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Preparation of a novel diphosphine–palladium macrocyclic complex possessing a molecular recognition site. Oxidative addition studies†

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A disphosphine-palladium(0) complex capable of recognising barbiturates has been prepared. Oxidative addition studies with a barbitiurate:aryl iodide conjugate provided new Pd(II) complexes where the positioning of the Pd-bound aryl group is controlled by the molecular recognition event.

In our quest for combining molecular recognition with transition metal catalysis, we recently embarked on a program with the objective of identifying new Pd^0–ligand complexes, which possess a receptor domain capable of binding and subsequently positioning on the metal center the reactants undergoing C–C bond formation.[1] A long standing goal is to develop receptor-based ligands, which can influence the reactivity of the catalyst, as well as control the stereo- and regioselectivity of the products formed in the coupling reactions (*e.g.* Heck reaction).[2] In this way, the inherent directive properties of the reactants may be superseded by such enzyme-like reactions.[3]

In this paper, we reveal our first steps in this direction, providing an example of a Pd^0–receptor complex which is capable of binding guests *via* a hydrogen-bonding network. Interestingly, this molecular recognition event places a Pd-bound aryl group with respect to the metal–ligand complex in a configuration which is not favoured in the absence of the recognition event (Structures **A** and **B**). The ability to manipulate the coordination geometry at a metal center could have interesting implications for the reactivity of such complexes, including their catalytic properties.

In a recent report, we disclosed the preparation of a series of diphosphine ligands possessing Hamilton's barbiturate binding domain, such as the receptor **1**.[1,4] Whereas, some of these ligands were found to rapidly form well-defined macrocyclic *cis*-Pd^0 complexes upon the addition of $Pd(dba)_2$, none of these metal complexes displayed an affinity for including barbiturates in their cavity. Attributing this inability for recognition to detrimental conformational changes of the binding domain upon macrocyclization with Pd^0, a more flexible homologue to **1**, namely the diphosphine **2**, was therefore synthesised (see ESI†).

Mixing one equivalent of **2** with $Pd(dba)_2$ in $CDCl_3$ led to a complicated mixture of metal complexes as determined by ^{31}P NMR spectroscopy. Nevertheless, addition of excess phenyl iodide afforded a spectrum revealing a single peak at 23.8 ppm suggesting an oxidative addition step had occurred with the formation of a sole *trans*-Pd^{II} macrocyclic species. More interesting was the observation that the addition of barbital (**3**) to the $Pd(dba)_2$:**2** mixture leads to the immediate formation of two broad singlets of equal integration indicative of a *cis*-macrocyclic $Pd^0(dba)$(**2**) complex.[5] This template effect resulting from the binding of barbital was confirmed in the ^1H NMR spectrum, where the characteristic downfield shifts upon hydrogen bonding of the host's amide NH's (approx. 1.5 ppm) were observed.

Next, the aryl iodide-containing barbiturate **4** was tested for its capacity to undergo oxidative addition in comparison to phenyl iodide. The reaction was monitored by ^{31}P NMR after the addition of the aryl iodide to a solution of $Pd(dba)_2$ and **2** in $CDCl_3$. A *cis*-complex is formed by the appearance of two broad singlets at 23.7 and 29.5 ppm, which rapidly disappear over a period of approx. 15 min. with the simultaneous formation of a singlet at 24.7 ppm attributed to the *trans*-product **6** from oxidative addition (Fig. 1). To our delight, the barbiturate unit was also bound in the receptor

