Oligo-ligandosides: a DNA mimetic approach to helicate formation

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A novel 'ligandoside' dimer, where 2,2′-bipyridine chelators are attached to the anomeric carbons of a D-ribose–phosphate backbone, forms double stranded multinuclear complexes.

The distinct geometry of coordination complexes has been extensively employed for the programmed assembly of exquisite structures.[1] Among these assemblies, double stranded multinuclear complexes known as helicates, have attracted special attention due to their structural resemblance to the DNA double helix and intriguing stereochemistry.[2] While some control over the stereochemical elements involved in helicate formation (*e.g.* the helix chirality and the relative orientation of non-symmetrical strands) has been achieved, controlling this multicomponent assembly remains a challenging problem.[3]

Although assembling helical complexes was inspired by the structure of the DNA double helix, none of the structural elements inherent to DNA has been exploited in helicate design. This is especially intriguing as both the chirality of the DNA helix and its anti-parallel orientation are encoded in the sugar–phosphate backbone.[4] We have sought to explore if incorporation of native DNA structural elements into synthetic binders can be employed to dictate the formation of defined complexes. In these novel structures, ligands are attached to the anomeric carbon of the D-ribose–phosphate backbone replacing the DNA nucleobases (Fig. 1). Unlike helicates where the ligands are integrated into the helical backbone, here the ligands project away from the backbone. Importantly, the backbone phosphodiester groups may be considered as 'built-in' counter ions that can balance the charges associated with metal complex formation. In this contribution we present the design and synthesis of first generation polynuclear complexes based on this approach.

The building block for synthesizing these polytopic ligands is a nucleoside mimic, coined ligandoside, where the heterocyclic base is replaced by a metal-binding ligand.[5,6] Our first model is based on 2,2′-bipyridine (bpy) as a chelator (Scheme 1). A methylene bridge is introduced between the bpy and the sugar to allow for a more relaxed structure and dimensions similar to the DNA double helix. The synthesis of the binding strand utilizes the standard DNA phosphoramidite chemistry.[7] The 5′-protected ligandoside **1** is converted to the phosphoramidite **2** or to the 3′-protected acetate **3**. The two components are then coupled in the presence of 1*H*-tetrazole. Oxidation of the trivalent phosphorus with iodine–water–pyridine mixture gives the phosphate triester derivative **4**. Removal of the protecting groups provides the ditopic ligand **5** (Scheme 1). The structure of **5** was confirmed by NMR and MS.† The development of this phosphoramidite chemistry is particularly attractive for future solid phase synthesis of longer oligomeric strands.

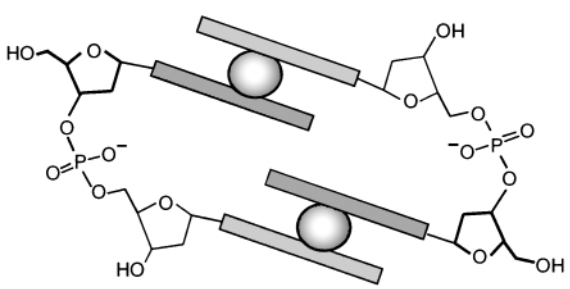
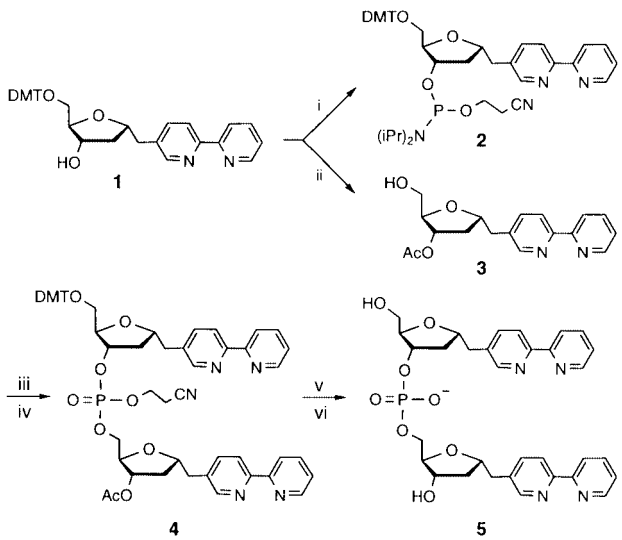


Fig. 1 Schematic representation of a DNA mimetic metal binding dimer.

