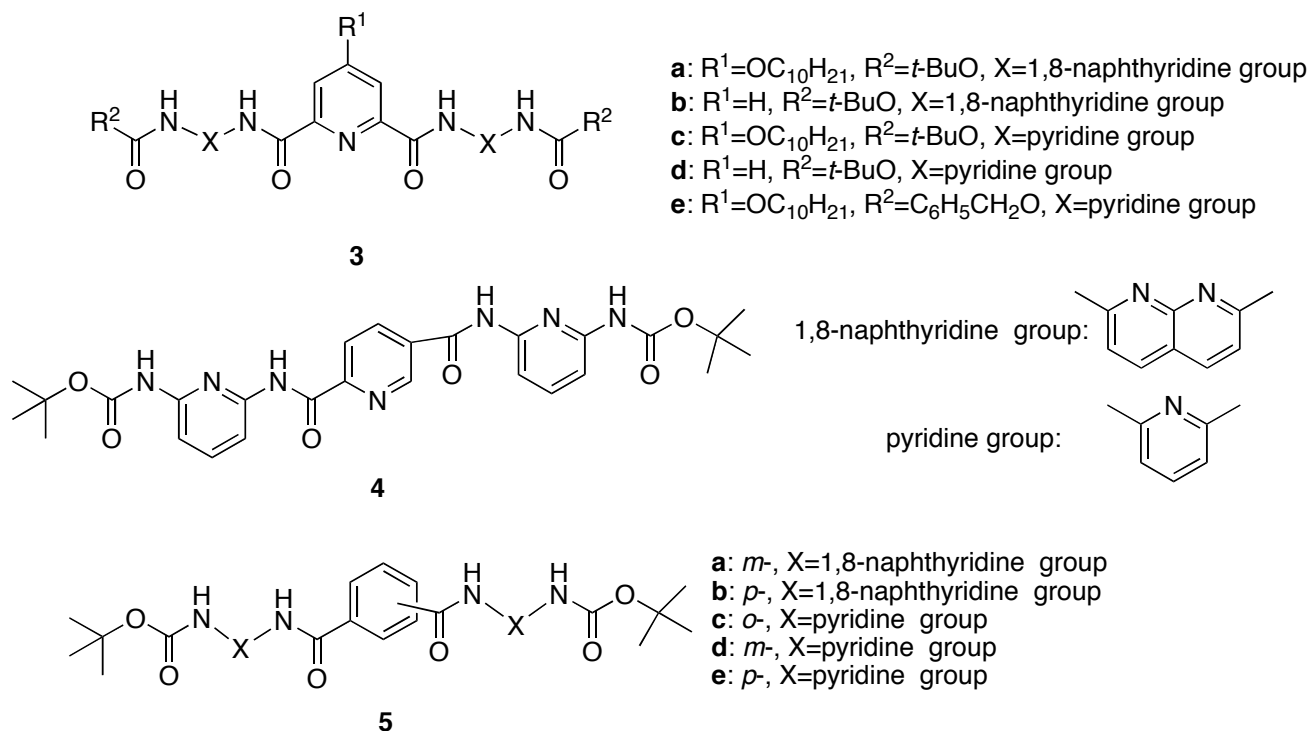
Scheme 2

Syntheses.

