Enantiomeric Self-Recognition of a Facial Amphiphile Triggered by $[\{Pd(ONO_2)(en)\}_2]$**

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DNA, RNA, and proteins are composed of homochiral building blocks and undergo multiple levels of self-assembly to generate Nature's functional macromolecules. This hierarchical self-assembly process involves several types of noncovalent interactions and often results in the generation of additional elements of chirality at the supramolecular level. Supramolecular chemists have devised methods to prepare chiral molecular aggregates by the (self-)association of achiral molecules,[1] by the use of enantiomerically pure molecules that induce further elements of chirality in polymers[2] and molecular aggregates,[3] and by the use of racemic mixtures of ligands that undergo enantiomeric self-recognition.[4] Elucidation of the factors that dictate chirality in supramolecular systems may result in a better understanding of their natural counterparts, in the design of improved enantioselective catalysts, and in supramolecular materials with enhanced properties. We present a new model system for the study of enantiomeric self-recognition that is based on the hydrophobically driven self-association of facial amphiphile (±)-**1** in the presence, but not in the absence, of **2** (Figure 1).

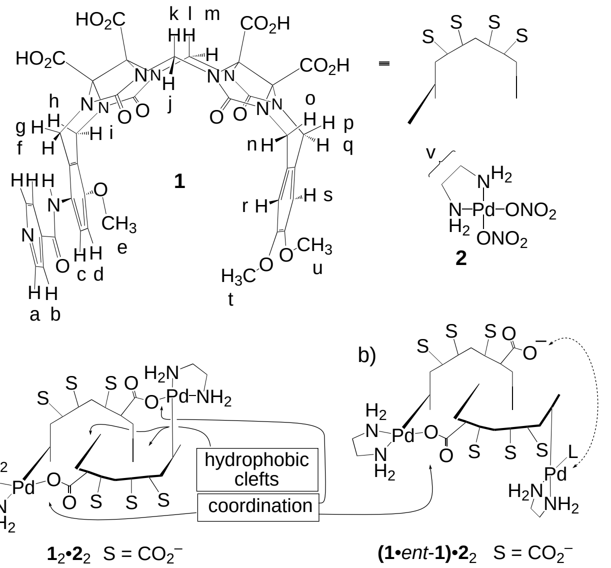

Figure 1. Schematic drawings of a) the observed aggregate $\mathbf{1}_2\cdot\mathbf{2}_2$, and the undetected aggregate b) $(\mathbf{1}\cdot\textit{ent}\text{-}\mathbf{1})\cdot\mathbf{2}_2$. The dashed arrow indicates the palladium–carboxylate interaction that cannot be formed in the heterochiral aggregate.

Amphiphilic molecular clips are known to undergo self-association to yield dimers.[5][6] We have recently shown that methylene-bridged glycoluril dimers, with hydrophilic carboxylate solubilizing groups on their convex face, undergo hydrophobically driven self-association in water to yield tightly associated, discrete, dimeric assemblies.[7] Towards the goal of creating structurally defined molecular aggregates of larger numbers of molecules, we designed **1**, which contains a hydrophobic cleft and a pyridyl ligand. We anticipated that **1** might undergo hydrophobic dimerization and coordination-driven self-assembly of the type pioneered by Fujita and coworkers.[8] Herein, we report that the addition of **2** to an aqueous solution of racemic **1** triggers the formation of a single molecular aggregate $\mathbf{1}_2\cdot\mathbf{2}_2$ (and *ent*-$\mathbf{1}_2\cdot\mathbf{2}_2$) by an enantiomeric self-recognition process (Figure 1a).

