Pseudo-allosteric regulation of the anion binding affinity of a macrocyclic coordination complex†

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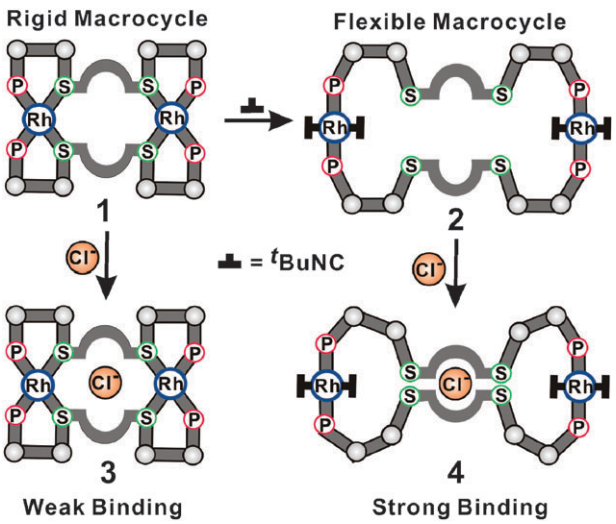
The anion binding affinity of a macrocyclic Rh complex can be allosterically regulated by reaction with a small molecule (an isocyanide), which effects a change in macrocycle size and shape.

Recent advances in coordination chemistry have led to the development of efficient synthetic methods for the selective formation of two- and three-dimensional supramolecular structures that exhibit new properties and functions, which sometimes exceed what is possible with small molecule systems.[1,2] Our group has been developing the weak-link approach (WLA) for the synthesis of supramolecular complexes.[3] The complexes made by the WLA are comprised of hemilabile ligands and metal nodes, and they can be chemically interconverted between rigid condensed structures and larger open macrocycles *via* ligand substitution reactions that, in the case of the condensed structures, displace the more weakly coordinating functionality of the hemilabile ligands. Using this approach, we have developed a variety of allosteric compounds, which use small molecules to regulate catalytic reactions, the formation of pseudo-rotaxanes, and enantiomer recognition.[4] Indeed, these structures have led to the first examples of allosteric enzyme mimics based upon coordination chemistry complexes,[4a] and new concepts for amplified chemical detection, where small molecules induce conformational changes, which trigger a catalytic reaction that generates a signaling agent.[4a–c,f,g]

Biological systems that employ ion channels often use allosteric regulatory events to control the recognition and transport of ions across membranes,[5] yet extension of this concept to man-made coordination-based systems is limited.[6] This prompted us to consider how one might design a coordination complex with anion binding properties[7] that can be allosterically controlled,[8] **1–4** (Scheme 1). Herein, we describe the synthesis and characterization of one such complex based upon a Rh(I) macrocycle **1** synthesized *via* the WLA.

To synthesize macrocycle **1**, the new phosphinothioether hemilabile ligand **5** was first prepared (Scheme 2). Ligand **5** was made in 75% yield by the reaction of 2,6-pyridinedicarbonyl dichloride and 4-(2-(diphenylphosphino)ethylthio)-phenylamine[9] in the presence of NEt_3 in CH_2Cl_2. The reaction of **5** with $[Rh(nbd)_2][B(C_6F_5)_4]$ (nbd = norbornadiene) in CH_2Cl_2 resulted in the formation of a cyclic dinuclear Rh(I) complex **6a** in 96% yield. Complex **6a** exhibits a single $^{31}P\{^1H\}$ NMR resonance at δ 65.1 (d, J_{Rh-P} = 162 Hz), which is highly diagnostic of κ^2-P,S ligand coordination to Rh(I).[3] The ^1H NMR spectrum shows a single resonance for the amide proton at δ 9.50 and aromatic resonances similar to those of the metal-free ligand, indicating a symmetric structure in the solution-state (Fig. 1a and b). Electrospray ionization mass spectrometry (ESI-MS) of **6a** exhibits a parent ion at 908 m/z corresponding to the $[M\text{-}2B(C_6F_5)_4]^{2+}$ ion. Elemental analysis of the complex also supports the proposed structure (see ESI†). The solid-state structure of **6a** was confirmed by a single-crystal X-ray diffraction study (Fig. 2).‡ The Rh(I) centers exhibit distorted-square-planar geometries with *cis*-S and *cis*-P coordination environments. Four N–H protons are directed to the center of the macrocycle, suitable for anion binding. Reaction of the PS ligand with $[Rh(nbd)_2][BF_4]$ and $[RhCl(CO)_2]_2$ gave related complexes but with different



Scheme 1 Schematic representation describing the strategy for allosterically controlling the anion binding affinity of a macrocycle. Reaction of the macrocycle with a small molecule (^{t}BuCN) at a metal-based regulatory site increases the macrocycle size and changes its flexibility, leading to an increased affinity for chloride ions.

