Minimal complementary hydrogen-bonded double helices†

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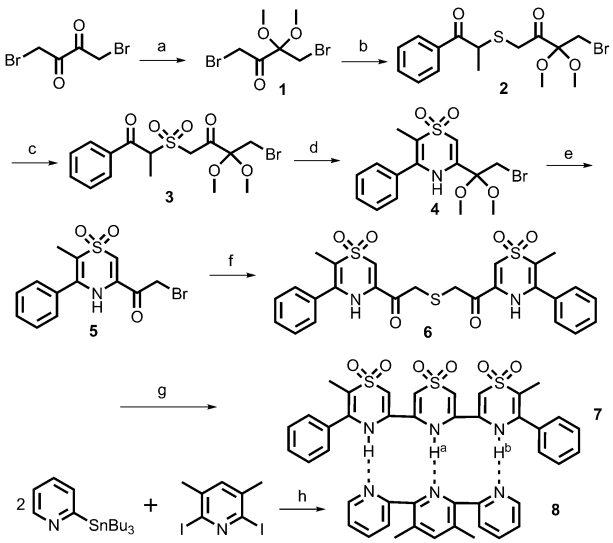
Molecular strands incorporating three hydrogen bond donor (D) or acceptor (A) heterocycles form highly stable double helical complexes through a complementary AAA–DDD array structure.

The design and characterization of linear oligomers that self-assemble into double helical structures has been a subject of interest to chemists since the elucidation of the double helix structure of DNA in 1953.[1] Transition metal templates have been widely used in the construction of artificial double helical complexes (helicates) from linear multidentate ligands.[2] The use of other non-covalent interactions as the driving force in the self-assembly of these types of complexes is less common. Aromatic stacking interactions,[3–5] anion templates,[6] and salt-bridges[7] have all been applied in this context. The great majority of these investigations have been concerned with the dimerization of identical linear oligomers to form homoduplex products. There are very few examples of artificial double helices that form from complementary strands to give heteroduplexes.[3e,j,4c,5c,7] Notably, Yashima, Furusho and coworkers have demonstrated that two complementary molecules may interact *via* amidinium–carboxylate salt bridges in a sequence dependent manner resembling the hybridization of ss-DNA.[7]

We have reported the formation of a double helical complex based on self-associating molecular strands containing alternating hydrogen bond donors (D) and acceptors (A) but its dimerization constant was very low (K_{dimer} = 5 M^{-1} at 298 K).[8] Herein, we report the formation of minimal complementary AAA–DDD hydrogen bonded double helices stabilized by three hydrogen bonds that exhibit much larger binding constants.

Molecular strand **7** was designed to include three thiazine-1,1-dioxide heterocycles that would present a DDD hydrogen bond sequence complementary to terpyridyl derivative **8** that presents an AAA pattern (Scheme 1). The synthesis of DDD component **7** is straightforward and can be executed in seven steps from commercially available 1,4-dibromobutane-2,3-dione. The AAA component **8** was synthesized in a single step from 2-tributyltinpyridine and 2,6-diiodo-3,5-lutidine *via* Stille coupling.

Unfortunately, **7** is completely insoluble in nonpolar solvents such as chloroform that are commonly used to mediate the self-assembly of systems based on hydrogen bonding. However, the addition of a molar equivalent of complementary



Scheme 1 Syntheses of **7** and **8**. *Reagents and conditions*: (a) $HC(OMe)_3$, conc. H_2SO_4; (b) 2-mercapto-propiophenone, K_2CO_3, CH_3CN; (c) m-CPBA, CH_2Cl_2, −78 °C to rt; (d) NH_4OAc/AcOH, reflux; (e) formic acid, reflux; (f) NaSH, H_2O, CH_2Cl_2; (g) (i) UHP/TFAA, CH_3CN, (ii) NH_4OAc/AcOH, reflux; (h) $Pd(PPh_3)_4$, toluene, reflux.

