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Self-Assembly of a Highly Stable, Topologically Interesting Metallamacrocycle by Bridging Gold(I) Ions with Pyridyl-2,6-diphenyl^{2-} and Diphosphanes**

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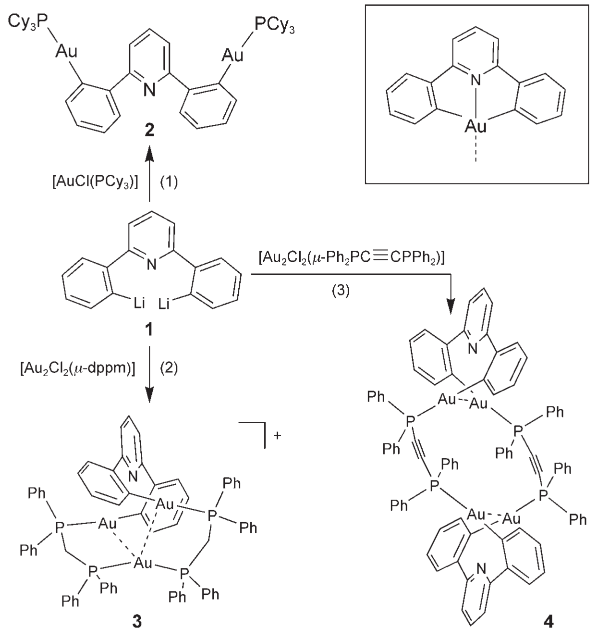
Metallamacrocycles constructed through self-assembly play an important role in the development of molecular architecture and topology.[1] There have been numerous reports on fascinating molecular assemblies that consist of metallamacrocycles, from catenanes,[1a] pseudorotaxanes,[1a,c] and helicates[1a,b,d] to molecular polygons/polyhedrons.[1d] The Möbius strip is another intriguing topology that has attracted considerable attention from chemists[2] but remains rarely seen in synthetic molecular assemblies. Previous reports are almost all confined to Möbius arrangements of electronic orbitals or spins, including many theoretical studies on Möbius aromaticity or delocalization,[2] together with the syntheses of a Möbius aromatic hydrocarbon[3] and a magnetic Möbius strip.[4] The synthesis of a molecular Möbius strip, an organic molecule consisting of three crown ether rings, was first realized in 1982.[5] Recently, a Möbius strip of $NbSe_3$ single crystals was reported.[6] Herein, we report the formation of a molecular assembly that contains a highly robust metallamacrocycle, with the bonds directly attached to the metallamacrocycle adopting a Möbius arrangement.

We have been exploring the chemistry of gold complexes with a pyridyl-2,6-diphenyl^{2-} (CNC) ligand. Our previous work led to the isolation of several Au^{III}–CNC complexes[7] that contain the tridentate CNC ligand (see the inset of Scheme 1). In the course of developing the chemistry of Au^{I}–CNC complexes, we conceived that $[Li_2(CNC)(tmeda)_2]$ (**1**; tmeda = *N*,*N*,*N'*,*N'*-tetramethylethylenediamine)[8] would be a useful alkylating agent. Treatment of **1** with $[Au(PCy_3)Cl]$ (Cy = cyclohexyl) in dry toluene gave $[Au_2(CNC)(PCy_3)_2]$ (**2**; reaction 1, Scheme 1) in 80% yield. Complex **2** is thermally stable and undergoes decomposition to give metallic gold at > 325 °C. The ^{31}P NMR spectrum of **2** in CD_2Cl_2 shows one sharp singlet at $\delta = 57.35$ ppm. The X-ray crystal structure of **2**[9] (see the Supporting Information) features a CNC ligand that bridges two Au^{I} ions, an unreported coordination mode of the CNC dianion in its coordination chemistry.[10]



Scheme 1. Syntheses of **2**–**4** from **1** (note the omission of the tmeda ligands in **1** for clarity). The inset depicts the coordination mode of the CNC ligand in previously reported gold complexes.