Syntheses of the new molecular strands (**3~5**) have been achieved according to Schemes 3-6. 2,7-Diamino-1,8-naphthyridine (**6**) [9-11] was monoprotected by treatment with di-*tert*-butyl dicarbonate (Boc$_2$O) to give *tert*-butyl *N*-(7-aminonaphthyridin-2-yl)carbamate (**7**), which reacted with pyridine-2,6-bis(carbonyl chloride) derivatives (**9a**, **b**) prepared from the corresponding pyridine-2,6-dicarboxylic acid derivatives (**8a**[6], **b**) to give **3a**, **b** in 58 and 37% yields, respectively. [12]
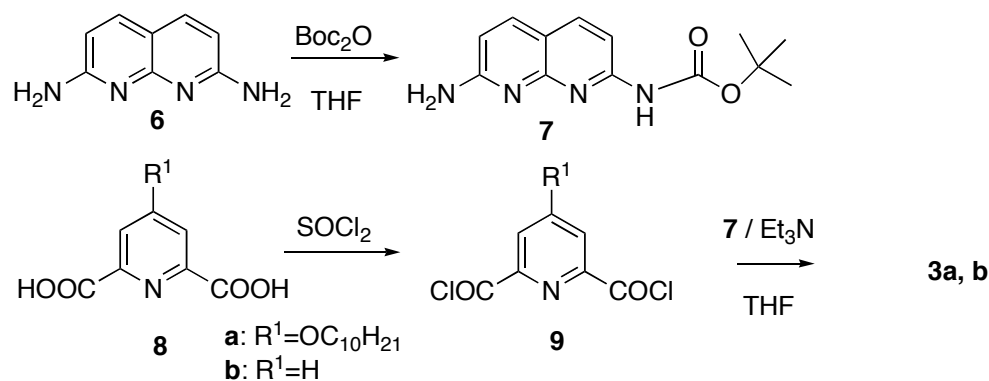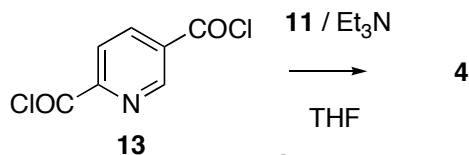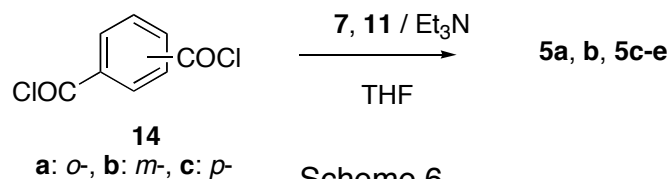
Scheme 3
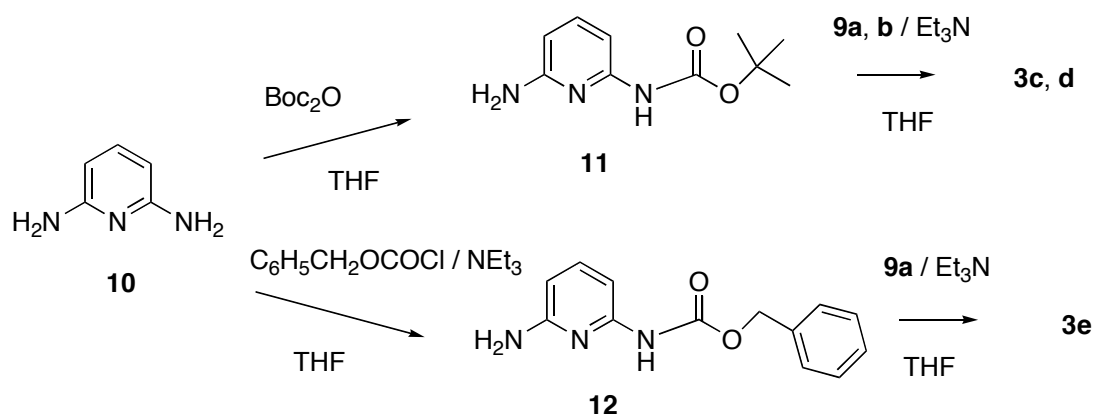
Scheme 4

2,6-Diaminopyridine (**10**) was monoprotected by treatment with di-*tert*-butyl dicarbonate (Boc$_2$O) to give *tert*-butyl *N*-(6-aminopyridyl)carbamate (**11**) (Scheme 4). The monoamine (**11**) reacted with pyridine-2,6-bis(carbonyl chloride) derivatives (**9a, b**) to give **3c, d** in 66 and 54% yields, respectively. 2,6-Diaminopyridine (**10**) was also monoprotected by treatment with benzyloxycarbonyl chloride to give benzyl *N*-(6-aminopyridyl)carbamate (**12**), which reacted with 4-decyloxypyridine-2,6-bis(carbonyl chloride) (**9a**) to give **3e** in 66% yield (Scheme 4).

