ChemComm

COMMUNICATION

View Article Online
View Journal | View Issue

Cite this: *Chem. Commun.*, 2017, 53, 561

Received 17th November 2016,
Accepted 8th December 2016

DOI: 10.1039/c6cc09198a

www.rsc.org/chemcomm

Supramolecular bidentate phosphine ligand scaffolds from deconstructed Hamilton receptors†

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There is constant demand for new ligand archictectures on which inorganic and organometallic structures can be leveraged. An important, but often synthetically challenging, class of ligands is bidentate phosphines. Here we report self-assembling, supramolecular bidentate ligand scaffolds based on deconstructed Hamilton receptors with binding affinities up to 800 ± 100 M^{-1}.

New ligand architectures provide valuable platforms on which inorganic and organometallic chemistry can be supported, controlled, and leveraged for applications including bioinorganic chemistry, materials science, and catalysis. Of the numerous ligand platforms available, phosphine ligands are among the most ubiquitous not only in chemical catalysis,[1] but also the construction of metal organic hybrid systems including metal–organic frameworks,[2–4] supramolecular coordination complexes,[5,6] and molecular capsules.[7–9] Yet the design and diversity of self-assembling architectures based on phosphine ligands is frequently limited by challenging phosphine derivatization. This drawback is particularly acute for the design and derivatization of bidentate phosphine ligands. To combat these obstacles, researchers have begun to employ supramolecular techniques in ligand design.[10–14] In addition to creating large, meaningful ligand libraries from fewer components,[15,16] supramolecular ligand libraries are more amenable to the implementation of high throughput screening methodologies for identifying unique chemical structures, reactivity, and materials with novel properties.

Supramolecular approaches to the construction of functional bidentate ligands employ principles of molecular recognition to develop ligands with compatible donor–acceptor sites inherent in the ligand framework. Pioneering work by Breit,[16–18] as well as van Leeuwen and Reek,[19,20] demonstrated that functional bidentate ligands can be created through incorporation of non-covalent interactions in the ligand scaffold, such as hydrogen bonding and metal ligation. However, few supramolecular approaches to bidentate ligand construction are based on self-assembling host–guest systems. Moreover, a self-assembling ligand system that uses host–guest interactions to control the magnitude of bidentate character of monodentate ligands would enable precise tuning of the shape and size of new metal–organic hybrid systems based on host–guest binding affinities and guest characteristics. Furthermore, control over typical bidentate ligand parameters, such as bite angle, can be achieved through the use of different host–guest combinations making this approach amenable to combinatorial screening techniques.

Of the many host–guest architectures, the synthetic barbiturate receptor first synthesized by Hamilton[21] lends itself well to phosphine modification.[22,23] The receptor is characterized by six hydrogen bonds formed between the two complimentary donor–acceptor–donor (DAD) and acceptor–donor–acceptor (ADA) faces of the host and guest, respectively. We envisioned that bifurcation of the ligand scaffold would create a more flexible and accommodating host pocket upon metal ligation, as well as allow for precise control over the "bidentate" nature of the ligand through the use of derivatized barbiturate guests. Additionally, coordination of the ligands to the metal would provide the necessary preorganization required for guest binding, thus favoring complete assembly of the supramolecular ligand structure (Fig. 1). This design strategy would generate a new class of multicomponent self-assembled phosphine ligands that mimic bidentate structures upon guest binding. Herein, we report the design, synthesis, characterization, metal coordination, and binding affinities of such self-assembled ligand scaffolds and demonstrate that host–guest chemistry can be used to access bidentate coordination motifs from simple, modular, monodentate ligand components.