In view of the propensity of the CNC ligand to bridge Au^{I} ions, we envisioned that this ligand could have a unique application in constructing Au^{I} metallamacrocycles. Previously, a wide variety of Au^{I} metallamacrocycles had been prepared by employing isocyanide-, acetylide-, pyridine-, carboxylate-, and phosphane-based bridging ligands,[11] notable examples of which are the singly and doubly braided [2]catenanes reported by Puddephatt and co-workers.[11b,c]

Our strategy for constructing the metallamacrocycles presented herein is through self-assembly from **1** and Au^{I}–diphosphane complexes (reactions 2 and 3, Scheme 1). Reaction of **1** with $[Au_2Cl_2(\mu\text{-dppm})]$ (dppm = bis(diphenylphosphanyl)methane) in dry toluene for 24 h gave a yellow suspension. Removal of the solvent followed by extraction with dry $CHCl_3$ and slow evaporation of the $CHCl_3$ extract afforded $[Au_3(CNC)(\mu\text{-dppm})_2]Cl$ (**3**-Cl) as yellow crystals in 86% yield. Under similar conditions, the reaction of **1** with $[Au_2Cl_2(\mu\text{-}Ph_2PC{\equiv}CPPh_2)]$ resulted in the formation of $[Au_4(CNC)_2(\mu\text{-}Ph_2PC{\equiv}CPPh_2)_2]$ (**4**), which was isolated as yellow crystals in 75% yield by diffusion of Et_2O into a solution of $CHCl_3$. Treatment of **3**-Cl with excess $LiClO_4$ and $LiPF_6$ produced $[Au_3(CNC)(\mu\text{-dppm})_2]ClO_4$ (**3**-ClO_4) and $[Au_3(CNC)(\mu\text{-dppm})_2]PF_6$ (**3**-PF_6), respectively, in about 95% yield. In the solid state, complexes **3**-Cl, **3**-ClO_4, and **3**-PF_6 exhibited a high thermal stability similar to that of **2**; complex **4** is less stable and decomposed at 150 °C and subsequently gave metallic gold at 250 °C.

X-ray crystal-structure determinations of **3**-Cl·8.5 $CHCl_3$, **3**-PF_6·CH_2Cl_2·5 $CHCl_3$, and **4**·3 $CHCl_3$[9] revealed a 16-mem-

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bered $C_8NP_4Au_3$ metallamacrocycle in **3** and a 26-membered $C_{16}N_2P_4Au_4$ metallamacrocycle in **4** (see Figure 1 and the Supporting Information). The Au atoms in **3** and **4** form a $\{Au_3\}$ triangle and a $\{Au_4\}$ parallelogram, respectively, with intramolecular Au···Au contacts of 3.015(29)–3.040(29) Å for **3** (Au1···Au2, Au2···Au3) and 3.178(10) Å for **4** (Au1···Au2, Au1′···Au2′), which fall within the range of 2.9–3.2 Å expected for the occurrence of weak $Au^I\cdots Au^I$ interactions.[12] The Au–C bond lengths of 2.034(14)–2.070(16) Å in **3** and 2.077(39)–2.091(14) Å in **4** are comparable to those in **2** (2.053(9)–2.059(13) Å).

