Coordination-Driven Assembly of Molecular Clefts

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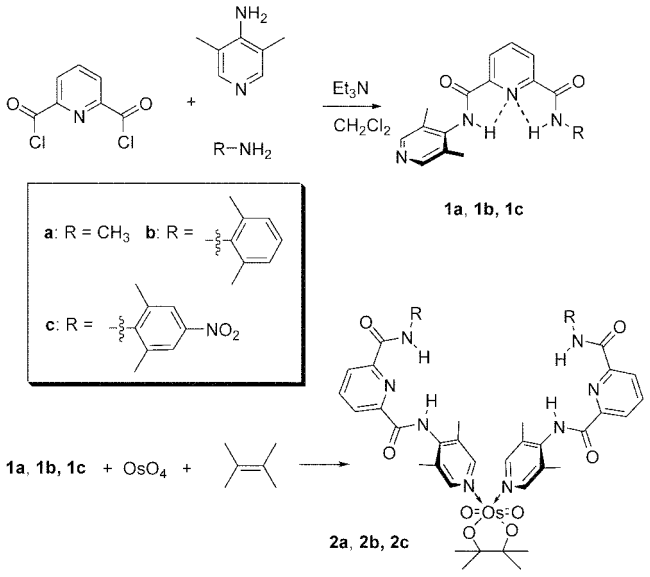
Concerted multi-point interactions are a prerequisite for selective and strong bindings between receptor and substrate. To do so, two or more binding groups must be covalently connected to an appropriate spacer that provides the right distance and orientation complementary to a target substrate. This covalent method is highly reliable but requires multi-step, time-consuming synthesis. An alternative method is to use the self-assembly that collects molecular fragments in a preprogrammed way to yield the desired receptor. Due to its proper strength and directionality, the metal-ligand interaction has been demonstrated to be most useful for this purpose and successfully implemented for the self-assembly of numerous macrocycles and cages.[1] However, only a few of noncovalent, self-assembled molecular clefts have been reported to date,[2] despite a wide spread use of covalent counterparts as artificial receptors.

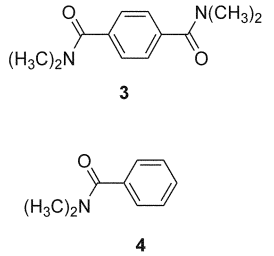
We reported a few years ago the self-assembly of discrete, neutral macrocycles by the combination of osmium tetraoxide, alkene, and bispyridyl ligand.[3] Using this self-assembling motif, we have here prepared new molecular clefts **2a**, **2b** and **2c** that are capable of binding a terephthalamide by multiple hydrogen bonds. The hydrogen bonding sites of **2a**, **2b** and **2c** are based on the pyridine-2,6-dicarboxamide scaffold where two amide hydrogens are inwardly oriented by a virtue of weak, internal N (pyridyl)···H-N (amide) hydrogen bonds. Owing to the conformational rigidity, the pyridine-2,6-dicarboxamide skeleton has been used as an important building block for the construction of many supramolecular structures.[4]

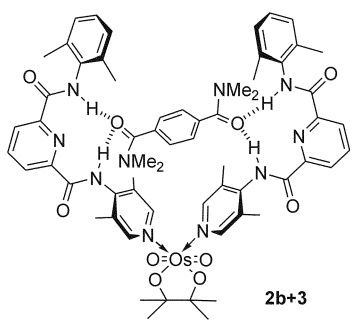


Scheme 1

Ligands **1a**, **1b** and **1c** were prepared in one pot by sequential coupling reactions of pyridine-2,6-dicarbonyl dichloride with 4-amino-3,5-lutidine[5] and the corresponding amine (aminomethane, 2,5-dimethylaniline or 2,5-dimethyl-4-nitroaniline[6]) in 18-22% isolated yields. When each of the ligands was mixed with osmium tetraoxide and 2,3-dimethyl-2-butene in an equal molar ratio, the clefts **2a**, **2b** and **2c** were self-assembled within a few minutes. The reactions proceeded quantitatively but the isolated yields were 70-79%. Elemental analyses and spectroscopic data were all consistent with the structures of the clefts **2a**, **2b** and **2c**.[7]

The binding ability of the clefts **2a**, **2b** and **2c** was revealed by ^{1}H NMR titration experiments, using *N,N,N',N'*-tetramethylterephthalamide (**3**) as the guest. The experiments were performed at 24 ± 1 °C by the addition of the guest solution (10 mM in $CDCl_3$) to a $CDCl_3$ solution containing each cleft (2 mM in $CDCl_3$). Under these conditions, time-averaged resonances for the free and the complexed species were always observed. Two NH signals of the cleft were largely downfield shifted upon addition of **3**, indicative of hydrogen bonding formation. For example, two NH signals of the cleft **2b** were gradually downfield shifted from 8.94 and 9.32 ppm to 9.70 and 10.60 ppm, respectively. Nonlinear least squares fitting methods[8] of these titration curves gave the association constant of 360 ± 20 M^{-1} between **2b** and **3**. The titration curves generated from both NH changes gave essentially an identical association constant within experimental error (<10%), indicating that both NHs are participated in the same binding event. Job plot[9] confirmed a 1 : 1





Scheme 2

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(**2b**/**3**) stoichiometry of the complex, showing the maximum complex formation at the mol fraction of 0.5.