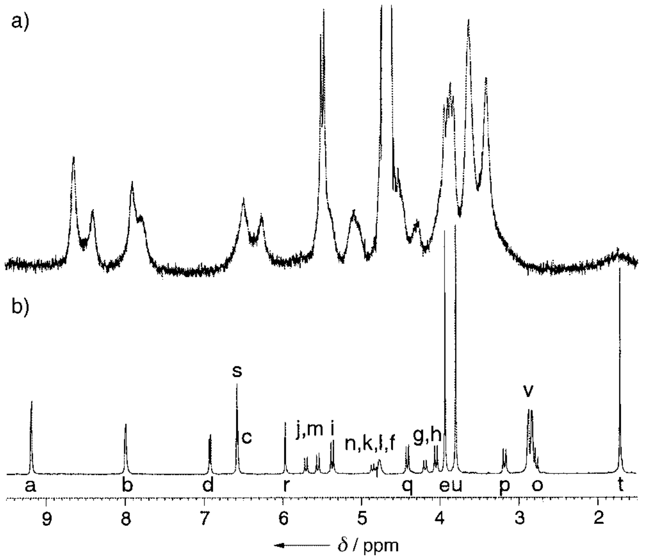

Figure 2. ^1H NMR spectra before and after the addition of **2**. a) (±)-**1** (400 MHz, 5 mM, pD 7.4, 298 K), and b) $\mathbf{1}_2\cdot\mathbf{2}_2$ (500 MHz, 2.5 mM, pD 7.4, 298 K). The broad resonance at 4.7 ppm is caused by incomplete suppression of residual HOD.

After synthesizing (±)-**1**, we investigated its self-association properties in the absence of **2**.[5][7b] The ^1H NMR spectrum of **1** in buffered D_2O at 25 °C showed two sets of resonance signals (Figure 2a), which suggests that two diastereomeric aggregates were formed, namely, $\mathbf{1}\cdot\textit{ent}\text{-}\mathbf{1}$ and the pair of enantiomers $\mathbf{1}_2$ and *ent*-$\mathbf{1}_2$. At 60 °C, we observed a single set of resonances and measured the dissociation constant of the aggregate by ^1H NMR dilution experiments ($K_d = 337 \pm 40$ μM). The addition of **2** to a solution of (±)-**1** resulted in dramatic changes in its ^1H NMR spectrum (Figure 2b), indicative of a well-defined molecular aggregate of **1** and **2**.

To elucidate the structure of this aggregate, we determined the relative stoichiometry of **1**:**2** by ^1H NMR titration experiments, in which the **1**:**2** ratio was changed from 1:0 to 1:4 ([**1**] = 4 mM). Based on the precedent of Fujita and coworkers,[8] we expected to observe clean aggregate formation at a 2:1 ratio of **1**:**2**. In contrast, however, a single discrete aggregate (Figure 2b) was only observed when the ratio of **1**:**2**

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was between 1:1 and 1:4, which suggests that the relative stoichiometry is $\mathbf{1}_n \cdot \mathbf{2}_n$. This stoichiometry was confirmed by ^{1}H NMR spectral integration of the resonance signals for **1** ($H_a - H_u$) versus **2** (H_v; see Figure 2 for assignments).

A major challenge in self-assembly studies is an accurate determination of absolute stoichiometry. To determine the value of n in aggregate $\mathbf{1}_n \cdot \mathbf{2}_n$, we turned to analytical ultracentrifugation (AUC).[9] AUC is a first-principles analytical technique that allows equilibrium thermodynamic measurements in dilute solution and offers advantages over the techniques commonly used in synthetic self-assembly studies (vapor-pressure osmometry (VPO), gel-permeation chromatography (GPC), and ES–MS). For example, VPO suffers from low sensitivity (±3 mmolal), aggregates often dissociate during GPC experiments, and ES–MS experiments occur in the desolvated gas phase. We performed sedimentation-equilibrium measurements with solutions of $\mathbf{1}_n \cdot \mathbf{2}_n$ (50 μM) containing an excess of **2** (200 μM). In this experiment we were able to selectively monitor $\mathbf{1}_n \cdot \mathbf{2}_n$, as it has an absorption maximum at 278 nm ($\varepsilon = 6700\ \mathrm{M}^{-1}\,\mathrm{cm}^{-1}$), whereas **2** has an absorption minimum. The results are well explained by a model of a single homogenous species with a molecular weight of 2632 ± 125. Comparison of the measured molecular weight with those calculated for $\mathbf{1}_2 \cdot \mathbf{2}_2$ and $\mathbf{1}_3 \cdot \mathbf{2}_3$ ($[(\mathbf{1}\text{-}4\,H^+)_2 \cdot (\mathbf{2}\text{-}2\,NO_3^-)_2] \cdot 4\,Na^+$: 2214; $[(\mathbf{1}\text{-}4\,H^+)_3 \cdot (\mathbf{2}\text{-}2\,NO_3^-)_3] \cdot 6\,Na^+$: 3322) strongly suggests the absolute stoichiometry $\mathbf{1}_2 \cdot \mathbf{2}_2$. When the standard techniques such as VPO, GPC, and ES–MS do not provide accurate molecular weights, AUC is a powerful alternative that should be considered in synthetic self-assembly studies.[7b, 9]

