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Controlling Orthogonal Self-Assembly through Cis-Trans Isomerization of a Non-Covalent Palladium Complex Dimer

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The *trans*-configured square-planar complex of dichloropalladium and chiral monodentate phosphine ligands forms self-complementary dimers through 16 hydrogen bonded amides and π-π stacking in chlorinated solvents. The self-assembly is controled by cis-trans isomerisation of the metal center, where *trans*-configuration governs the dimer formation.

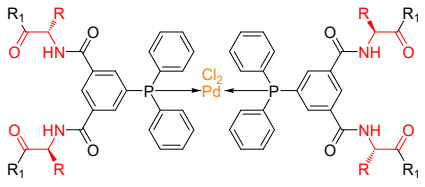
Supramolecular architectures incorporating transition metals have gained increasing attention due to their potential applications in molecular recognition, sensing, and catalysis.[1] Various strategies were developed for the construction of such compounds,[2a] exploiting coordination geometry of the metal center and ligand structure, often incorporating orthogonal interactions[2b–d] as an important tool in the self-assembly process. Of great interest is the simultaneous use of metal coordination and non-covalent interactions (e.g. hydrogen-bonding, lipophilic interactions…), successfully used in the construction of dendritic[3a] and polymeric[3b–d] nano-structures. However, discrete assemblies of small metal complexes held by non-covalent interactions in solution have seldom been investigated in the field of molecular recognition, especially with respect to chirality.[4]

Palladium complexes have been extensively explored as supramolecular building blocks in discrete self-assembly,[2,4f,5] due to the bond directionality and small number of possible isomers (i.e. cis/trans) of the square-planar coordination. However, palladium atom is very frequently *cis*-configured, with seldom implementation of monodentate ligands compared to bidentate and bridging ligands. In cases of *trans*-configuration, supramolecular polymeric structures are formed,[3c,d] rather than discrete assemblies.

Although amino acids represent a convenient source of chirality and short peptides are known to exhibit various non-covalent assemblies,[6] metal complexes thereof have seldom been exploited, in a controllable manner, as non-covalent supramolecular synthons,[7] contrary to the purely organic derivatives.[8] Recently, we reported a novel hydrogen bonded system which incorporates amino acids and metal ions, exhibiting supramolecular chirality inversion upon metal complexation in organic solvents.[9]

Herein, we present an unprecedented chiral supramolecular system, self-assembled through orthogonal interactions (metal coordination, hydrogen bonding, and π-π stacking), forming discrete dimeric structure through 16 hydrogen-bonds and π-π stacking in chlorinated solvents, where *trans*-configuration of dichloropalladium complex is shown to be crucial for the self-assembly process. Despite the substantial amount of literature concerning palladium in the field of self-assembly, the trans-cis isomerisation has, surprisingly, not been utilised to control the formation of non-covalent self-complementary chiral molecular associates.

The ligands (**1**) were prepared according to the procedure from our previous work on chiral supramolecular phosphine-rhodium catalysts.[10] Palladium complexes (**2**) (Scheme 1) were obtained in quantitative yields (^{1}H NMR) by dissolving the ligand and $(CH_3CN)_2PdCl_2$ (2:1) in dichloromethane (**2b**) or



1a; R = Bz, R_1 = NH_2
1b; R = Bz, R_1 = OMe
1c; R = Me, R_1 = NH_2

2a; R = Bz, R_1 = NH_2
2b; R = Bz, R_1 = OMe
2c; R = Me, R_1 = NH_2

Scheme 1. The prepared ligands and palladium(II) complexes thereof.

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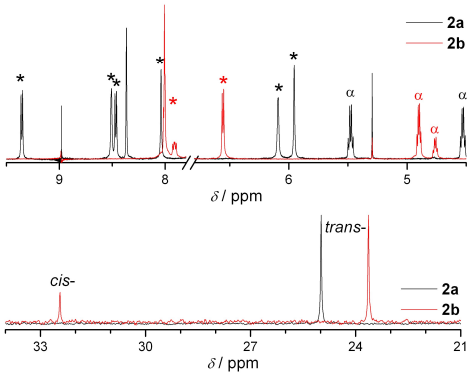

Figure 1. ^{1}H (top) and ^{31}P NMR spectra (bottom) of the complexes in chloroform-d_1, indicating hydrogen-bonding and cis/trans isomers. Amide and alpha protons are marked with asterisk and α, respectively.

dichloromethane/ methanol (**2a**,**c**), and left at room temperature overnight.