8 to a heterogeneous mixture of **7** and chloroform yields the soluble hydrogen bonded complex **7·8**. The ^{1}H NMR spectrum of the complex in $CDCl_3$ displays extreme downfield shifts for the thiazine dioxide NH protons of **7** at 12.88 (H^a) and 12.00 (H^b) ppm as would be expected from a strong hydrogen bond interaction with **8** (Fig. 1). Using the chemical shift of the thiazine NH proton of **14b** (see below) in $CDCl_3$ as a reasonable approximation of free **7** in this solvent, we calculate complexation induced shifts $\Delta\delta$ = 5.60 (H^a) and 4.73 (H^b) ppm. In addition, significant upfield shifts of the phenyl proton resonances of **7** are the result of either π-stacking with the pyridyl rings of **8**, or induction due to hydrogen bonding, or a combination of the two effects. Dilution of an equimolar solution of **7·8** to 1×10^{-4} M results in no change of the chemical shifts of the resonances observed

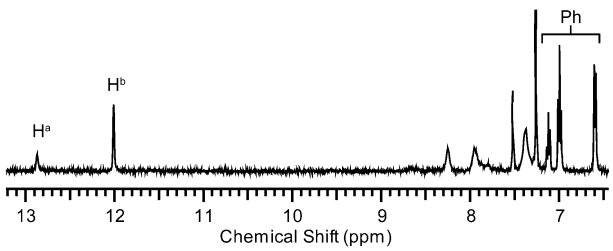


Fig. 1 Downfield region of the ^{1}H NMR spectrum of **7·8** in $CDCl_3$ at 298 K.

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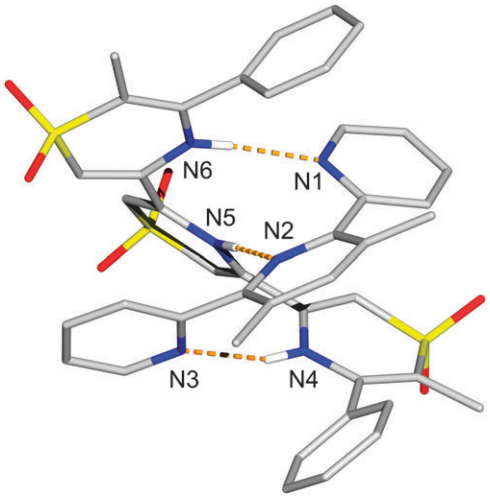
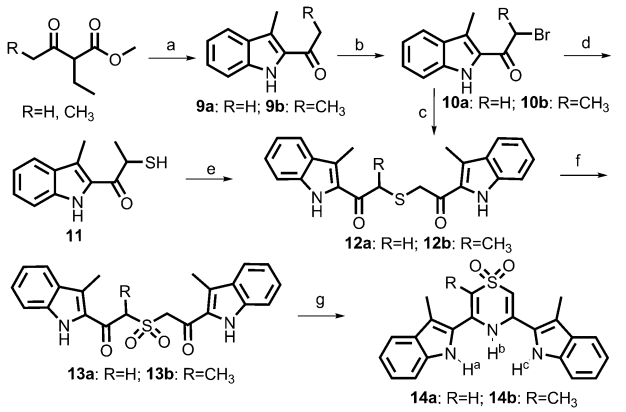


Fig. 2 Stick representation of the solid state structure of **7·8**. All C–H hydrogen atoms have been removed for clarity. NH···N hydrogen bonds are indicated by dashed orange lines.