The observation of a single aggregate by ^{1}H NMR spectroscopy implies that only one of the two possible aggregates is formed, that is, the racemic mixture $\mathbf{1}_2 \cdot \mathbf{2}_2$ and *ent*-$\mathbf{1}_2 \cdot \mathbf{2}_2$ by an enantiomeric self-recognition process, or $(\mathbf{1} \cdot \textit{ent}\text{-}\mathbf{1}) \cdot \mathbf{2}_2$ by a heterochiral recognition process. We assigned most of the resonance signals in the ^{1}H NMR spectrum of $\mathbf{1}_2 \cdot \mathbf{2}_2$ to specific protons by 2D NMR spectroscopic techniques (COSY and ROESY spectra) and chemical-correlation arguments. Geometrical features of the aggregate were deduced, based on intermolecular (intra-aggregate) cross-peaks in the ROESY spectrum and ^{1}H NMR spectroscopic changes in the chemical shift (Figure 3). In particular, the ROESY spectrum shows cross-peaks between signals arising from protons on the pyridyl rings, and those from methylene protons on the convex face of the opposing dimethoxy xylylene ring ($H_a - H_o$; $H_a - H_p$; $H_b - H_o$; $H_b - H_p$), which indicates that these groups form close intermolecular contacts in $\mathbf{1}_2 \cdot \mathbf{2}_2$. A prominent feature in the ^{1}H NMR spectrum is the OCH_3 (t) resonance at 1.7 ppm, which shifts upfield by more than 2 ppm. This large upfield shift strongly suggests that this methoxy group is located in the shielded region, defined by the two xylylene rings of a second molecule. Examination of Corey–Pauling–Koltun (CPK) models reveals that these intermolecular contacts are only possible in the aggregate that is formed by enantiomeric self-recognition, $\mathbf{1}_2 \cdot \mathbf{2}_2$ and *ent*-$\mathbf{1}_2 \cdot \mathbf{2}_2$. The resulting geometry (Figure 3) places the two pyridyl rings in the vicinity of H_o, H_p, and one of the carboxylate solubilizing groups on the convex face of the other molecule of **1**. Simultaneous coordination of these two carboxylate groups to the two palladium centers locks the aggregate into a well-defined geometry.[10] In the hypothetical aggregate based on heterochiral recognition (Figure 1 b), only one carboxylate–palladium interaction is possible. The dashed arrow shows the sizable distance between the remaining carboxylate group and the palladium center; the lack of this second carboxylate–palladium interaction drives the enantiomeric self-recognition process.

In conclusion, we have shown that (±)-**1** self-associates in water to form a diastereomeric mixture of aggregates. Upon addition of **2**, an enantiomeric self-recognition process is triggered, which results in the formation of an unexpected 2:2 aggregate, $\mathbf{1}_2 \cdot \mathbf{2}_2$ and *ent*-$\mathbf{1}_2 \cdot \mathbf{2}_2$. This enantiomeric self-recognition process is driven by the presence of an additional coordination interaction between the Pd centers and the carboxylate solubilizing groups, which is not possible in the hypothetical aggregate resulting from heterochiral recognition. This new model system offers the opportunity to study enantiomeric self-recognition processes in water and may provide insights into related biological and catalytic processes.