The monoamine (**11**) reacted with pyridine-2,5-bis(carbonyl chloride) (**13**)[13] to give **4** in 59% yield (Scheme 5).

Scheme 5

The monoamine (**7**) reacted with **14b, c** to give **5a, b** in 57 and 40% yields, respectively (Scheme 6). The monoamine (**11**) reacted with **14a, b, c** to give **5c, d, e** in 23, 55, and 77% yields, respectively (Scheme 6).

Scheme 6

Formation and characterization of inclusion complexes.
The ability of the molecular strands synthesized here to form inclusion complexes with various organic solvent molecules was investigated. These complexes were obtained according to the following general procedure. Oligocarboxamide molecular strands were heated and solved with organic solvents.

Table 1 Host-guest Ratio of Inclusion Complex of **3-5**

guest	3a	3b	3c	3d	3e	4	5a	5b	5c	5d	5e
acetone	—	—	—	—	—	—	—	—	—	—	—
methanol	—	—	—	—	—	—	—	—	—	—	—
toluene	—	—	—	—	—	—	—	—	—	—	—
cyclopentanone	—	—	—	—	—	1 : 1	—	1 : 1	—	—	1 : 1
cyclohexanone	—	—	—	—	—	1 : 1	—	1 : 1	—	—	1 : 1
AcOEt	—	—	—	—	—	—	—	—	—	—	—
THF	1 : 1	—	1 : 1	—	—	1 : 2	—	1 : 1	—	—	1 : 2
dioxane	1 : 1	1 : 2	—	1 : 2	1 : 1	1 : 1	—	1 : 1	—	—	1 : 2
DMF	1 : 1	—	1 : 1	1 : 1	1 : 1	1 : 2	1 : 1	3 : 1	—	1 : 2	1 : 2
DMSO	1 : 1	1 : 1	1 : 1	1 : 1	1 : 1	1 : 2	—	1 : 3	—	1 : 2	1 : 2
CH_2Cl_2	—	1 : 1	—	—	—	—	—	2 : 1	—	—	—
pyridine	1 : 2	1 : 1	1 : 1	1 : 1	1 : 1	1 : 2	1 : 1	1 : 1	1 : 1	1 : 1	1 : 1

The solution was kept at room temperature to allow the formation of inclusion complexes (Table 1). Table 1 shows the host-guest ratio for the inclusion complexes formed by **3a-e**, **4**, **5a-e**, with typical organic solvents.   The host-guest ratio was determined by ^{1}H NMR spectra or TG.   It should be noted that the *p*-substituted carboxamide hosts (**4**), (**5b**), and (**5e**) displayed significant ability to form such inclusion complexes.   This ability may be due to the host's formation of a supramolecular zigzag chain in the crystal lattice, as indicated by X-Ray study[14] for complexes of **5e**, with guest molecules being accommodated between the chains.