The absorption spectrum of ligand **5** shows the characteristic π–π* absorption bands of the aromatic bpy at 242 and 287 nm. Upon titration with Cu^+ under an inert atmosphere, new bands at 266 and 300 nm appear with three isosbestic points (Fig. 2). An additional metal to ligand charge transfer (MLCT) band at 440 nm, characteristic of copper–bpy complex formation, also emerges. The titration establishes a 1 : 1 ratio between the metal and the ligand. This stoichiometry can be attributed either to the formation of a mononuclear (**5**Cu) or a dinuclear ($\mathbf{5}_2Cu_2$) complex. ESI mass spectrometry reveals the formation of a mononuclear complex only (*m*/*z* 696 calcd. for **5**CuNa). The pattern and isotopic distribution exclude the possibility that this peak represents the doubly charged complex $\mathbf{5}_2Cu_2$.

Titration of ligand **5** with Pd^{2+} results in the appearance of new absorption bands at 248 and 314 nm with two isosbestic points (Fig. 2). The mass spectrum indicates the formation of the mononuclear complex **5**Pd (*m*/*z* 739 calcd. for **5**Pd) together with a dinuclear species (*m*/*z* 1479 calcd. for $\mathbf{5}_2Pd_2$–H, 1500 calcd. for $\mathbf{5}_2Pd_2Na$–H). It is difficult to establish the actual equilibrium ratio between the various species in the mass spectrum due to their different ionization abilities.‡

Upon titration of ligand **5** with Ag^+ in MeOH, complex formation is manifested as a shift in absorption bands to 250 and 296 nm associated with the appearance of three isosbestic points (Fig. 2). This titration verifies the formation of a 1 : 1 complex between the metal ion and the ditopic ligand (Fig. 2). The ESI mass spectrum indicates the formation of the dinuclear complex $\mathbf{5}_2Ag_2$ (*m*/*z* 1483 calcd. for $\mathbf{5}_2Ag_2H$, 1505 calcd. for $\mathbf{5}_2Ag_2Na$).



Scheme 1 *Reagents and conditions*: i, 2-cyanoethyl-*N*,*N*,*N*′,*N*′-tetraisopropylphophordiamidite, 1*H*-tetrazole, CH_3CN, 1.5 h; ii, a. Ac_2O, Py, 12 h, b. 8 : 2 AcOH–H_2O, 1.5 h; iii, 1*H*-tetrazole, CH_3CN, 3 h; iv, I_2–THF–H_2O–Py; v, 8 : 2 AcOH–H_2O, 1 h; vi, NH_4OH, CH_3CN–MeOH, 12 h.

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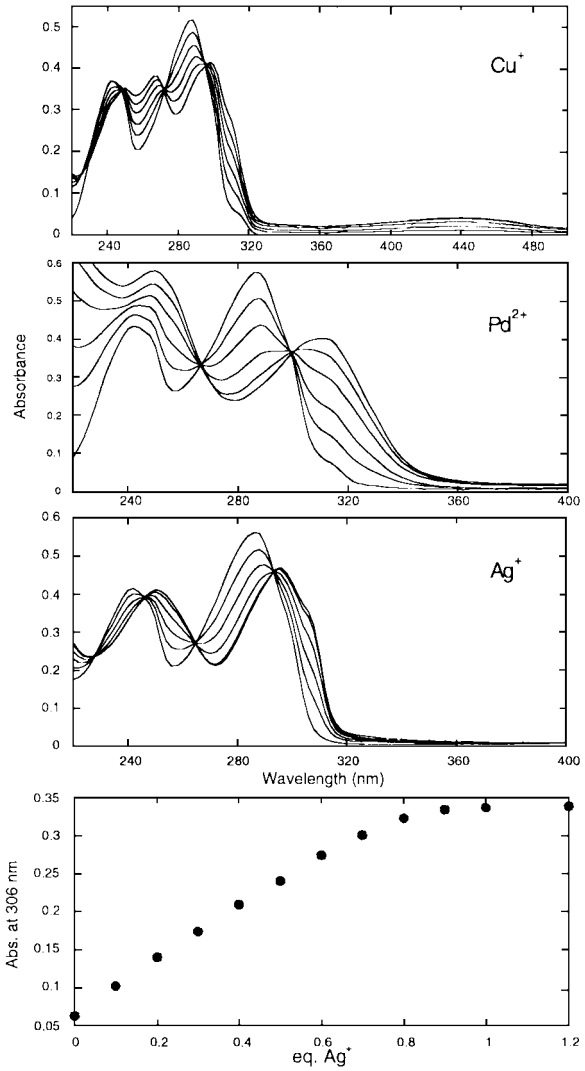

