Molecular Recognition and the Design of Solid State Structures: Protonation-induced Conformational Change and Self-assembly of 2,6-Diamidopyridinium Phosphates

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Protonation of 2,6-diamidopyridine with diaryl phosphates leads to a conformational change in the pyridine from inwardly to outwardly directed amide-NH groups and a resultant self-assembly of the anion and cation into an alternating cocrystal with a novel hydrogen bonding motif.

The rational design of new solid state structures represents an important challenge in modern organic chemistry that has implications in the development of non-linear optical, conducting, magnetic and molecular electronic systems.[1] A particular goal involves the construction of solids with an ordered and predictable arrangement of two or more molecular components. To achieve this, carefully positioned interacting groups must be incorporated into the two components to provide both direction and orientation to the cocrystal. Hydrogen bonds have been extensively used to this end since they can be readily incorporated into and provide a complementary link between different subunits.[2] However, the directionality of the hydrogen bonding groups plays a critical role in determining molecular properties. In molecular recognition, hydrogen bonding sites are usually directed *inwards* (or *endo*) to converge on a central cleft or cavity. The result is a receptor that can form discrete 1 : 1 complexes with a complementary substrate (Fig. 1*A*).[3] In contrast, positioning the hydrogen bonding groups in an *outwards* (or *exo*) direction can lead to a self-assembly of the same components into an alternating polymeric complex (Fig. 1*B*).[4,5]

This simple relationship between binding group directionality and function prompted our search for a single component that would, under different conditions, serve as *either* a convergent receptor *or* a self-assembling subunit. Such a component might then switch between structures as a function of environment and so provide a macroscopic expression of microscopic molecular changes.[6]

Acylated mono- and di-aminopyridine derivatives have been used extensively in the design of synthetic molecular receptors.[7] In every case where an X-ray crystal structure is available, both substrate-free[8] and substrate-bound[8c,9] forms of the receptors have been shown to take up the parallel orientation of hydrogen bonding sites shown in Fig. 2.[8c] This conformation is expected owing to a favourable electrostatic interaction betweeen the pyridine-N and amide-NH groups, and corresponds to an *inwardly* (or *endo*) directed receptor capable of multiple H-bonding to a single substrate (as in Fig.

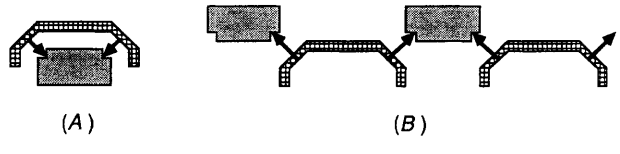

Fig. 1 Hydrogen bonding sites: (*A*) directed inwards; (*B*) directed outwards

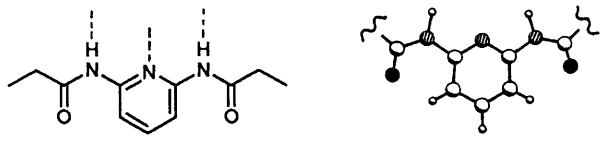

Fig. 2 Parallel hydrogen bonding arrangements in acylaminopyridine receptors

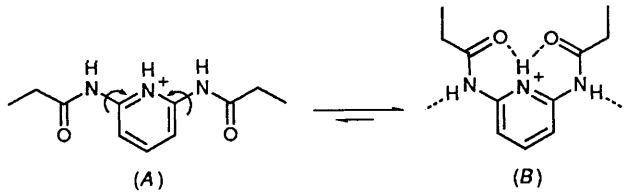

Fig. 3 Effect of protonation on hydrogen bonding orientation

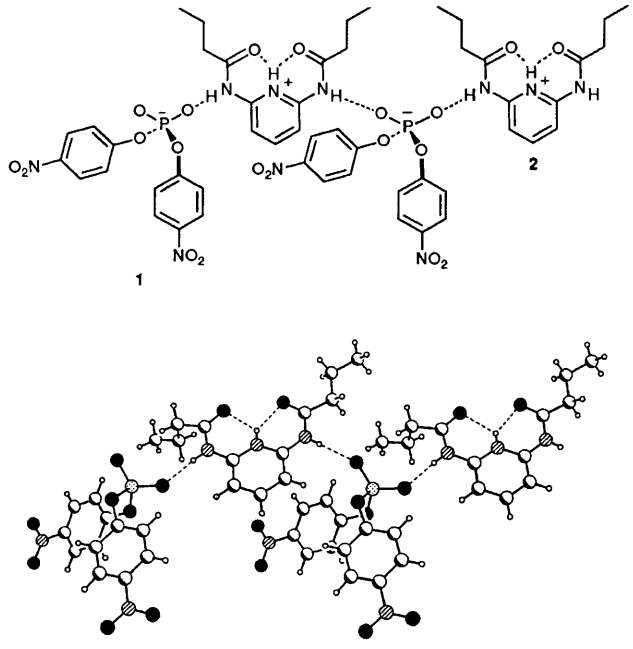

Fig. 4 X-Ray crystal structure of 2,6-dibutyramidopyridinium bis(4-nitrophenyl)phosphate

1*A*). A repulsive interaction can be introduced and the parallel orientation can be destabilized by simply protonating the pyridine ring. This should lead to a rotation about the pyridine–amide bond and formation of two intramolecular hydrogen bonds to the carbonyl oxygen (Fig. 3). The resulting conformation (Fig. 3*B*) now contains two *outwardly* (or *exo*) directed amide-NH groups capable of intermolecular hydrogen bonding.