The effects of Hamilton receptor bifurcation and backbone rigidity on guest binding have been previously reported and indicate that substitution at the distal amide and the rigidity of the backbone have significant effects on guest binding and host aggregation.[24] To encourage guest inclusion, while limiting host aggregation, we hypothesized that neopentyl substitution

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† Electronic supplementary information (ESI) available. CCDC 1488913–1488916. For ESI and crystallographic data in CIF or other electronic format see DOI: 10.1039/c6cc09198a

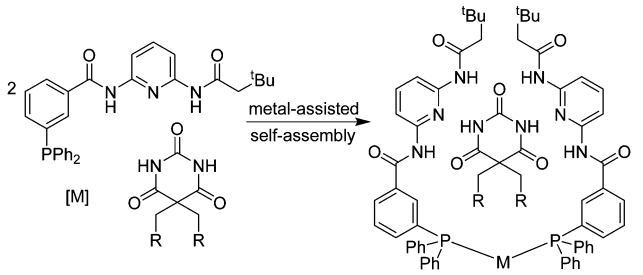
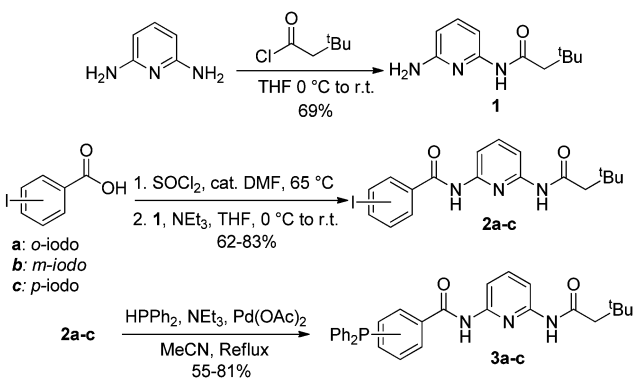


Fig. 1 Metal-assisted self-assembly of a bifurcated, phosphine modified Hamilton receptor.

at the host distal amide would result in optimal binding affinities. Moreover, we envisioned that the regioisomerism of the appended phosphorus group in the bifurcated receptor system would play a critical role in the geometry and size of the host binding pocket. Specifically, we hypothesized that the *meta*-substituted ligand would provide the most pre-organized host pocket, but may be sterically congested upon metal complexation. Therefore, the *para*-substituted isomer could alleviate the steric congestion and have minor effects on host pocket pre-organization. To investigate these postulates, a suite of regioisomers containing neopentyl substituted distal amides was synthesized according to Scheme 1.

2,6-Diaminopyridine was subjected to mono-amidation conditions using 3,3-dimethylbutyryl chloride to give the mono-substituted pyridine (**1**), which was then used for subsequent amidation of the *ortho*-, *meta*-, and *para*-substituted iodobenzoyl chlorides to afford compounds **2a–c**, respectively. Palladium-mediated couplings of $HPPh_2$ and **2a–c** in the presence of base resulted in the desired phosphine ligands **3a–c** in moderate to good yields. This highly modular, three-step synthesis allows for fine control over the electronic and steric parameters of the ligand scaffold through substitution at both the phosphorus and diaminopyridine backbone.

Single crystals suitable for X-ray diffraction of all three isomers were grown from THF/pentane vapor diffusion under an inert atmosphere (Fig. S1, ESI†). Notably, all regioisomers co-crystallized with one molecule of THF, which was hydrogen bonded to the proximal amide N–H and THF oxygen. The preference for the hydrogen bond at the proximal amide is likely due to the potential negative steric interactions between the neopentyl group and the



Scheme 1 Synthesis of phosphine ligands **3a–c**.

THF molecule. This observation is in agreement with our hypothesis that bulky substituents discourage host aggregation, but allow for guest inclusion.

To generate a host scaffold with two properly oriented DAD faces to bind the incoming barbiturate guest, the ligands must adopt a *cis*-geometry about the metal center. A common method for determining ligand geometry is to use Pt(II) salts that form square planar complexes upon the addition of two equivalents of ligand. These square planar, d^8 Pt complexes display distinct $^1J_{(Pt-P)}$ couplings constants for their *cis*- (>3000 Hz) or *trans*- (<3000 Hz) isomers.[25] To investigate the coordination properties of our ligand scaffold, Pt(II) complexes **4b–c** were prepared using one equivalent of $[Cl_2Pt(COD)]$ with two equivalents of the desired ligand in CH_2Cl_2 (Fig. 2a). Following the complexation *via* $^{31}P\{^1H\}$ NMR spectroscopy shows clean conversion upon the addition of ligand to the $Pt(COD)Cl_2$ (Fig. 2b and c).