Fig. 2 Uv-vis titrations of di-ligandoside monophosphate **5** in MeOH with a. $Cu(CH_3CN)_4BF_4$ in CH_3CN, b. $Pd(CH_3CN)_4(BF_4)_2$ in CH_3CN, c. $AgCF_3SO_3$ in MeOH. Bottom: a representative curve illustrating the formation of a 1 : 1 complex.

The theoretically predicted pattern and isotopic distribution perfectly matches the experimentally observed one (Fig. 3).

These results demonstrate that threading ligands on a sugar–phosphate backbone can lead to the formation of double stranded structures. In the prototypical ligandoside system described here, the formation of double stranded structures is in competition with the formation of single stranded complexes. This can be attributed to the flexibility of both the sugar–phosphate backbone and the bpy–CH_2 ligand. It is anticipated that further refinement of the ligand structure (*i.e.* changes to the bridging unit between the sugar and the ligand, changes to the connection position of the bpy ring) will further increase the tendency to form double stranded structures.

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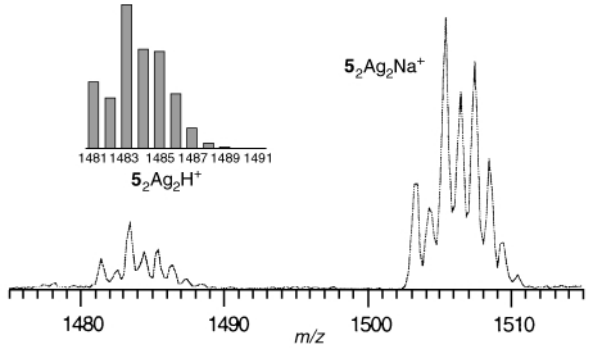

Fig. 3 ESI mass spectrum of the dinuclear complex $\mathbf{5}_2Ag_2$ and its sodium adduct. The insert shows the corresponding theoretical isotopic pattern.

Notes and references

† Full synthetic procedures will be published elsewhere. The DMT-protected **1** is chromatographically resolved into the α and β anomers. Structural assignment is based on NOE experiments, where the β anomers shows a key NOE signal between the H-1′ and H-4′. Selected data for **5**: ^{1}H NMR (400 MHz, CD_3OD) δ 8.61 (br s, 2H, bpy), 8.51 (br d, J = 10.0 Hz, 2H, bpy), 8.24 (br d, J = 7.6 Hz, 2H, bpy), 8.18 (br d, J = 7.6 Hz, 2H, bpy), 7.90 (m, 2H, bpy), 7.82 (m, 2H, bpy), 7.39 (m, 2H, bpy), 4.62 (m, 1H, H3′$_a$), 4.37 (m, 2H, H3′$_b$ and H1′$_b$), 4.26 (m, 1H, H1′$_a$), 4.06 (m, 1H, H4′$_a$), 3.95 (m, 1H, H4′$_b$), 3.89 (m, 2H, H5′$_b$), 3.57 (m, 2H, H5′$_a$), 3.04–2.84 (m, 4H, C*H*$_2$bpy), 2.37 (m, 1H, H2′$_b$), 2.28 (m, 1H, H2′$_a$), 1.91 (m, 1H, H2′$_a$), 1.71 (m, 1H, H2′$_b$). FAB-MS calcd for $C_{32}H_{35}N_4O_8P$ 635 found *m*/*z* 635.

‡ The mononuclear complex is singly charged and may appear as the major component since it can be detected with no further dissociation.

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