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[11] Crystal data for **3** and **4**: **3**: $C_{20}H_{28}F_6KO_6P$, $M_r = 548.49$, monoclinic, space group $P2_1/n$, $a = 10.44(6)$, $b = 17.38(8)$, $c = 14.53(13)$ Å, $\beta = 94.4(3)^\circ$, $V = 2629(30)$ Å^3, $Z = 4$, $\rho_{calcd} = 1.386$ Mg m^{-3}, $F(000) = 1136$, $\lambda = 0.71073$ Å, $T = 193(2)$ K, $\mu(Mo_{K\alpha}) = 0.337$ mm^{-1}, crystal size $0.1 \times 0.4 \times 0.7$ mm^3, $1.83 \le \theta \le 26.37^\circ$, 15730 reflections (5367 independent, $R_{int} = 0.0358$), $T_{min} = 0.825186$, $T_{max} = 1.0$, 311 parameters, $R1$ [$I > 2\sigma(I)$] = 0.0424, $wR2$ (all data) = 0.0985, max. residual electron density: 0.423 e Å^{-3}. **4**: $C_{28}H_{44}F_6KO_{10}P$, $M_r = 724.70$, monoclinic, space group $P2_1/c$, $a = 11.964(2)$, $b = 12.251(2)$, $c = 23.154(3)$ Å, $\beta = 96.195(3)^\circ$, $V = 3374.0(8)$ Å^3, $Z = 4$, $\rho_{calcd} = 1.427$ Mg m^{-3}, $F(000) = 1520$, $\lambda = 0.71073$ Å, $T = 173(2)$ K, $\mu(Mo_{K\alpha}) = 0.290$ mm^{-1}, crystal size $0.01 \times 0.5 \times 0.6$ mm^3, $1.71 \le \theta \le 21.97^\circ$, 13038 reflections (4108 independent, $R_{int} = 0.0798$), $T_{min} = 0.749166$, $T_{max} = 1.000000$, 4108 parameters, 440 restraints, $R1$ [$I > 2\sigma(I)$] = 0.0599, $wR2$ (all data) = 0.1424, max. residual electron density: 0.529 e Å^{-3}. Data for both structures were collected at low temperature using oil-coated shock-cooled crystals on a Bruker-AXS CCD 1000 diffractometer. Semi-empirical absorption corrections were employed.[23] The structures were solved by direct methods (SHELXS-97)[24] and refined using the least-squares method on F^2.[25] CCDC-166948 (**3**) and -166949 (**4**) contains the supplementary crystallographic data for this paper. These data can be obtained free of charge via www.ccdc.cam.ac.uk/conts/retrieving.html (or from the Cambridge Crystallographic Data Centre, 12, Union Road, Cambridge CB2 1EZ, UK; fax: (+44) 1223-336-033; or deposit@ccdc.cam.ac.uk).

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Cation-Promoted Hierarchical Formation of Supramolecular Assemblies of Self-Organized Helical Molecular Components**

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Helical conformations of organic and inorganic entities have received much attention as a result of their occurence in many biological systems. Maintained by multiple hydrogen bonds and electrostatic interactions, α-helices are involved in