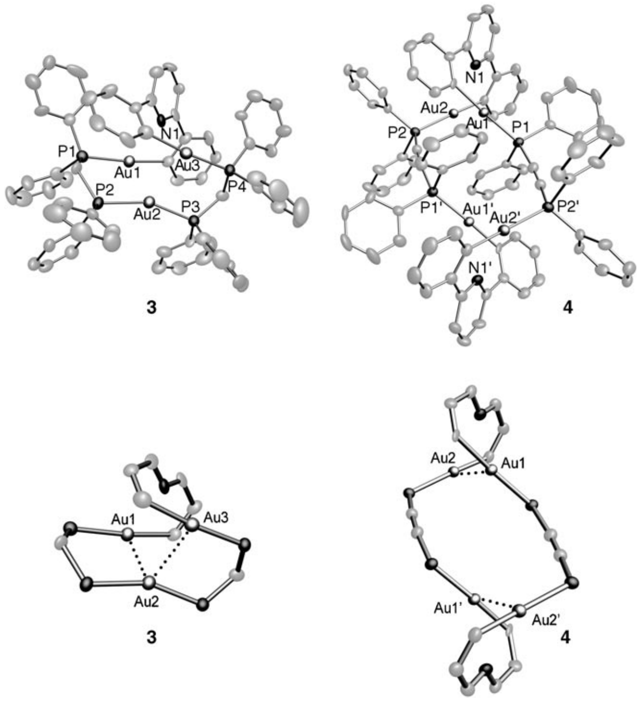

Figure 1. Perspective structures of **3**-Cl and **4** determined by X-ray crystallography along with the metallamacrocycles in the two complexes. For **4**, there is a crystallographic center of symmetry located in the center of the molecule.

Interestingly, the bonds directly attached to the 16-membered metallamacrocycle $C_8NP_4Au_3$ in **3** adopt a Möbius arrangement. The Möbius strip that passes through the $C_8NP_4Au_3$ ring and the P–C and C–C bonds directly attached to the ring is depicted in Figure 2. As a Möbius strip is chiral, the crystal structure of **3** contains pairs of *P* and *M* enantiomers (see the Supporting Information), thus rendering **3** to be racemic.

Further examination of the structures of **3**-Cl·8.5 $CHCl_3$ and **3**-PF_6·CH_2Cl_2·5 $CHCl_3$ revealed the existence of intramolecular C–H···π interactions, as indicated by the close contacts (2.787–3.113 Å) between one of the methylene hydrogen atoms in each dppm ligand (see the Supporting Information) and the carbon atoms of the nearest phenyl rings of the CNC ligand. In both crystal structures, **3** exists as dimers, each of which consists of a pair of *P* and *M* enantiomers linked by two intermolecular C–H···π interactions (a C–H bond of a dppm phenyl group with the nearest phenyl ring of the CNC ligand; closest H···C distances: 2.826 Å for **3**-Cl·8.5 $CHCl_3$ and 2.848 Å for **3**-PF_6·CH_2Cl_2·5 $CHCl_3$). For each of the dimers in **3**-Cl·8.5 $CHCl_3$, there are also four intermolecular C–H···π interactions that arise from the C–H bonds of four $CHCl_3$ molecules (two inside and two outside the dimers) and the nearest CNC phenyl rings (closest H···C distances: 2.540 and 2.739 Å for the interactions outside and inside the dimers, respectively).

Figure 2. Arrangement of the bonds directly attached to the 16-membered metallamacrocycle $C_8NP_4Au_3$ of **3** along a Möbius strip. A Möbius strip is a unique single-sided surface, as evident by following the track of the arrows.

The structure of **3** remains intact in solution, as revealed by mass-spectrometric and NMR spectroscopic analysis; for example, complex **3**-Cl exhibits a prominent cluster peak at *m*/*z* 1589 in the FAB mass spectrum, which is assignable to $[Au_3(CNC)(\mu\text{-dppm})_2]^+$. The ^{31}P NMR spectra of **3**-Cl, **3**-ClO_4, and **3**-PF_6 each show two multiplets (AA′BB′ system) with $\delta \approx 30$ (P^1 and P^4) and 37 ppm (P^2 and P^3; assignment based on the $^{31}P,^1H$ HOESY NMR spectra shown in the Supporting Information), which is consistent with the C_2-symmetic structure of the molecule of **3**. In the ^1H NMR spectra of **3**-Cl, **3**-ClO_4, and **3**-PF_6, the H^a signal ($\delta \approx 1.2$ ppm) is substantially upfield from that of H^b ($\delta \approx 4.0$ ppm; see the Supporting Information for an example), a phenomenon attributable to the shielding of H^a by the phenyl ring of the CNC ligand. The NOESY NMR spectrum of **3**-Cl shows a cross peak between H^a and H^3 (see the Supporting Information). These data are in agreement with the intramolecular C–H···π interactions in the crystal structures of **3**-Cl and **3**-PF_6.