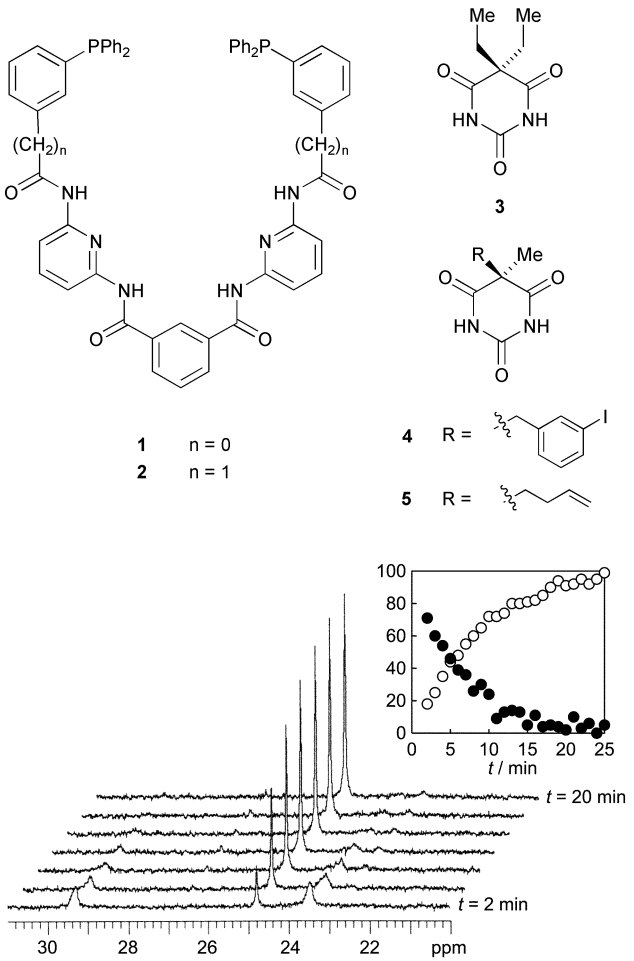
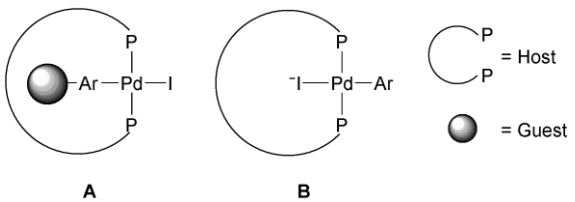


Fig. 1 ^{31}P NMR spectra from t = 2 min to t = 20 min of the oxidative addition of **4** to $Pd(dba)_2$:**2** showing the decay of **4**:**2** and build-up of **6**. Inset: Normalized integrals of $Pd^0(dba)$(**4**:**2**) complex (●) and **6** (○) from ^{31}P NMR as a function of time.



† Electronic supplementary information (ESI) available: crystallographic data of **6** and **7**, ^1H NMR spectrum of complex **6**, and experimental procedure and spectral data. See http://www.rsc.org/suppdata/cc/b3/b309863j/

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of the Pd^{II}-complex as indicated from its ^1H NMR spectrum, again by the observation of the large amide proton shifts (see ESI†).‡

Suitable crystals of *trans*-complex **6** were grown by slowly diffusing pentane into this $CDCl_3$ solution. The crystal structure representation of **6** establishes the anticipated structure involving the hydrogen bonding network (Fig. 2).§ The barbiturate was bound in a fashion similar to that observed in previous crystal structures reported with compounds possessing this receptor domain and barbital, with the guest deviating from the plane of the host by 24°.[4a,7] A P–Pd–P angle of 166° clearly revealed the *trans*-nature of this complex.¶

In order to determine whether this 3D structural preference of the complex is a result of the combined effects of the host–guest interaction and the covalent Pd–C bond formed from **4**, attempts were made to obtain crystal structures of a simple barbiturate bound to the Pd^{II} complex prepared from the oxidative addition of phenyl iodide to the $Pd(dba)_2$:**2** mixture. Crystals of the complex **7** were obtained with the barbiturate **5** in its cavity (Fig. 3).‖ As with **6**, both complexes reveal a similar curled-up structure necessary for the phosphines to bind to the metal center. A comparable P–Pd–P angle of 177° was measured and the guest also deviated from the plane of the receptor by 30°. The crystal structure revealed another interesting feature, notably the positioning of the aryl group and the iodide with respect to the metal diphosphine complex. In comparison to **6**, these substituents have reversed their positioning, with the aryl group pointing in the opposite direction away from the receptor cavity. As it is unlikely that the butenyl group is the direct cause of this deviation since this group is oriented away from the host and metal center, it demonstrates that the preferred configuration of such complexes is as shown with the compound **7**. Linking of the aryl group to the barbiturate as in the complex **6** overrides this preference because of the combined efforts of the six hydrogen bondings.

These two examples provide an interesting case of how the coordination geometry at a palladium metal center can be controlled by molecular recognition. The influence this effect will have in coupling reactions is currently under investigation. In addition, we are attempting to obtain suitable crystals of the *cis*-Pd^0 complexes in order to compare these structures with the above-obtained *trans*-Pd^{II} compounds. This work will be reported in due course.