X-Ray crystal structure analyses[14] have been carried out for the inclusion complexes, **3c•pyridine•0.5H$_2$O** and **5e•2DMF** in order to reveal the site of the host molecule where the guest molecules are connected. Crystals were grown from corresponding pyridine and DMF solutions by slow evaporation at room temperature.   In **3c•pyridine•0.5H$_2$O**, the host molecule (**3c**) can be described as having a lobster shape, the head of which is the pyridine ring containing N12, with the two arms catching the guest molecule and the tail being formed by the aliphatic chain (Figure 1).
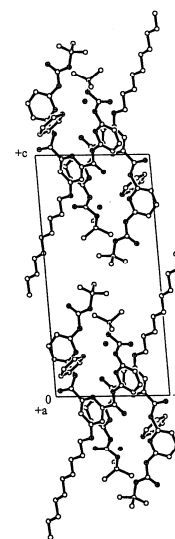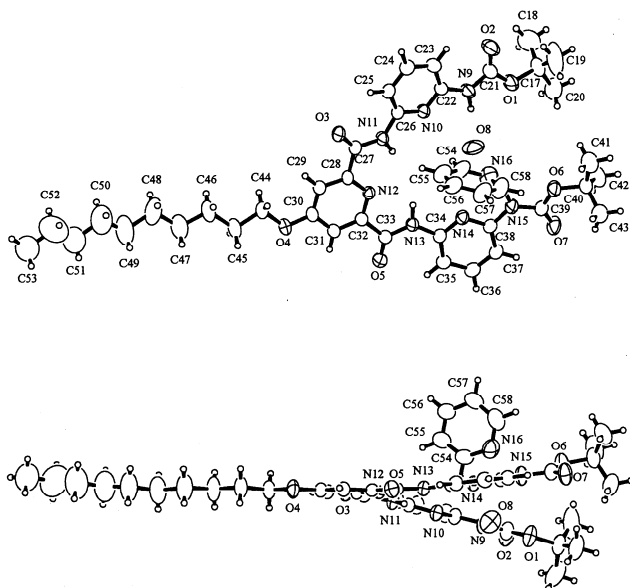

Figure 1. (a) The molecular structure of **3c•py•0.5H$_2$O**, and (b) The side view.

Figure 2. The crystal structure of **3c•py•0.5H$_2$O** projected along the *a* axis.

The dihedral angles of the pyridine rings N10/C22-C26 and N14/C34-C38 in the arms of the host (**3c**) with respect to the head pyridine plane (N12/C28-C33) are 14.5(1)° and 8.3(1)°, respectively, and the dihedral angle between the arm pyridine rings is 22.0(1)°. The N11-H11 and N13-H13 moieties of the amide groups form intramolecular hydrogen bonds with the head N12 atom. The water O8 atom is located between the two arms of the host (**3c**), and is connected to both N9 and N15 atoms via N-H•••O hydrogen bonds. The guest pyridine molecule is connected to one of the arms of the host (**3c**) by an N15-H15•••N16 hydrogen bond, but the pyridine ring is nearly perpendicular to and shifted away from the plane of the arm. In the crystal, there are π-π stacking interactions between one of the arms of the host, where the N12 and N14 pyridine rings and amide groups C27/N11/O3 and C33/N13/O5 are involved. These moieties are stacked along the *a* axis to form a column (Figure 2). However, the overlap of the aromatic rings in the column is relatively poor.

In **5e•2DMF**, the host (**5e**) shows an extended and slightly curved structure, having a local inversion center (Figure 3). The dihedral angles between the amide moiety and the aromatic ring, to which the amide group is connected, are 12.0(4)-32.2(3)°, except for the 1.3(3)° angle between the amide O3/C27/N11 and pyridine ring (N10/C22-C26). The dihedral angles between the central benzene (C28-C33) and the pyridine rings (N10/C22-C26 and N13/C35-C39) are 26.7(4)° and 16.3(4)°, respectively, and that between the two pyridine rings is 16.5(4)°. The guest DMF molecules are connected to the host molecule (**5e**) by N11-H11•••O7 and N12-H12•••O8 hydrogen bonds. In the crystal, the host molecules are connected by N9-H9•••N13[i] (symmetry code (i) 3/2-x, 1/2+y, 1/2+z) and N10•••H14[i]-N14[i] hydrogen bonds, forming a polymer chain (Figure 4). A side view of the chain can be seen in Figure 5, where the host molecules (**5e**) look like rods, with both ends being bound together via hydrogen bonds, forming zigzag chains along the [011] direction. The guest DMF molecules are connected to the host by hydrogen bond and are located in the cavity between the chains.
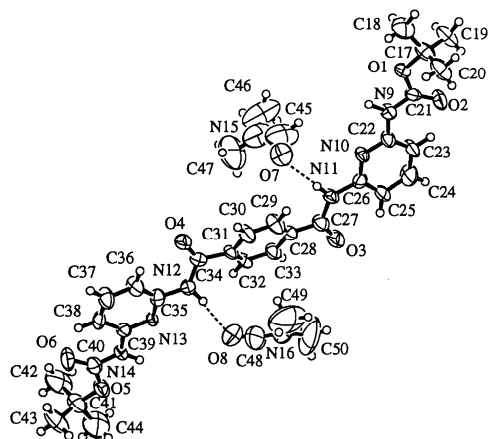