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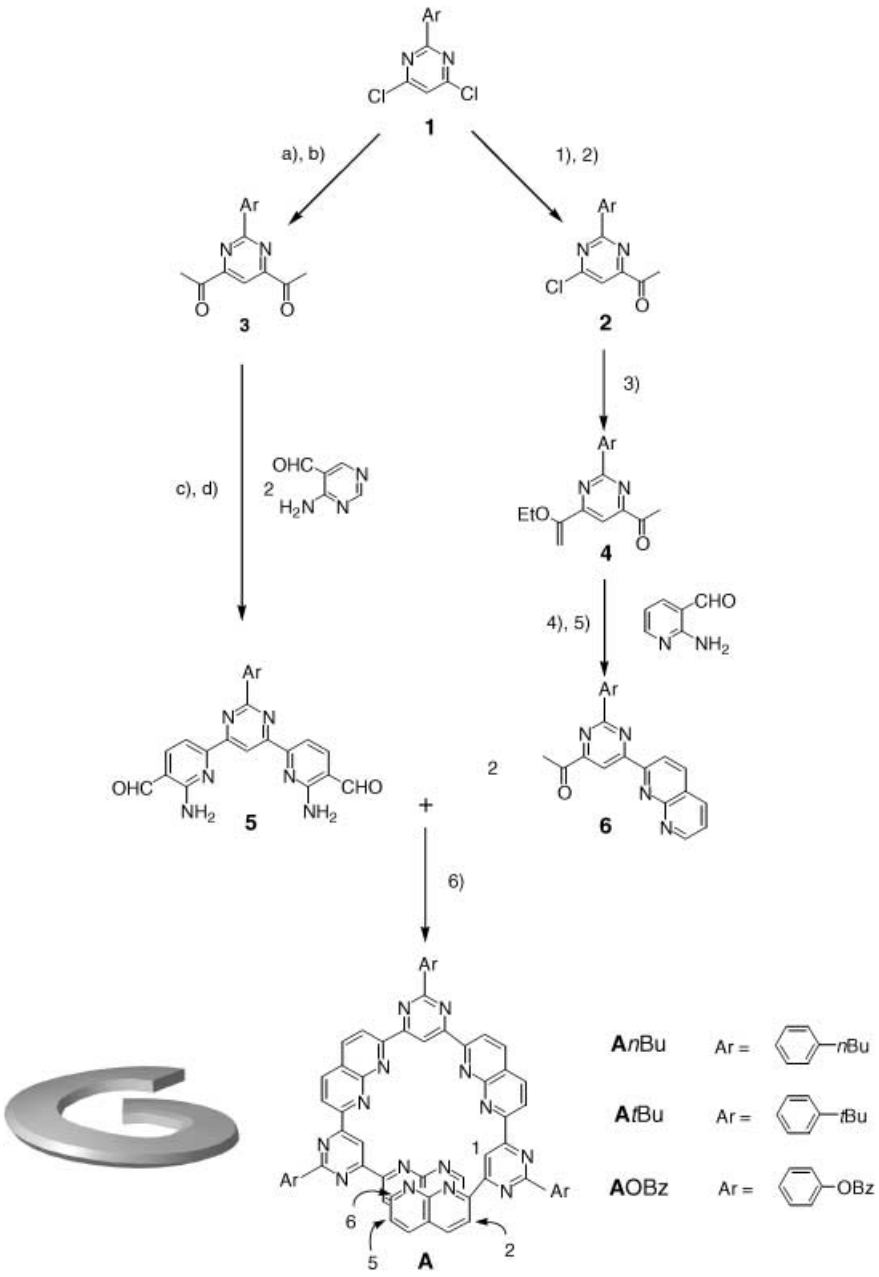
numerous natural architectures, such as ion channels[1] and pumps,[2] which require highly ordered subunits. Likewise, in artificial systems, self-organization into a helical spatial arrangement may be induced through hydrogen bonding,[3] steric interactions,[4] solvophobic effects,[5a,b] cation binding,[5c] and/or local conformational preferences.[6] In particular, helicity codons based on specially designed sequences of heterocyclic units enforce the self-organization of linear molecular strands into multiturn helical entities.[7] As a consequence of the primary helix encoding, the preferred conformer may present further specific interactions and undergo a second level, hierarchical self-assembly[7c, 8, 9] to form polymolecular assemblies. This process may be induced by association with a substrate.[3d, 10]

Of particular interest is the potential ability of such helically wrapped species to present functional properties such as ion binding and possibly channel-like ion conduction. To this end, the central void must have a diameter sufficient for the inclusion of metallic or organic cations. Replacement of the pyridine group in the previously described pyridine–pyrimidine (py–pym) helicity codon[7] by 1,8-naphthyridine (napy) should provide such an increase in size. Herein we describe a new type of oligomeric strand composed of alternating pym and napy heterocycles (**A**, Scheme 1), where the interheterocyclic *transoid* conformational preference of 2,2′-bipyridine-like units may be expected to enforce helix formation.[7] In view of the large dipole moment of napy (4.1 D in benzene, 25 °C),[11] the helical entity **A** should present a very polar interior and be able to bind a variety of cationic species, which themselves could thereafter promote helix aggregation. Acyclic and macrocyclic structures containing rigidly maintained napy units have been described and found to bind guanidinium ions.[12]



