A large enhancement in the binding affinity of artificial hosts by Os^{VI} chelation

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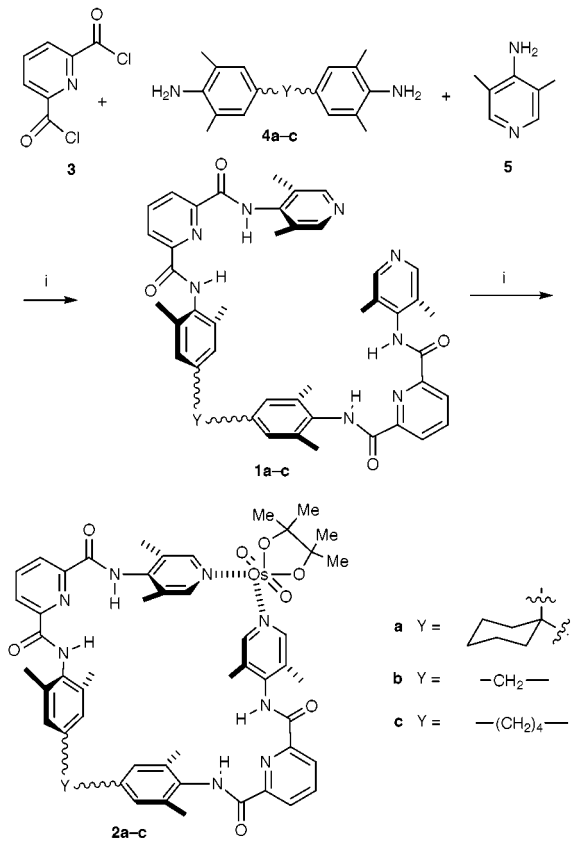
Mononuclear Os^{VI}-chelated macrocycles, self-assembled from OsO_4, 2,3-dimethylbut-2-ene and bispyridyl ligands, bind diamides much more strongly than the Os^{VI}-free ligands ($\Delta\Delta G$ = −14.6 kJ mol^{-1}).

Self-assembly by weak noncovalent interactions has recently attracted a great deal of attention in the area of host–guest and supramolecular chemistry. The strategy has been effectively used to synthesise artificial receptors in which two or more subunits are spontaneously coordinated to a metal ion to generate a binding cavity complementary to the targeted substrates.[1] On the other hand, metal ion chelation to one part of a flexible host may result in the structural reorganisation of another binding site, leading to allosteric behaviour in the binding events.[2–5] Here, we have prepared three bispyridyl ligands **1a**–**c** that spontaneously self-assemble into the corresponding macrocyclic complexes **2a**–**c** in the presence of alkene and OsO_4,[6,7] and compared the binding affinities of **1a**–**c** and **2a**–**c** toward diamide guests.

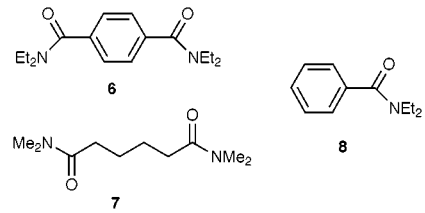
As shown in Scheme 1, the bispyridyl ligands **1a**–**c** were prepared by dropwise addition of diamines **4a**–**c** followed by aminolutidine **5** to a solution of pyridine-2,6-dicarbonyl dichloride **5** in CH_2Cl_2. The yields were 10–18% after repeated chromatography. The neutral macrocyclic complexes **2a**–**c** were spontaneously assembled within a few minutes by addition of OsO_4 (~1 equiv., 0.1 M in toluene) to a 1:1 molar mixture of the ligands **1a**–**c** and 2,3-dimethylbut-2-ene in a $CHCl_3$ at room temperature. After concentration, the residues were thoroughly washed with Et_2O to afford the Os^{VI}-complexes **2a**–**c** as brown solids (66–88% yield).



Scheme 1 *Reagents and conditions*: i, $EtNPr^i_2$, 0 °C to room temp.; ii, 2,3-dimethylbut-2-ene, OsO_4.