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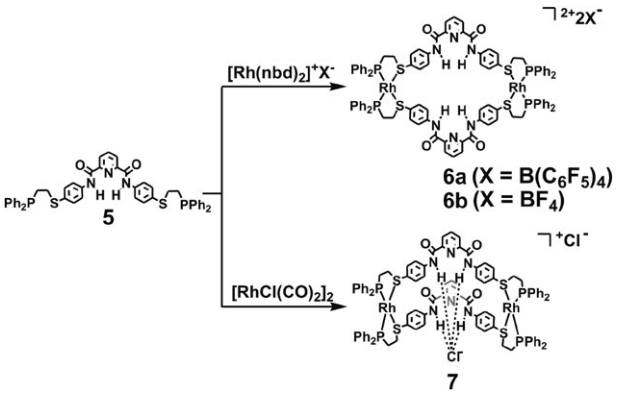


Scheme 2 Syntheses of macrocyclic complexes *via* the WLA.

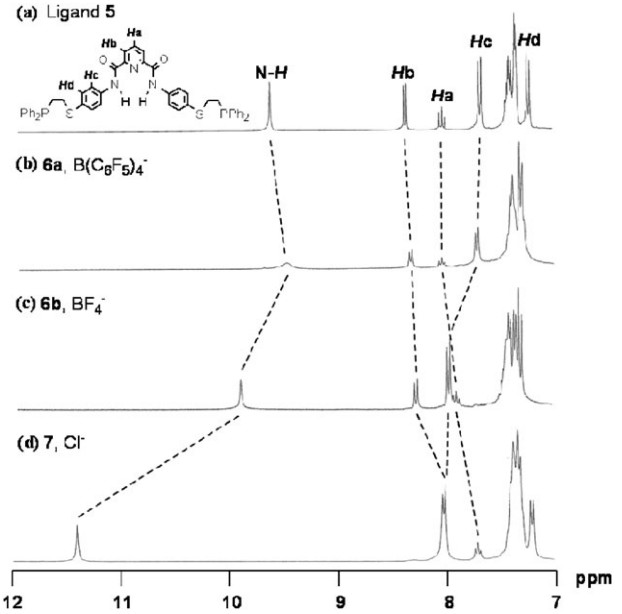


Fig. 1 The aromatic and amide regions of the ^{1}H NMR spectra for **5**, **6a**,**b** and **7** in CD_2Cl_2 (300 MHz, 23 °C, 10 mM), respectively.

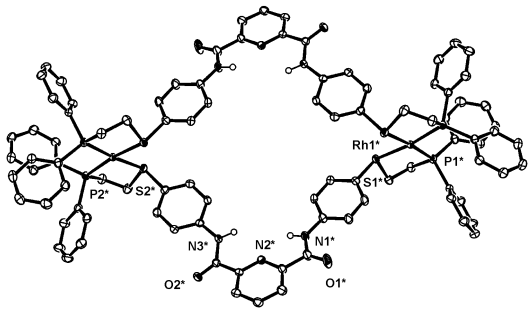


Fig. 2 ORTEP drawing of complex **6a** with thermal ellipsoids drawn at 50% probability. Solvent molecules, counter anions and hydrogen atoms except for amide protons have been omitted for clarity. Selected bond distances (Å) and angles (°): Rh(1)–P(1) = 2.2449(8), Rh(1)–P(2) = 2.2437(8), Rh(1)–S(1) = 2.3385(8), Rh(1)–S(2) = 2.3394(7), P(1)–Rh(1)–P(2)* = 97.34(3), P(1)–Rh(1)–S(1) = 85.78(3), P(1)–Rh(1)–S(2)* = 172.63(3), P(2)*–Rh(1)–S(1) = 175.06(3), P(2)*–Rh(1)–S(2)* = 85.34(3), S(1)–Rh(1)–S(2)* = 92.02(3).