When the cleft **2b** was titrated with a monoamide, *N,N*-dimethylbenzamide (**4**) under the same conditions, the NH chemical shift changes were too small ($\Delta\delta < 0.1$ ppm) to determine accurately the association constant ($K_a < 5$ M^{-1}). This observation strongly supports that two pyridinedicarboxamide binding sites of **2b** are simultaneously involved in the binding to form multiple hydrogen bonds with the diamide guest **3**, like in a proposed structure of the complex (**2b**+ **3**, Scheme 2). Finally, association constants of other clefts, **2a** and **2c**, with **3** were determined to be 80 ± 10 M^{-1} and 480 ± 20 M^{-1}, respectively, under the same conditions. These results suggest that the arylamide NH (in **2b** and **2c**) is better hydrogen-bonding donor than the alkylamide NH (in **2a**) and the nitro substituent at the *para* position (in **2c**) slightly increases the hydrogen donor ability.

In conclusion, three molecular clefts have been self-assembled by simply mixing osmium tetraoxide, 2,3-dimethyl-2-butene, and pyridyl ligands. The clefts have two hydrogen-bonding sites in a convergent way and bind a diamide guest by multiple hydrogen bond formation. The cleft can be conveniently modified at will by the variation of the ligand, and consequently this approach may provide an opportunity to construct more elaborate molecular cleft-type receptors.

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7. Physical and spectroscopic properties. **2a**: dark brown solids, mp >100 °C (decomp). IR (KBr) 3448, 1670, 831 cm^{-1}. ^1H NMR ($CDCl_3$, 250 MHz) δ 9.42 (s, 2H, NH), 8.62 (s, 4H), 8.44 (d, J = 7.7 Hz, 4H), 8.12 (t, J = 7.7 Hz, 2H), 7.74 (br s, 2H, NH), 3.08 (d, J = 4.8 Hz, 6H), 2.28 (s, 12H), 1.48 (s, 12H). ^{13}C NMR ($CDCl_3$, 63 MHz) δ 164.7, 162.2, 149.6, 148.8, 140.1, 132.4, 90.7, 54.1, 27.1, 25.3, 16.9. Anal. Calcd for $C_{36}H_{44}N_8O_8Os$: C, 47.67; H, 4.88; N, 12.35. Found: C, 47.70; H, 4.87; N, 12.30. **2b**: dark brown solids, mp > 100 °C (decomp). IR (KBr) 3448, 1686, 830 cm^{-1}. ^1H NMR ($CDCl_3$, 250 MHz) δ 9.32 (s, 2H, NH), 8.94 (s, 2H, NH), 8.65 (s, 4H), 8.54 (d, J = 7.8 Hz, 4H), 8.20 (t, J = 7.8 Hz, 2H), 7.18-7.11 (m, 6H), 2.31 (s, 24H), 1.47 (s, 12H). ^{13}C NMR ($CDCl_3$, 63 MHz) δ 161.3, 160.8, 148.8, 148.5, 148.1, 146.6, 146.4, 137.4, 134.0, 126.9, 123.7, 123.6, 120.0, 90.5, 25.0, 19.4, 16.5. Anal. Calcd for $C_{50}H_{56}N_8O_8Os$: C, 55.24; H, 5.19; N, 10.31. Found: C, 55.24; H, 5.20; N, 12.29. **2c**: dark brown solids, mp > 100 °C (decomp). IR (KBr) 3445, 1699, 826 cm^{-1}. ^1H NMR ($CDCl_3$, 250 MHz) δ 9.30 (s, 2H, NH), 9.09 (s, 2H, NH), 8.64 (s, 4H), 8.56 (d, J = 7.8 Hz, 4H), 8.20 (t, J = 7.8 Hz, 2H), 8.01 (s, 4H), 2.42 (s, 12H), 2.31 (s, 12H), 1.46 (s, 12H). ^{13}C NMR ($CDCl_3$, 63 MHz) δ 161.5, 161.3, 149.4, 148.6, 148.5, 148.0, 140.0 135.3, 133.2, 130.9, 128.6, 127.9, 126.7, 90.2, 24.8, 18.8, 16.4.
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