Elemental analysis of the products agreed well with 1:1:1 molar composition of OsO_4, 2,3-dimethylbut-2-ene and the ligand. Their IR spectra show a strong, characteristic band near 830 cm^{-1} diagnostic of the *trans* O=Os=O moiety of the octahedral dioxoosmium^{VI} complexes.[8] In the ^{1}H NMR spectra, the lutidyl C–H resonances of **2a**–**c** were shifted downfield (~0.28 ppm) relative to those for ligands **1a**–**c**, as expected upon coordination of the nitrogen to the Os^{VI} ester. The ^{1}H NMR spectra remain constant over a wide range of concentrations (0.25–10 mM) and temperatures (−40 to 40 °C) in $CDCl_3$, indicating that no aggregation or dissociation occurs under these conditions. ^{1}H NMR integration also confirmed a 1:1 molar ratio of the ligand and 2,3-dimethylbut-2-ene. The FAB-MS analyses strongly support the formation of mononuclear complexes **2a**–**c**. For example, the mass spectrum of **2a** shows the molecular ion [MH$^+$] peak at 1169.4 (intensity 1.8%, 1168.4 calc. for $C_{56}H_{64}N_8O_8{}^{192}Os$), [M − O]$^+$ at 1152.4 (intensity 3.3%), and [M − $(O_2C_2(CH_3)_4)$]$^+$ at 1052.4 (intensity 2.4%). The observed isotopic distribution patterns of all these peaks are consistent with those calculated for the mononuclear macrocycle **2a**. The complexes **2b** and **2c** also show the same FAB-MS spectral behaviour as seen for complex **2a**.

The binding properties of hosts **1a**–**c** and **2a**–**c** with diamide guests **6** and **7** were revealed in $CDCl_3$ by ^{1}H NMR titration



experiments, performed by adding the guest solution (5–10 mM) to the host stock solution (1–2 mM, 500 μl) in small potions. The time-averaged signals for the free and bound species were observed due to a fast exchange on the NMR time–scale. The association constants (K_a/M^{-1}) were calculated by non-linear least-squares fitting[9] of the titration data, which corresponded well to the expression for a 1:1 binding isotherm. All the hosts contain two different NH protons, and both N–H signals of the hosts were significantly downfield shifted ($\Delta\delta \geq$ 1 ppm) when guests **6** and **7** were added, indicating significant hydrogen bond formation. As a representative example, the two NH signals in the Os^{VI} complex **2a** were shifted downfield from δ 8.83 and 9.22 to δ 9.80 and 10.62, respectively, upon complexation with terephthalamide **6**. The titration curves, plotting either NH chemical shift change *vs.* equivalents of guest, gave essentially identical association constants within experimental error (<5%), indicating that both NHs are involved in a single binding mode.

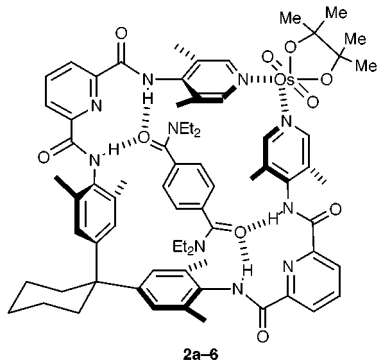
As seen in Table 1, the association constants between Os-free ligands **1a**–**c** and guests **6** and **7** decrease in the order **1a** > **1b** > **1c**. This is expected because **1a** contains conformationally the most rigid linker, while **1c** possesses the most flexible

Table 1 Association constants (K_a/M^{-1}) of ligands **1a–c** and Os complexes **2a–c** with diamide guests **6** and **7** in $CDCl_3$ at 25 ± 1 °C

Guest	Ligand	K_a/M^{-1} [a]	Os complex	K_a/M^{-1} [a]	$\Delta\Delta G°$/ kJ mol^{-1} [b]
6	**1a**	2800	**2a**	1.7×10^4	−4.5
6	**1b**	580	**2b**	1.9×10^4	−8.6
6	**1c**	80	**2c**	2.9×10^4	−14.6
7	**1a**	210	**2a**	1.6×10^4	−10.7
7	**1b**	95	**2b**	2.9×10^4	−14.2
7	**1c**	30	**2c**	6.1×10^3	−13.2