Figure 3. The molecular structure of **5e•2DMF**. The broken lines show
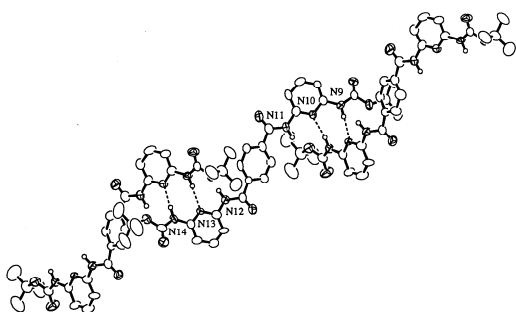N-H•••O hydrogen bonds between the host and guest molecules.

Figure 4. The molecular chain of the host **5e**
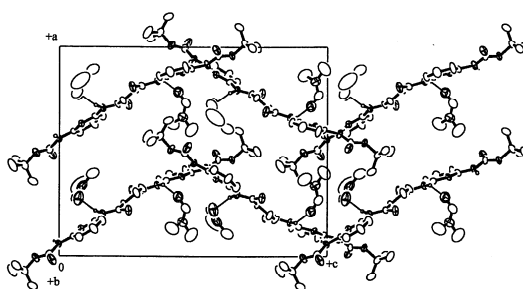connected via N-H•••N hydrogen bonds.

Figure 5. The crystal structure of **5e•2DMF**
projected along the *b* axis.

Further studies of the relationship of the inclusion ability and the crystal structures for the oligocarboxamide molecular strands are now in progress.