Analysis of the $^1J_{(Pt-P)}$ coupling constants confirms a *cis*-geometry of both complexes with coupling constants of 3666 Hz and 3647 Hz for **4b** and **4c**, respectively. Attempts to synthesize Pt complexes with ligand **3a**, however, resulted in the complete disappearance of a phosphorus resonance, suggesting decomposition or possible formation of polymeric species causing significant peak broadening. The inability to form discrete species with **3a** is likely due to the steric crowding about the metal center that would occur in a *cis*-arrangement of the ligands.

To further study the ligand isomerism and host pocket geometry, single crystals of **4b** were grown from THF/MeCN: pentane *via* vapor diffusion and analyzed by X-ray diffraction. Analysis of the structure confirms the *cis*-orientation about the Pt center (Fig. 3). Interestingly, the complex co-crystallizes with two molecules of THF, each bound to a different phosphine ligand and amide. Consequently, the structure adopts a dimeric motif with both intra- and intermolecular hydrogen bonds.

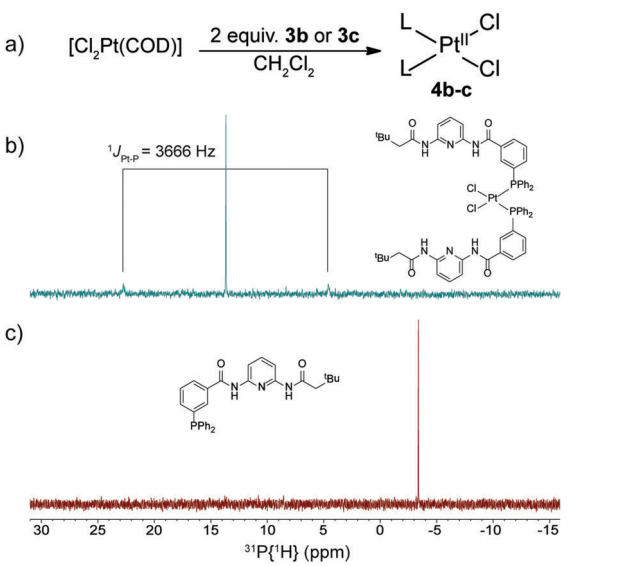


Fig. 2 (a) Synthesis of *cis*-PtL_2Cl_2 complexes **4b–c**. (b) $^{31}P\{^1H\}$ NMR (202 MHz) of free **3b** (c) $^{31}P\{^1H\}$ NMR (202 MHz) of *cis*-PtL_2Cl_2, **4b**.

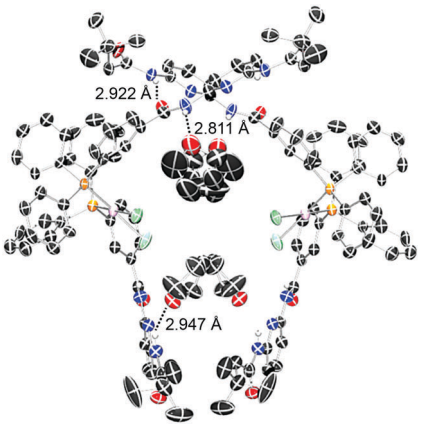


Fig. 3 ORTEP representations of **4b** with thermal ellipsoids drawn at 50% probability. Dimeric form of structure showing intra- and inter-molecular hydrogen bonds with non-hydrogen bonding hydrogens omitted for clarity.

The intramolecular hydrogen bonds occur between the proximal amide N–H of one phosphine and the distal amide oxygen of the other phosphine, with a calculated distance of 2.922 Å, to effectively encapsulate the THF guests. The intermolecular hydrogen bonds between the THF molecules and the upper and lower amides have calculated distances of 2.947 Å and 2.811 Å, respectively. The positioning of the host pocket *cis* to the chloride ligands may help to explain the low association constants (*vide infra*) as potential negative steric interactions would occur between the chloride ligands and incoming guest. Despite numerous attempts to crystalize the host–guest complex **4b**⊂**5a**, we were unable to obtain crystals suitable for X-ray diffraction.