Scheme 1. Synthesis of the polyheterocyclic strands **A**. a) 1-tributylstannylethyl vinyl ether (2.1 equiv), $[Pd(PPh_3)_2Cl_2]$ (0.05 equiv), DMF, 80 °C, 6 h; b) acetone, 2 N HCl, room temp., 70% (two steps); c) 4-aminopyrimidine-5-carboxaldehyde (2.2 equiv), KOH (cat.), EtOH, reflux, 0.5 h; d) 2 N HCl in H_2O, reflux, 65% (two steps). 1) 1-Tributylstannylethyl vinyl ether (1.1 equiv), $[Pd(PPh_3)_2Cl_2]$ (0.03 equiv), DMF, 80 °C, 6 h; 2) acetone, 2 N HCl, room temp., 89% (two steps); 3) 1-tributylstannylethyl vinyl ether (1.1 equiv), $[Pd(PPh_3)_2Cl_2]$ (0.03 equiv), DMF, 80 °C, 6 h, 92%; 4) 2-aminonicotinaldehyde (1.1 equiv), KOH (cat.), EtOH, reflux 4 h; 5) acetone, 2 N HCl, room temp., 84% (two steps); 6) pyridine, KOH (cat.), reflux, 3 h, 80%. Bz = benzyl.

A series of molecular strands based on napy–pym sequences was synthesized by using the Friedländer methodology (Scheme 1). The 2-aryl-4,6-dichloropyrimidines **1**, which were obtained following published procedures[13] from commercially available bromo-4-butylbenzenes and 4-hydroxybenzonitrile, were used as starting compounds. Stille coupling of the substituted dichloropyrimidines **1** with 1.1 or 2.1 equivalents of 1-tributylstannylethyl vinyl ether gave respectively the mono- **2** or diacetyl **3** derivative after acidic deprotection of the vinyl ether group. A second Stille coupling on **2** yielded the unsymetrically protected ketone **4**, which was condensed with 2-aminonicotinaldehyde[14] and deprotected to give the terminal end **6** of the strands. The diketone **3** was subjected to base-catalyzed condensation with 2.2 equivalents of 4-aminopyrimidine-5-carboxaldehyde, followed by acidic hydrolysis of the terminal pyrimidine to give the compounds **5**. Alkyl- and *O*-benzyl-substituted pyrimidines **5** bearing bis(aminopyridylcarboxaldehyde) were thereby prepared in reasonable yields. The final condensation of **5** and **6** was efficiently performed in pyridine using catalytic amounts of potassium hydroxide and yielded sequences **A** containing four napy and three pym groups. Longer strands were also synthesized by using the same methodology.

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On the basis of ealier results involving $(py\text{-}pym)_n$ strands,[7] $(napy\text{-}pym)_n$ sequences may be expected to adopt a predetermined well-defined helical conformation. The presence of such a shape in solution was supported by ^{1}H NMR spectroscopic studies. The strong upfield shift of the terminal napy protons (up to 0.5 ppm relative to a shorter non-overlapping strand) in the well-resolved and sharp spectrum of **A***t*Bu is consistent with overlapping aromatic rings and is diagnostic of the helical folding[7] represented by structure **A**, which defines an internal cavity with a diameter of about 3.5 Å. This helical arrangement was confirmed by NOE crosspeaks in a ROESY experiment which shows that protons 1 and 2 are close to protons 6 and 5, respectively.

The ^{1}H NMR spectra of the three helices bearing various substituents in deuterated chloroform showed increased line broadening when the substituent was less bulky (from *t*Bu, to OBz, and to *n*Bu), which is suggestive of intermolecular association at millimolar concentrations. Self-aggregation was confirmed by other experiments: increasing the concentration or the ionic strength of the medium (for example, by addition of NEt_4I in $CDCl_3$) led to signal shifts indicative of proton shielding (especially for the terminal napy groups). Marked broadening was produced by the addition of a polar solvent such as acetonitrile—a solvophobic aggregation effect reminiscent of solvophobic folding.[5a,b]

Most interestingly, self-association of helical monomers was strongly influenced by cationic additives. Titrations of the *n*Bu-substituted one-turn helix **A***n*Bu with alkali metal salts (cesium and potassium picrates) showed a strong upfield shift of all the ^{1}H NMR signals (by approximately 2 ppm) and broadened signals at millimolar concentrations (Figure 1).