counter anions (**6b** and **7**, respectively) in near-quantitative yields (Scheme 2). Since BF_4^- is a stronger hydrogen bonding

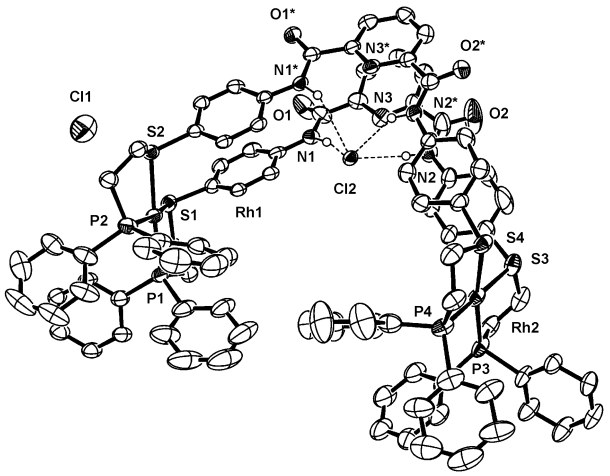
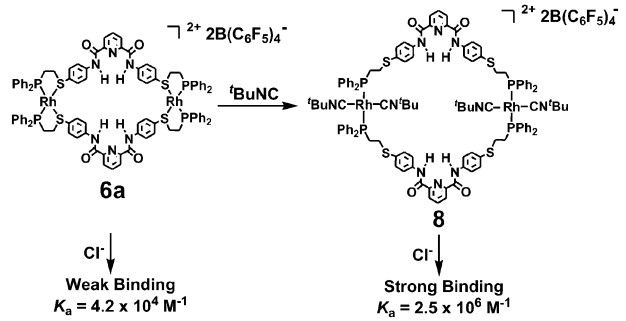


Fig. 3 ORTEP drawing of complex **7** with thermal ellipsoids drawn at the 50% probability. Solvent molecules and hydrogen atoms except for amide protons have been omitted for clarity. Selected bond distances (Å) and angles (°): Rh(1)–P(1) = 2.240(2), Rh(1)–P(2) = 2.240(2), Rh(1)–S(1) = 2.364(2), Rh(1)–S(2) = 2.356(2), Rh(2)–P(3) = 2.245(2), Rh(2)–P(4) = 2.247(2), Rh(2)–S(3) = 2.362(2), Rh(2)–S(4) = 2.3414(2), N(1)–Cl(2) = 3.404(4), N(1)*–Cl(2) = 3.265(4), N(2)–Cl(2) = 3.277(6), N(2)*–Cl(2) = 3.292(2), P(1)–Rh(1)–P(2) = 96.40(6), P(1)–Rh(1)–S(1) = 85.77(6), P(1)–Rh(1)–S(2) = 176.78(5), P(2)–Rh(1)–S(1) = 168.80(5), P(2)–Rh(1)–S(2) = 85.58(5), S(1)–Rh(1)–S(2) = 92.77(5), P(3)–Rh(2)–P(4) = 97.94(5), P(3)–Rh(2)–S(3) = 85.48(5), P(3)–Rh(2)–S(4) = 171.00(5), P(4)–Rh(2)–S(3) = 175.67(5), P(4)–Rh(2)–S(4) = 85.36(5), S(3)–Rh(2)–S(4) = 90.87(5).