Scheme 2 Syntheses of **14**. *Reagents and conditions*: (a) (i) NaOH, $EtOH/H_2O$, (ii) PhN_2Cl, 0 °C, (iii) formic acid, reflux; (b) $PhNMe_3Br_3$, THF, reflux; (c) for **12a**: Na_2S, acetone/water, 0 °C to rt; (d) for **11**: (i) KSAc, DMF, (ii) cysteamine hydrochloride, $NaHCO_3$, MeOH; (e) for **12b**: Et_3N, CH_3CN; (f) *m*-CPBA, DMF, −25 °C to rt; (g) NH_4OAc/AcOH, reflux.

for the complex, allowing an estimation of the lower limit for the association constant (K_a) of 1×10^5 M^{-1}.[9]

The solid state structure of complex **7·8** further supports the hydrogen bonded nature of the complex in solution. Single crystals were grown by slow diffusion of isopropyl ether into a chloroform solution of **7·8** and analyzed by X-ray diffraction.‡ The complex crystallizes with the two molecular strands intertwined in a double helical coconformation (Fig. 2). The three NH groups of the thiazine-1,1-dioxide heterocycles form short primary hydrogen bonds with the three nitrogen atoms of the pyridyl rings (*N*6H···*N*1 = 2.85, *N*5H···*N*2 = 2.88, *N*4H···*N*3 = 3.06 Å and N6H···N1 = 162, N5H···N2 = 177, N4H···N3 = 169°, respectively). Three carbon atoms (*ipso*, *ortho*, and *meta*) of a terminal phenyl ring of **7** are positioned over and engaged in π-stacking with the central pyridyl ring of **8** (C···π(pyridyl least squares plane) = 3.59, 3.37, and 3.42 Å) providing further rationalization of the upfield shifts observed for the attached phenyl proton resonances in the ^{1}H NMR spectrum.

The insolubility of **7** in chloroform prompted us to incorporate different donor groups into this scheme in an effort to modify the solubility of the DDD component. Incorporation of 3-methylindole (skatole) heterocycles as terminal donor groups was a straightforward and potentially versatile alteration. A Japp–Klingemann/Fischer indole synthesis was employed as a route to 2-acylskatole intermediates **9a/b** (Scheme 2).[10] These were carried forward to elaborate the central thiazine dioxide ring, in a similar manner to the methods used to synthesize **7**, producing **14a** and **14b**.

14a also displayed very poor solubility in non-polar solvents. However, in this case we were able to crystallize **14a** by slow diffusion of isopropyl ether into an acetone solution and gained some insight into the likely reason for the insolubility of both **7** and **14a**. The single crystal X-ray analysis‡ revealed a structure composed of antiparallel C_2 symmetric 1-D chains (Fig. 3) that lie along the *b* direction of the lattice. The chains are held together by four intermolecular hydrogen bonds between the donor NH groups of one

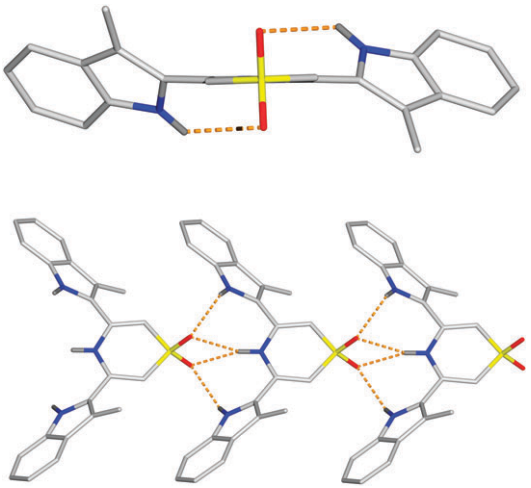


Fig. 3 Stick representations of the solid state structure of **14a**. View along *b* direction (top). View perpendicular to *b* direction (bottom). All C–H hydrogen atoms have been removed for clarity. NH···N hydrogen bonds are indicated by dashed orange lines.

molecule of **14a** and the sulfone oxygen atoms of the next in the chain. The individual molecules reside in a helical conformation such that each indole NH donor forms a hydrogen bond with one or the other of the two sulfone oxygen atoms in the adjacent molecule (*N*H···*O* = 3.04 Å and NH···O = 139°). The thiazine NH donor participates in a bifurcated hydrogen bonding arrangement with both oxygen atoms of the same sulfone (*N*H···*O* = 3.10 Å and NH···O = 149°). In non-polar solvents this intermolecular attraction is likely strong enough to generate the observed insolubility of **14a** (and by analogy **7**).