[a] Titrations were duplicated and errors in K_a are within 10% for $K_a < 1 \times 10^4$ M^{-1} and within 30% for $K_a > 1 \times 10^4$ M^{-1}. [b] $\Delta\Delta G° = \Delta G°$(Os complex) − $\Delta G°$(ligand).

linker. More important a trend in the association constants is that Os complexes **2a–c** bind the guests **6** and **7** much more strongly than the corresponding Os-free ligands **1a–c**. The difference in the binding energy is up to $\Delta\Delta G° = -14.6$ kJ mol^{-1}, depending on the linker group; the more flexible the linker is, the greater the difference observed. The large enhancements of the association constants in the Os^{VI} complexes are possibly attributed to the following two factors. One is the conformational preorganization of the hosts **2a–c** as a consequence of Os^{VI} chelation, which greatly reduces the conformational entropy loss upon association of the host and guest. Another contributing factor may be the increased hydrogen-bonding donor ability of the lutidyl N–H protons as a result of Os^{VI} chelation to the terminal nitrogens.



2a–6

The ligand **1a** and its Os^{VI} complex **2a** strongly bind diamide guest **6**, while they bind only slightly the monoamide analogue, *N*,*N*-diethylbenzamide **8** ($K_a \leq 15$ M^{-1} in $CDCl_3$, observed $\Delta\delta_{max} \leq 0.15$ ppm). The Job plots[10] showed a 1:1 stoichiometry between the host **1a** or **2a** and the diamide guest **6**. These observations clearly indicate that two hydrogen-bonding sites in the hosts must simultaneously participate in the complexation, as shown in the proposed structure of the complex **2a**·**6**. Additional evidence for the complex structure was obtained from ^{1}H NMR spectroscopy (Fig. 1). When **2a** and **6** are mixed in a 1:1 molar ratio, the NH signals of the host **2a** are largely downfield shifted ($\Delta\delta \geq 1$ ppm), and more importantly, the aryl C–H signal of the guest **6** is significantly upfield shifted ($\Delta\delta \sim 1.5$ ppm). The latter strongly suggests that the guest **6** is located inside the cavity surrounded by the host aryl walls,

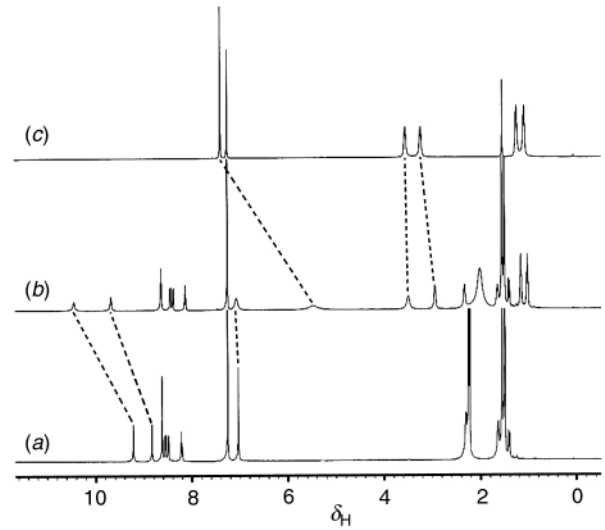


Fig. 1 ^{1}H NMR spectra of (*a*) host **2a** (3 mM), (*b*) host **2a** (3 mM) + guest **6** (3 mM), and (*c*) guest **6** (3 mM) in $CDCl_3$ at 25 °C.

which induce an anisotropic shielding environment in the ^{1}H NMR spectrum.

In conclusion, we have shown the self-assembly of cleft-like bispyridyl hosts into the corresponding macrocycles by Os^{VI} ester chelation, which significantly increases the binding affinity toward guests. Further studies are underway to develop optically active hosts for the chiral recognition of peptide derivatives.

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