In contrast, the 26-membered metallamacrocycle $C_{16}N_2P_4Au_4$ in **4**, which consists of a pair of *P*- and *M*-$[Au_2(CNC)P_2]$ moieties,[13] exhibits a fluxional behavior in solution. This is evident from the variable-temperature ^1H NMR (60 to −53 °C)[14] and ^{31}P NMR spectra of **4** in $CDCl_3$ (see the Supporting Information for further details). We propose that **4** is partially changed to its conformer **5** upon dissolution in $CDCl_3$, and there is an equilibrium between **4** and **5** in solution (Figure 3).[15] Indeed, the EXSY spectrum of **4** at −53 °C shows cross signals of H^3–$H^{3'}$, H^4–$H^{4'}$, H^5–$H^{5'}$,

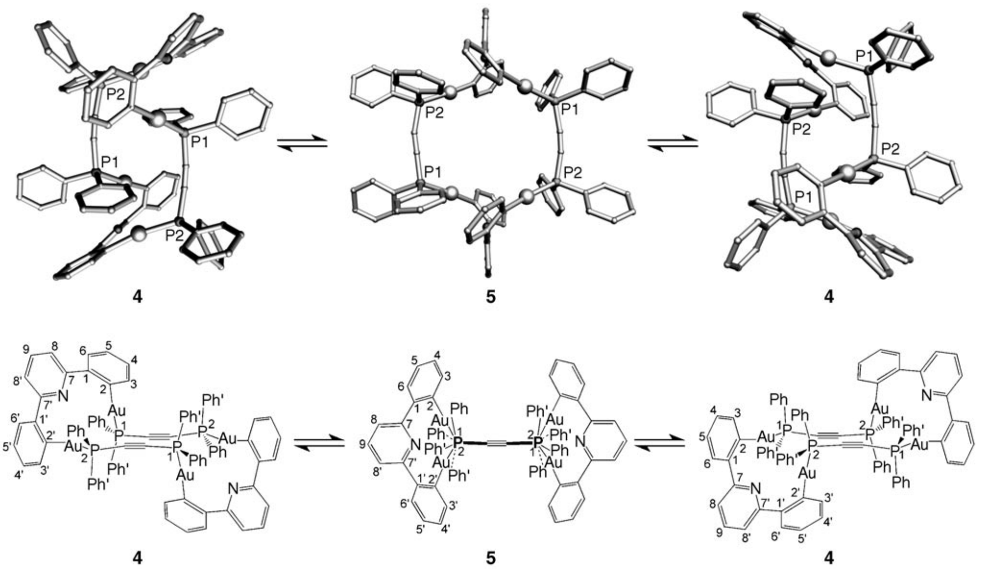

Figure 3. Proposed conformational changes of **4** in solution viewed from the top (upper) and side (lower) of the molecules. The structure of **5** was built using Chem3D 5.0 on the basis of the crystal structure of **4**.

H^6–$H^{6'}$, H^8–$H^{8'}$, and Ph–Ph′ pairs (see Figure 3 and the Supporting Information), together with the cross signals that possibly arise from the exchanges between **4** and **5**, in accordance with the conformational changes shown in Figure 3. Notably, the H^3, H^4, and $H^{3'}$ signals of **4** ($\delta = 5.7$–6.3 ppm) are considerably upfield from the corresponding signals of **3** ($\delta \approx 6.9$–7.1 ppm), which could result from intramolecular C–H···π interactions (see the Supporting Information). Such C–H···π interactions do not exist in **5**, consistent with the downfield shift of these signals, particularly for H^3, upon increasing temperature (which increases the **5**/**4** molar ratio).