We surmised that steric crowding of the sulfone in **14a** would reduce or prevent the aggregation observed in the solid state by hindering the close intermolecular approach of the NH donors. Hence, the addition of a methyl group to the 2-position of the thiazine dioxide ring in **14b** was anticipated to improve its solubility in nonpolar solvents. To our

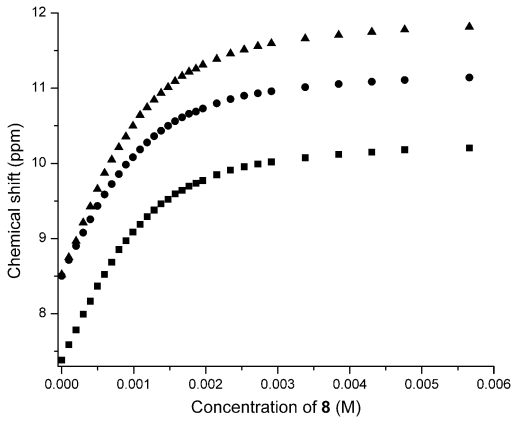


Fig. 4 Complexation induced chemical shift changes of NH protons of **14b** (H^a (●), H^b (■), H^c (▲)) upon titration with **8** in $CDCl_3$ at 298 K.

satisfaction, the addition of this group does render **14b** soluble in chloroform.

The successful dissolution of **14b** in chloroform allowed a determination of the association constant using ^{1}H NMR. **14b** was titrated with a solution of **8** in $CDCl_3$ at 298 K and changes in the chemical shifts of the NH resonances were monitored during the addition (Fig. 4). The data were fitted to a 1 : 1 host : guest binding model[11] using non-linear regression software to yield a K_a value of 3700 M^{-1} ($\Delta G = -20.4$ kJ mol^{-1}). The lower magnitude of the stability constant for **14b**·**8** in comparison to **7**·**8** is likely a result of the markedly weaker donor ability of skatole *versus* thiazine dioxide (which approximates a sulfonamide).

We have outlined the synthesis and characterization of a series of DDD triple hydrogen bond donor molecules that form stable to very stable double helical complexes with terpyridyl derivative **8**. It should be noted that accessing **14b** analogues with significantly greater hydrogen bond donor character (*e.g.* similar to thiazine dioxide), and likely much higher K_a values, can be accomplished by the addition of withdrawing groups to the 5-positions of the indole rings; a simple modification of the syntheses outlined in Scheme 2. We are currently pursuing these alterations and investigating the utility of the resulting molecular components in supramolecular polymer applications.

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Notes and references

‡ Crystal data for **7**·**8**: $C_{43}H_{38}N_6O_6S_3$·$HCCl_3$, M = 950.34 g mol^{-1}, triclinic, a = 12.1851(4), b = 12.7756(4), c = 15.7666(5) Å, α = 82.465(1)°, β = 77.978(1)°, γ = 70.320(1)°, U = 2255.40(12) Å^3, T = 150 K, space group $C2/c$, Z = 2, 143 783 reflections measured, 14 429 unique reflections (R_{int} = 0.0804), $R(F^2 > 2\sigma)$ = 0.0456, $R_w(F^2$, all data) = 0.1181. CCDC 783459. For **14a**: $C_{22}H_{19}N_3O_2S$, M = 389.46 g mol^{-1}, monoclinic, a = 27.937(6), b = 6.7394(13), c = 9.871(2) Å, β = 92.11(3)°, U = 1857.24(60) Å^3, T = 150 K, space group $C2/c$, Z = 2, 6382 reflections measured, 1657 unique reflections (R_{int} = 0.0637), $R(F^2 > 2\sigma)$ = 0.0482, $R_w(F^2$, all data) = 0.1289. CCDC 783460.

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