ACKNOWLEDGEMENTS

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12. Typical syntheses: ***tert*-Butyl *N*-(7-aminonaphthyridin-2-yl)carbamate (7)**
    Di-*tert*-butyl dicarbonate (2.72 g, 12.5 mmol) dissolved in THF (10 mL) was added dropwise to 2,7-diamino-1,8-nphthyridine (**6**) (2.0 g, 12.5 mmol) dissolved in THF (40 mL).   The mixture was heated for 10 h at 60 °C.   The mixture was evaporated, separated by column chromatography (silica gel, 9/1 EtOAc/methanol) to give **7** as a colorless powder (2.01 g, 62% yield).   Compound (**7**): mp 198.7 °C (decomp); IR (KBr): ν_{max} 3318, 3190, 1728, 1602 cm^{-1}; ^{1}H NMR (300 MHz, CDCl$_3$): δ 7.98 (d, *J* = 8.78 Hz, 1H), 7.91 (d, *J* = 8.78 Hz, 1H), 7.79 (d, *J* = 8.78 Hz, 1H), 7.41 (br s, 1H), 6.64 (d, *J* = 8.78 Hz, 1H), 4.97 (br s, 2H), 1.55 (s, 9H); FAB-MS: m/z (%): 261.1 (100) [MH$^+$].
    2,6-Bis[*N*-(7-*tert*-butoxycarbonylaminonaphthyridin-2-yl)carbamoyl]-4-decyloxypyridine (3a)
    4-Decyloxypyridine-2,6-dicarboxylic acid (**8a**) (0.5762 g, 1.78 mmol) and thionyl chloride (1.2 mL) were refluxed for 1 h.   After evaporation, the residue was used in the next step.   *tert*-Butyl *N*-(7-aminonapthyridin-2-yl)carbamate (**7**) (0.9275 g, 2.56 mmol) and triethylamine (0.3964 g, 0.547 mL, 3.918 mmol) were dissolved in dry THF (7 mL), and previously prepared 4-decyloxypyridine-2,6-bis(carbonyl chloride) (**9a**) (0.6413 g, 1.78 mmol) in dry THF (0.75 mL) was added dropwise at room temperature.   The reaction was allowed to proceed for an additional 1 h at room temperature.   The mixture was filtered and separated by column chromatography (silica gel, 1/1 EtOAc/hexane) to give **3a** as a colorless powder (0.8311 g, 58% yield).   Compound (**3a**): mp 273.0 °C (decomp); IR (KBr): ν_{max} 3312, 1733, 1613 cm^{-1}; ^{1}H NMR (300 MHz, CDCl$_3$): δ 10.55 (s, 2H), 8.61 (d, *J* = 8.78 Hz, 2H), 8.12-8.28 (m, 6H), 8.01 (s, 2H), 7.54 (s, 2H), 4.22 (t, *J* = 6 Hz, 2H), 1.88 (m, 2H), 1.55 (s, 18H), 1.20-1.54 (m, 14H), 0.88 (br s, 3H); FAB-MS: m/z (%): 808.6 (100) [MH$^+$].
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14. *X-Ray Analyses*. Crystal structures of the two compounds were determined by the single-crystal X-Ray diffraction method.   The crystals of **3c**•py•0.5H$_2$O and **5e**•2DMF were sealed in capillaries

to avoid efflorescence. X-Ray intensity data were measured on a Rigaku-AFC7R four-circle diffractometer with Mo Kα radiation. Intensity decays of the standard reflections were 6% and 11%, respectively. Structure analyses were carried out with the programs SIR92, SHELXL97, and TEXSAN. For **3c**•py•0.5H$_2$O: the occupation factor of the guest water molecule was assumed to 50% based on the displacement parameter of the O atom. The H atoms were positioned geometrically except for the water molecule. Crystallographic data have been deposited at the CCDC, 12 Union Road, Cambridge CB2 1EZ, UK and copies can be obtained on request, free of charge, by quoting the publication citation and the deposition numbers CCDC 247689-247690.

3c•py•0.5H$_2$O: Chemical formula C$_{42}$H$_{57}$N$_8$O$_{7.5}$, Formula weight 793.96, Crystal system Triclinic, Space group $P\bar{1}$, $a/$Å 9.915(4), $b/$Å 10.365(4), $c/$Å 22.163(4), $\alpha/°$ 94.23(2), $\beta/°$ 91.30(2), $\gamma/°$ 94.73(3), $V/$Å^3 2263(1), Z 2, $D_{calcd}/$g cm^{-3} 1.165, $\mu/$mm^{-1} 0.081, Crystal size/mm 0.5×0.5×0.4, Temperature/K 299, Reflections measured 8943, Reflections independent 7984, Reflections with $I>2\sigma(I)$ 3751, Reflections used 7984, $R(F)/R$w(F^2) 0.058/0.202.

5e•2DMF: Chemical formula C$_{34}$H$_{46}$N$_8$O$_8$, Formula weight 694.79, Crystal system Orthorhombic, Space group $Pna2_1$, $a/$Å 17.304(7), $b/$Å 10.002(6), $c/$Å 21.924(8), $V/$Å^3 3795(3), Z 4, $D_{calcd}/$g cm^{-3} 1.216, $\mu/$mm^{-1} 0.088, Crystal size/mm 0.55×0.3×0.2, Temperature/K 293, Reflections measured 5074, Reflections independent 3434, Reflections with $I>2\sigma(I)$ 1122, Reflections used 3434, $R(F)/R$w(F^2) 0.060/0.191.