Addition of one equivalent of bis(4-nitrophenyl) hydrogen phosphate **1** to a CH_2Cl_2 solution of 2,6-dibutyramidopyridine **2** leads to a decrease in the electronic absorption at 292 nm and the formation of a new maximum at 325 nm. This is similar behaviour to that seen on bubbling HCl through a CH_2Cl_2 solution of **2** and corresponds to protonation of the pyridine ring. Colourless triclinic crystals of 2,6-dibutyramidopyridinium bis(4-nitrophenyl)phosphate were grown by diffusion of hexane into a toluene solution of **1** and **2**.† The X-ray structure is shown in Fig. 4 and confirms the formation of an alternating hydrogen-bonded cocrystal (as in Fig. 1*B*). The pyridine ring is protonated [pyrN···H distance, 0.81(5)Å] and two intramolecular hydrogen bonds are formed to the carbonyl-oxygen atoms [H···O, 1.97(5), 2.03(5) Å]. The amide-NH groups project outwards and form hydrogen bonds to the two oxygens of a bridging phosphodiester [NH···OP, 1.89(5), 1.98(6)Å]. Overall, the structure shows a highly ordered assembly of the two components into a ribbon arrangement with the intermolecular hydrogen bond network at its core. The nature and direction of these interactions control the specific features of the structure. In particular, the anions and cations are

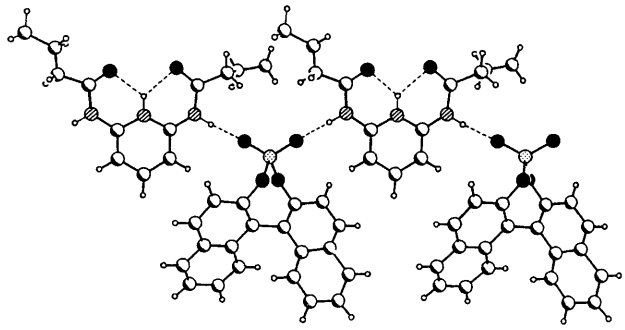

Fig. 5 X-Ray crystal structure of 2,6-dibutyramidopyridinium (*R*)-(−)-1,1′-binaphthyl-2,2′-diyl phosphate

segregated onto opposite sides of the ribbon and take up a parallel alignment to each other.

The organizing features apparent in Fig. 4 seem to be general. A similar type of alternating cocrystal structure results when equimolar amounts of 2,6-dibutyramidopyridine and diphenyl hydrogen phosphate are mixed.[10] Furthermore, asymmetry can be introduced into the structure by using optically active phosphodiesters. A 1:1 mixture of (*R*)-(−)-1,1′-binaphthyl-2,2′-diyl hydrogen phosphate and **1** gave, on slow evaporation from a tetrahydrofuran solution, orthorhombic crystals† with the structure shown in Fig. 5. Again, the hydrogen-bond network serves to align the two components into a highly ordered and parallel structure. This arrangement, coupled with the non-centrosymmetric nature of the crystal, holds potential for the design of solids with interesting optical properties.

In summary, we have demonstrated that 2,6-diacylaminopyridines undergo a discrete conformational change on protonation from an inwardly to an outwardly directed hydrogen-bonding receptor. When diaryl hydrogen phosphates serve as the acid a self-assembly takes place to form an ordered cocrystal with alternating acidic and basic subunits linked by a thread of hydrogen bonds. This motif appears to be general and offers an approach to the construction of new solid state structures with predictable arrangements of chiral, photoactive or redox-active subunits.

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† *Crystal data* for $C_{25}H_{28}N_5O_{10}P$: triclinic, $P\bar{1}$; a = 10.442(3), b = 11.353(3), c = 13.153(4) Å, α = 87.70(2), β = 80.37(2), γ = 67.24(2)°, V = 1415.1(7) Å^3, Z = 2, D_c = 1.383 g cm^{-3}, 23 °C. A Siemens R3m/E diffractometer was used to collect 4644 data (4° ≤ 2θ ≤ 48°) of which 2454 data with $F_o \geq 5\sigma(F_o)$ were used in the solution and refinement. No absorption correction was necessary [μ(Mo-Kα) = 1.53 cm^{-1}]. Structure was solved by direct methods which located all non-hydrogen atoms. Hydrogen atom positions were calculated [d(C–H) = 0.96 Å] except for nitrogen hydrogens which were located and refined. Structure refined to R_f = 5.51% and R_{wf} = 6.48%; GOF = 1.38, highest final difference peak, 0.33 e Å^{-3}.

Crystal data for $C_{33}H_{32}N_3O_6P$: orthorhombic, $P2_12_12_1$, a = 8.531(2), b = 11.765(2), c = 30.288(6) Å, V = 3040(1) Å^3, Z = 4, D_c = 1.306 g cm^{-3}, 23 °C. A Rigaku AFC5R diffractometer was used to collect 2637 data points (0° ≤ 2θ ≤ 120°) of which 1261 data with $F_o > 5\sigma(F_o)$ were used in the solution and refinement. No absorption correction was necessary [μ(Cu-Kα) = 11.88 cm^{-1}]. Structure was solved by direct methods which located all non-hydrogen atoms. Hydrogen atom positions were calculated [d(C–H) = 0.96 Å] except for nitrogen hydrogens which were located and refined. Structure refined to R_f = 6.93% and R_{wf} = 9.02%; GOF = 1.75, highest final difference peak, 0.28 e Å^{-3}.

Atomic coordinates, bond lengths and angles, and thermal parameters for both compounds have been deposited at the Cambridge Crystallographic Data Centre. See Notice to Authors, Issue No. 1.

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