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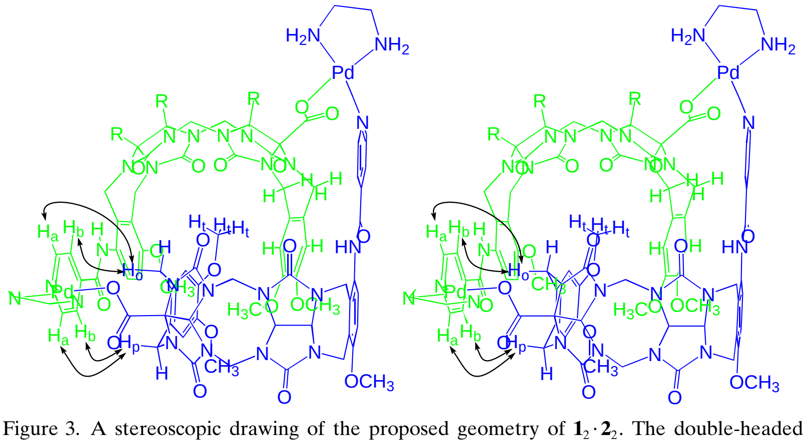

Figure 3. A stereoscopic drawing of the proposed geometry of $\mathbf{1}_2 \cdot \mathbf{2}_2$. The double-headed arrows denote cross-peaks that were observed in the ROESY spectrum.

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Crystal Engineering of Mixed-Metal Ru–Ag Coordination Networks by Using the *trans*-[RuCl$_2$(pyz)$_4$] (pyz = pyrazine) Building Block**

Lucia Carlucci, Gianfranco Ciani,* Francesca Porta, Davide M. Proserpio, and Laura Santagostini

In the rational development of new strategies for the crystal engineering of coordination networks[1] and of metal-based supramolecular architectures[2] the use of predetermined building blocks has assumed an increasing relevance in recent times. For example, molecular corners containing transition metals with programmed coordination angles, such as *cis*-protected Pd^{II} and Pt^{II} square-planar complexes, have been employed for the construction of frameworks and, particularly, of macromolecular polygons or polyhedral cages,[3] of potential utility for molecular recognition. We have recently employed the corner unit [Cu(2,2′-bpy)]$^{2+}$ (2,2′-bpy = 2,2′-bipyridine) for the self-assembly of polymeric species[4] and new architectures.[5] These building blocks generally work as acceptors and can be used with a variety of spacer ligands with different types of donor ends for the assembly of desired arrays. A different type of potentially useful metal-containing unit is represented by complexes containing ligands with *exo*-oriented donor functions. These complexes can be considered as nonconventional "ligands" in which the orientation of the donor groups can be controlled by the nature of the coordinated bases and by the coordination geometry at the metal center. Few examples of such species have been as yet reported, though they can find interesting applications for many purposes, such as the deliberate construction of *homo*- or *hetero*metallic networks with specific topologies, or the assembly of hydrogen-bonded frames, by using suitable (hydrogen-donor) organic molecules as spacers. Square-planar metal-porphyrinate complexes bearing four donor 4-pyridyl substituents on the macrocycle have been used, for instance, for the deliberate assembly of cooperite-like networks[6] and of other types of bimetallic frames.[7] Some other metal-containing "ligands" have been employed,[8] such as the anionic square-planar [Pt(CN)$_4$]$^{2-}$ [9] and digonal [M(CN)$_2$]$^-$ (M = Ag, Au)[10] species.

We have prepared as a new building block the neutral complex *trans*-[RuCl$_2$(pyz)$_4$] (**1**; pyz = pyrazine): it was obtained by reacting [RuCl$_2$(dmso)$_4$] in toluene with a large

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