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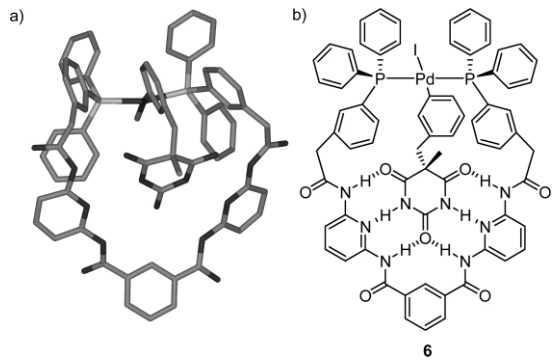

Fig. 2 (a) Crystal structure representation of the *trans*-metal complex **6**. (b) Schematic representation of the structure **6**.

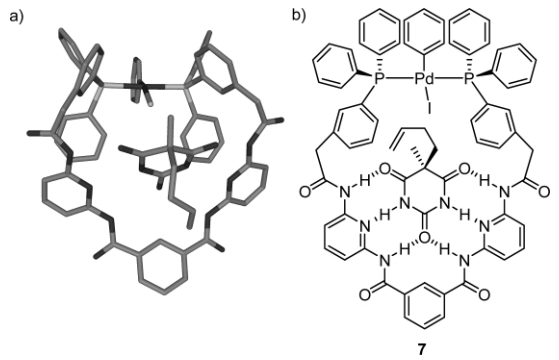

Fig. 3 (a) Crystal structure representation of the *trans*-metal complex **7**. (b) Schematic representation of the structure **7**.

Notes and references

‡ In the absence of palladium(0), the ligand **2** binds barbiturates with association constants of approx. 10^4 M^{-1} in $CDCl_3$.[1]

§ Crystal data for **6**: $C_{70}H_{57}IN_8O_7P_2Pd\cdot2(CHCl_3)\cdot0.3(H_2O)$, M = 1661.74, orthorhombic, a = 14.497(3), b = 29.039(6), c = 33.189(7) Å, U = 13972(5) Å^3, T = 120 K, space group *Pbca* (no. 61), Z = 8, μ(Mo–K_α) = 1.044 mm^{-1}, 213233 reflections measured, 12592 unique, 3237 significant ($> 2\sigma I$) used in all calculations. Due to the poor reflecting power constraints were applied in the refinement: all 8 phenyl rings were kept identical with *mm*2 symmetry, 2 pyridines likewise, the barbiturate kept at *mm*2 symmetry; hydrogen atoms in calculated positions; atomic displacement parameters for this part of the macrocycle–barbiturate complex including the hydrogen atoms were constrained to the TLS rigid body model.[6] The chloroform molecules were kept identical with idealised geometry, one of them disordered over two positions with occupations constrained to add up to 1.0. The atomic coordinates and thermal parameters given in the supporting material as well as bond lengths are calculated (with appropriate standard uncertainties) from the parameters refined. Because of the extensive use of constraints no analysis of details is possible, but the overall structure is well established. The final $R(F)$ was 0.133. CCDC 217698. See http://www.rsc.org/suppdata/cc/b3/b309863j/ for crystallographic data in .cif or other electronic format.

¶ The oxidative addition rate of the aryl iodide **4** to the $Pd^0(dba)$(**2**) complex was 5 times faster than that of phenyl iodide. The rate was not influenced by either the position of the iodide (*meta* to *para*) or the length of the barbiturates methylene (n = 0–2). Perhaps in these cases, the host is sufficiently flexible to allow the oxidative addition to occur with a wide variety of substrates. Support for this is seen from the *N*,*N*′-dibenzylation of **4**, which leads to an aryl iodide displaying a similar oxidative addition rate as that of phenyl iodide.

‖ Crystal data for **7**: $C_{64}H_{51}IN_6O_4P_2Pd\cdot C_9H_{12}N_2O_3\cdot2(CHCl_3)$, M = 1698.41, monoclinic, a = 9.743(2), b = 21.892(3), c = 17.360(3) Å, β = 91.177(5)°, U = 3702(1) Å^3, T = 120 K, space group $P2_1$, (no. 14), Z = 2, μ(Mo–K_α) = 0.987 mm^{-1}, 35623 reflections measured, 16807 unique, 11089 significant ($I > 3*\sigma I$) were used in all calculations. The structure deviates only little from space group $P2_1/m$, the largest deviations found for one pair of benzene rings and for the solvent; The final ethene group on the barbiturate is close to this mirror plane and is disordered; occupation factors for these atoms were constrained, and the displacements were kept isotropic and the same for the two parts of the same atom. The final $R(F)$ = 0.039. CCDC 217699. See http://www.rsc.org/suppdata/cc/b3/b309863j/ for crystallographic data in .cif or other electronic format.

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