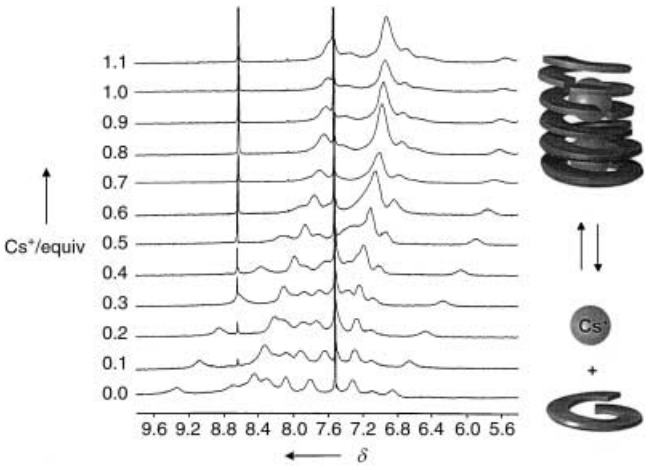

Figure 1. ^{1}H NMR titration of **A***n*Bu (2.7 mM in $CDCl_3/CD_3CN$ (1.7/1.0)) with cesium picrate (2.9 mM in the same mixture of solvents); right: representation of the formation of a stack of helical **A***n*Bu components containing Cs^+ ions.

Cations other than alkali ions appear to be even more efficient aggregate inducers, as evident from the line broadening of the NMR signals; indeed, hydronium and guanidinium[10] ions show stronger effects than the alkali ions. Thus, in a chloroform/ethanol/acetonitrile (3/6/2) mixture, the latter yield birefringent gels, which will be further characterized.

Electrospray mass spectrometry (ES-MS) studies gave results in line with the NMR spectroscopic data. Thus, when a 1/1 mixture of **A***n*Bu and potassium picrate was investigated in the same range of concentrations, mass signals corresponding to assemblies containing $x-y$ ions for x ligands ($y \leq x$) were detected (Figure 2). In addition to potassium ions,

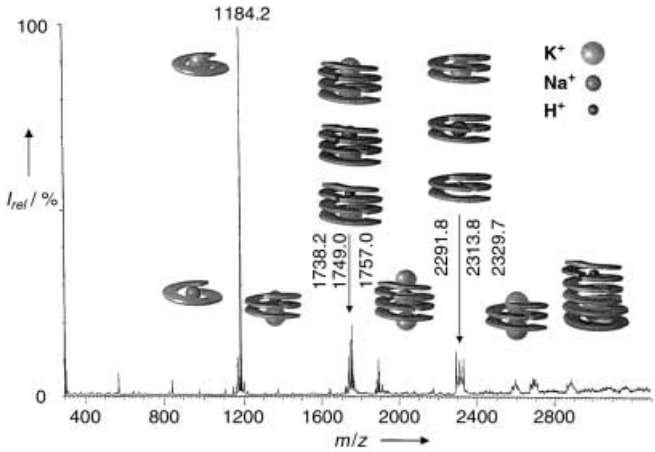

Figure 2. ES-MS spectrum of a 1/1 mixture of **A***n*Bu and potassium picrate (2.7 mM in $CHCl_3/CH_3CN$ (1.7/1.0)), 70 V. m/z: 1168.1 $[\mathbf{A}+Na]^+$, 1184.2 $[\mathbf{A}+K]^+$, 1176.4 $[2\,\mathbf{A}+K+Na]^{2+}$, 1738.2 $[3\,\mathbf{A}+K+H]^{2+}$, 1749.0 $[3\,\mathbf{A}+K+Na]^{2+}$, 1757.0 $[3\,\mathbf{A}+2\,K]^{2+}$, 1890.8 $[3\,\mathbf{A}+3\,K+Pic]^{2+}$, 2291.8 $[2\,\mathbf{A}+H]^+$, 2313.8 $[2\,\mathbf{A}+Na]^+$, 2329.7 $[2\,\mathbf{A}+K]^+$, 2597.4 $[2\,\mathbf{A}+2\,K+Pic]^+$, 2883.5 $[5\,\mathbf{A}+K+H]^{2+}$. The stacked structures shown are speculative, but agree with all the data obtained.