acceptor than $B(C_6F_5)_4^-$, the resonance for the amide N–H in **6b** exhibits a downfield shift compared to that of **6a** (Fig. 1b and c). Fig. 1d shows the N–H resonance of **7** at δ 11.40 indicating strong hydrogen bonding between the amide groups and Cl^-. The solid-state structure of **7** was confirmed by a single-crystal X-ray diffraction study (Fig. 3).‡ Interestingly, there are dramatic differences in the overall shape of **7** and **6a**, although the Rh(I) centers of **7** exhibit distorted-square-planar geometries similar to the Rh(I) centers in **6a**. Significantly, one of the Cl^- ions of **7** is located in the cavity of the macrocycle, and the other is outersphere with no evidence of a bonding interaction with the macrocycle. For the complexed Cl^- in **7**, the average distance between the Cl atom and the N atoms in the amide groups is 3.31 Å, consistent with a strong hydrogen bonding interaction between them. This complexation of Cl^- through hydrogen bonding is likely responsible for the severe structural differences between **6a** (cyclic) and **7** (saddle shape). Typically, Cl^- prefers a tetrahedral geometry with its four lone pairs interacting with four hydrogen donor groups,[10] but, in the solid-state, the crystal structure of **7** shows a pyramidal geometry with the Cl^- assuming the top position of the pyramid. This could be due to the rigidity of the condensed macrocycle due to the κ^2-P,S coordination at the Rh centers, which prevents the complexation of Cl^- in a manner that allows for a tetrahedral coordination geometry.

Condensed macrocycle **6a** can be opened quantitatively into a structurally flexible macrocycle **8** by reacting it with ^{t}BuNC in CH_2Cl_2 (Scheme 3). Complex **8** exhibits a single $^{31}P\{^1H\}$



Scheme 3 Binding affinity of Cl^- in closed and open states.

NMR resonance at δ 18.2, indicating κ^1-P,S coordination.[3] Complexes with two or three isocyanides on each Rh(I) center are possible products, but based upon ^{1}H NMR spectroscopic studies and integration of resonances associated with the ^{t}Bu groups, the tris-isocyanide structure can be ruled out. The conclusion that there are two rather than three isocycanides per Rh(I) center is also supported by elemental analysis. The *trans* configuration of **8** can be confirmed based upon a comparison with known simpler model complexes.[11]

Most interestingly, the Cl^- association constants (K_a)[12] of **6a** and **8**, measured in CH_2Cl_2 at 23 °C (Fig. S1 and S2 in ESI†), are significantly different. The open macrocycle **8** has a K_a (2.5×10^6 M^{-1}) approximately two orders of magnitude larger than the condensed macrocycle **6a** (4.2×10^4 M^{-1}) because of the conformational flexibility of **8** as compared with **6a**, which allows it to adopt a more optimal geometry for Cl^- binding.

In summary, we have synthesized a macrocyclic complex **6a** that can react with small molecules to induce a ring expansion, which significantly increases its affinity for chloride ion (60-fold increase). The expansion leads to greater conformational flexibility of the amide groups responsible for Cl^- binding, as evidenced by solid-state structures and solution spectroscopic data.

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Notes and references

‡ Crystallographic details for **6a**·$5CH_2Cl_2$; $C_{147}H_{92}B_2Cl_{10}F_{40}N_6O_4P_4Rh_2S_4$, M = 3600.33, yellow block, Bruker Smart 1000 CCD (Mo Kα radiation), T = 100(2) K, triclinic, spacegroup $P\bar{1}$, a = 11.7786(7) Å, b = 15.5130(9) Å, c = 22.633(2) Å, α = 71.650(4)°, β = 75.085(3)°, γ = 71.629(3)°, V = 3667.3(4) Å^3, Z = 1, D_{calc} = 1.630 g cm^{-3}, absorption coefficient 5.397 mm^{-1}, 33 224 measured reflections, 13 013 independent reflections [R_{int} = 0.0362], θ range for data collection 4.02° to 68.26°, R_1 = 0.0421, wR_2 = 0.1018, GOF = 1.045 [$I > 2\sigma(I)$]. CCDC 719264.

Crystallographic details for **7**·$4CH_2Cl_2$; $C_{98}H_{94}Cl_{10}N_6O_4P_4Rh_2S_4$, M = 2232.23, yellow block, Bruker Smart 1000 CCD (Mo Kα radiation), T = 100(2) K, monoclinic, spacegroup $P2(1)/c$, a = 17.477(5) Å, b = 37.81(1) Å, c = 15.719(4) Å, β = 110.518(4)°, V = 9729(4) Å^3, Z = 4, D_{calc} = 1.524 g cm^{-3}, absorption coefficient 0.821 mm^{-1}, 70 319 measured reflections, 17 150 independent reflections [R_{int} = 0.0506], θ range for data collection 1.24° to 25.00°, R_1 = 0.0622, wR_2 = 0.1734, GOF = 1.150 [$I > 2\sigma(I)$]. CCDC 719265.

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