Previous work in our lab has shown that deconstructed Hamilton receptors display 1 : 1 binding motifs, similar to the original Hamilton receptor.[24] The free rotation around the host P–C bond, however, could allow for a 2 : 1 binding motif if the enthalpic gain from hydrogen bond formation is greater than the entropic cost of creating a three component system. To confirm which binding motif was present, a Job plot for **4b** and **5a** was constructed using ^{1}H NMR spectroscopy. Following the chemical shift of the guest N–H resonance, the data support a 1 : 1 binding motif as evidenced by a maximum in the Job plot at 0.5 in H_2O sat. $CDCl_3$ and 1% DMSO in $CDCl_3$ (Fig. S4 and S6, ESI†).

To assess the efficacy of our self-assembling ligand system, ^{1}H NMR titrations of host complex **4b** and a synthetic barbiturate **5a** were performed and fit to a 1 : 1 model using the Thordarson method.[26] Due to solubility constraints of the guest, inverse titrations (excess host with constant guest) were required to generate adequate signal in the ^{1}H NMR experiments to accurately determine small chemical shift changes. Following the N–H resonance of the guest in a H_2O saturated $CDCl_3$ solvent system, a significant downfield shift is observed with a measured association constant of 800 ± 100 M^{-1} (Fig. 4). Switching to a more competitive solvent such as MeCN resulted in an attenuated, but measurable, binding constant of 19 ± 5 M^{-1} demonstrating the propensity of this system to self-assemble even in a competitive hydrogen bonding environment. Comparison between hosts **4b** and **4c** revealed that para-substitution of the phosphorus group leads to a less pre-organized host pocket, indicated by the lower association constant of 260 ± 20 M^{-1}. Taken together, these binding data demonstrate that ligand coordination facilitates barbiturate guest binding and that the geometry of the ligand architecture can be used to tune guest binding fidelities.

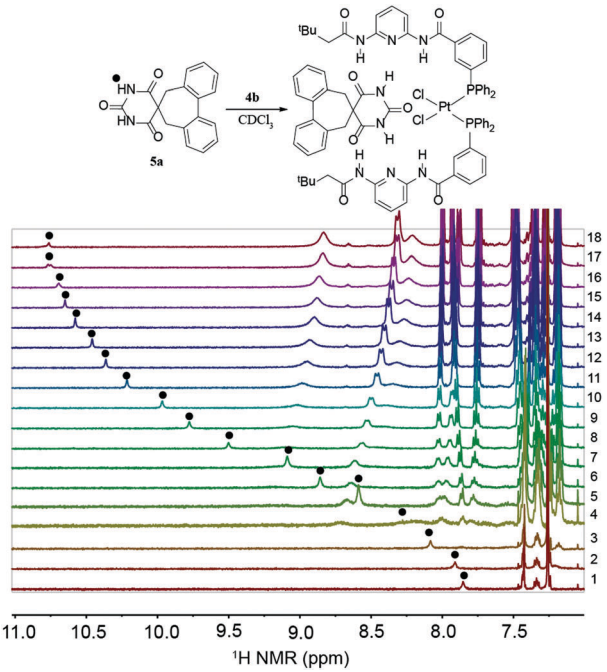


Fig. 4 Sample ^{1}H NMR titration of **4b** and **5a** in H_2O sat. $CDCl_3$.

In summary, we have developed a new supramolecular, self-assembling ligand scaffold motif based on a deconstructed Hamilton receptor. *cis*-PtL_2Cl_2 host complexes that bind synthetic barbiturate guests were synthesized and characterized both in solution and the solid state. This supramolecular system displays a 1 : 1 binding mode consistent with a deconstructed Hamilton receptor, and guest binding was observed in both competitive and non-competitive solvents. The ease and high modularity of the host synthesis as well as, the guest tunability make this scaffold poised for diverse applications ranging from acting as a building block for larger self-assembled structures and materials as well as applications in high-throughput and combinatorial screenings of catalytic reactions.

This work was supported by NSF Grant CHE-1506221. The NMR facilities at the UO are supported by the NSF (CHE-0923589, CHE-1427987), Oregon BEST, and ONAMI.

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