the binding of cesium, sodium, guanidinium ions as well as protons by the supramolecular helix aggregates also occurred. Divalent lead ions (introduced as the triflate salt) formed multiligand assemblies with **A***n*Bu: the ES-MS spectrum of a millimolar solution of the 1/1 complex in $CH_3CN/CHCl_3$ (1.7/1.0) showed mainly the $[3\,\mathbf{A}+2\,Pb]^{2+}$ adduct. These spectroscopic results agree with the formation of an assembly of stacked helices of component **A** containing cations in the internal void, as schematically represented in Figures 1 and 2.

The formation of a stack-type structure is supported by X-ray powder diffraction patterns, which yield a characteristic distance of 23–26 Å for the assemblies obtained with all the cations, as well as for the ligand itself. This value corresponds to the external diameter of the helix.[15]

The potassium-containing sample used for the ES-MS studies was investigated by transmission electron microscopy (TEM). Long interdigitated fibers were found (Figure 3), thus confirming by direct observation, the self-association into extended supramolecular assemblies. Single filaments could not be observed under the conditions used for sample preparation because of association. Similar observations were made with cesium ions. No clear textures were observed by TEM in the absence of added cations.

The present results show that the self-organization features resulting from the *transoid* conformational preference of the py–pym units[7] can be generalized to strands composed of sequences of alternating napy–pym heterocycles as a novel helicity codon, which enforces the formation of a helical

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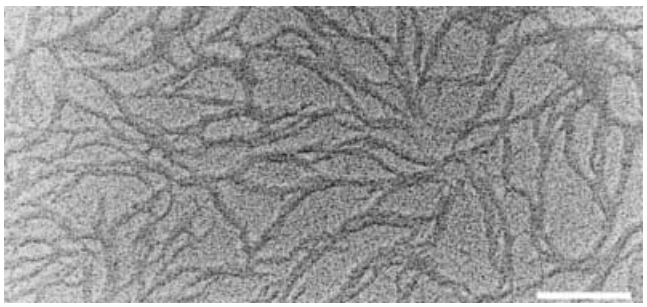

Figure 3. Transmission electron micrograph of a 1/1 mixture of **A***n*Bu and potassium picrate (3 mM in $CHCl_3/CH_3CN$ (1.7/1.0)). The white bar (bottom right) represents 200 nm. The sample was prepared as described in ref. [3d]).

foldamer[16] and generates a polar inner void towards the center of which all the napy electrical dipoles are directed. This arrangement induces cation complexation, which in turn promotes the multiple supramolecular association of ligands, through effects such as ion–dipole interaction and π stacking between the aromatic rings.

The hierarchical self-organization observed amounts to a sort of effector-induced growth process and is reminiscent of the self-assembly of the tobacco mosaic virus, where the formation of the helical protein coat results from the induced association of the peptide components by the nucleic acid strand occupying the central void of the polymolecular architecture. The formation of cation-containing polymolecular stacks of helical monomeric components suggests that such entities may potentially act as transmembrane ion channels[1, 17] that would not only conduct ions but also build up solely if suitable ions are present, thus presenting a most intriguing ability to perform a cation-selective self-regulation of ion flow.

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The Determination of the Absolute Configurations of Diastereomers of (*S*)-Camphanoyl 3-Hydroxy-5-oxohexanoic Acid Derivatives by X-ray Crystallography**

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Polyketides form a major class of secondary metabolites,[1] produced by fungi, lichens, and higher plants. 6-Methylsalicylic acid (6-MSA) is one of the simplest aromatic compounds produced by a polyketide biosynthesis pathway. It is assembled from one molecule of acetyl-coenzyme A (acetyl-CoA),

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