Complexes **3**-Cl, **3**-ClO_4, and **3**-PF_6 are remarkably stable both in organic solvents (such as CH_2Cl_2, $CHCl_3$, dimethylformamide (DMF), and dimethylsulfoxide (DMSO)) and under physiologically relevant conditions (see the Supporting Information). The high stability of **3**-Cl in solution relative to most self-assembled polynuclear Au^I compounds, including **4** (which decomposed within several days in a solution of $CHCl_3$ at room temperature), prompted us to examine its cytotoxic properties; gold compounds not only have long been used as antiarthritic drugs but also are promising antitumor agents,[16] and stability is an important issue in the design of new Au^I therapeutic agents. The cytotoxicities of **3**-Cl toward cancer cell lines (including cervical epithelioid carcinoma (HeLa) and nasopharyngeal carcinoma (SUNE1 and its cisplatin-resistant variant CNE1)) and normal lung fibroblast cells (CCD-19Lu) were determined by the 3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide (MTT) assay. From the cytotoxicity profiles (see the Supporting Information), the corresponding IC_{50} values (dose required for the inhibition of 50 % cellular growth) of the cancer cell lines were determined to be 6.53–8.20 μM, which are comparable to those of the clinically used cisplatin ($IC_{50} = 14.8$ (HeLa), 2.3 (SUNE1), and 8.9 μM (CNE1)). Importantly, **3**-Cl was found to be almost equally cytotoxic to SUNE1 and its cisplatin-resistant variant CNE1, with a resistance factor of 1.2 (IC_{50}(CNE1)/IC_{50}(SUNE1) ratio) less than one third of that observed for cisplatin (3.9). The IC_{50} value of **3**-Cl for normal human cells CCD-19Lu was determined to be 19.1 μM, thus indicating that this Au^I compound is 2.3–2.9-fold less toxic to normal cells than to the forging cancer cells.

In summary, we have observed a new coordination mode of the pyridyl-2,6-diphenyl^{2-} ligand and isolated two Au^I compounds that contain unprecedented types of gold metallamacrocycles. Both types of metallamacrocycle have intramolecular Au^I···Au^I and C–H···π interactions; the metallamacrocycle with stronger Au^I···Au^I and C–H···π interactions is highly robust in solution and shows interesting topological and cytotoxic properties, whereas the other exhibits a unique fluxional behavior in solution. The present work demonstrates that polydentate cyclometalating ligands, such as pyridyl-2,6-diaryl^{2-}, together with Au^I could be useful for constructing new classes of molecules with unprecedented topology and properties.

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PhD dissertation, The University of Hong Kong, **2005** (see the Supporting Information for the X-ray crystal structure of **1**[9]).

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[13] Although it is possible to generate the *P*,*P* or *M*,*M* analogues of **4**, no such structures were observed. Modeling studies revealed that the *P*,*P* or *M*,*M* structure renders all the phenyl groups of the two diphosphane ligands in an unfavorable eclipsed arrangement, in contrast with the favorable staggered arrangement of the phenyl groups of each diphosphane ligand in **4** (see the Supporting Information). The molecules of **4** in the crystal structure are linked by intermolecular $C-H\cdots\pi$ interactions (a C–H bond of a dppm phenyl group with the nearest dppm phenyl ring; closest $H\cdots C$ distances: 2.841 Å) to give 2D sheets.

[14] Further decrease in temperature resulted in freezing of the $CDCl_3$ solvent, which, together with the poor solubility of **4** in other solvents, hampered NMR measurements at lower than −53 °C.

[15] No molecules of **5** were observed in the crystal structure of **4**. The molecular symmetry of **4** (C_i) and **5** (C_{2h}) would result in the appearance of two singlets and one singlet, respectively, in their ^{31}P NMR spectra. The observation of only one singlet at 0 °C or above (see the Supporting Information) could arise from the rapid conformational changes depicted in Figure 3. Lowering the temperature to −40 °C causes the signals of **4** ($\delta = 17.8$, 14.7 ppm) and **5** ($\delta = 17.0$ ppm) to be resolved. The change from **4** to **5** can be effected by breaking the $Au^I\cdots Au^I$ interactions (note the longer $Au^I\cdots Au^I$ contact of 3.178(10) Å in **4** than that of 3.015(29)–3.040(29) Å in **3**), accompanied by intramolecular rotations to render the phenyl groups of each $Ph_2PC\equiv CPPh_2$ ligand in an eclipsed arrangement. Therefore, **5** should be energetically less favored than **4**, consistent with the increase in the amount of **4** but decrease in the amount of **5** upon lowering the temperature (see the Supporting Information).

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