^{1}H NMR of **2a** in chloroform-d_1 is highly resolved with sharp and well defined signals. It exhibits strongly down-field shifted amide protons (8.0–9.4 ppm), indicative of hydrogen bonding (Figure 1), also supported by the variable temperature measurements (Figure S10).[11] Aromatic protons of phenylalanine are substantially shifted up-field with comparison to similar compounds[12] (Figure S11), indicating involvement in aromatic stacking. Furthermore, two phenylalanine α-protons of equal intensities, and only one sharp singlet in ^{31}P NMR, characteristic of similar *trans*-dichloropalladium bis-triphenylphosphine complexes,[13] suggest a well-defined species in solution, where two phenylalanines in a single ligand are not symmetry-related. In methanol-d_4, **2a** shows a mixture of *cis*- and *trans*-isomers (≈ 4:1), while in acetonitrile-d_3, only *cis*-isomer is observed (Table S1, Figure S12). Variable solvent composition measurements (acetonitrile/ chloroform) showed only *cis*- and *trans*-**2a** (Figures S14,15), implying a simple cis-trans equilibrium. The ester analogue, **2b**, exhibits both isomers in all the aforementioned solvents (Table S1). The amide proton signals of *trans*- and *cis*-**2b** in chloroform-d_1 are found at 6.6 ppm and 8.0, respectively, indicating that only *cis*-isomer is hydrogen bonded, possibly in an intramolecular fashion due to the *cis*-arrangement of the ligands (as found in the X-ray crystal structure of **2c**, see later). In addition, alanine complex, **2c**, shows mostly *cis*-isomer in both acetonitrile-d_3 and methanol-d_4 (Figure S12), and is insufficiently soluble for NMR measurements in chloroform.

Dimerization of trans-**2a** in solution is strongly supported by DOSY[14] measurements. Diffusion coefficients of **2a** and **2b** in chloroform-d_1 were determined 0.49 × 10^{-9} and 0.61 × 10^{-9} m^2 s^{-1}, respectively. Since the two complex molecules are very similar in size, the lower diffusion of **2a** strongly indicates molecular association. In addition, a 30 % acetonitrile/ chloroform solvent mixture gave diffusion coefficients for the *trans*- and *cis*-**2a**, 0.57 × 10^{-9} and 0.69 × 10^{-9} m^2 s^{-1}, respectively, underlining the importance of trans- configuration for molecular association. The calculated hydrodynamic radius[15] (8.9 Å) and aggregation number (1.7) of the two independent experiments (Table S2) are in an excellent agreement with the assumption of a dimeric and monomeric species (Figure S29). Tentative covalent dimerization through chloride displacement (e.g. by amide coordination) is highly unlikely since it would result in a cationic species having fairly deshielded phosphorous signals (≈ 29 ppm), as found in similar cationic *trans*-Pd complexes.[16]

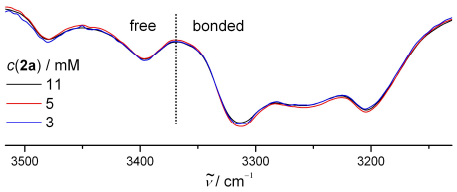

Figure 2. FT-IR (dichloromethane) intercept of the N–H stretching region, indicating free and hydrogen bonded amide protons of **2a**. The spectra are corrected for concentration.

Additional support for hydrogen bonding of **2a** in solution was obtained from FT-IR measurements in dichloromethane (Figure 2). Almost all six different N–H stretching vibrations (3480–3200 cm^{-1}) were resolved and assigned as free and hydrogen bonded,[17] in an excellent agreement with the ^{1}H NMR chemical shift data. At different concentrations the IR spectra were unchanged, indicating that the hydrogen bonds are formed within a strongly associated dimer that behaves as a single molecule, also supported by ^{1}H NMR (Figure S16).

Circular Dichroism (CD) measurements of **2a** in chlorinated solvents revealed a bisignate Cotton effect[17] (exciton coupling) at 344 nm in the palladium absorbing UV-Vis region (Figure 3), strongly suggesting proximity of palladium chromophores (i.e. in a dimer). In acetonitrile or methanol, the exciton couplet is not present, as in the case of **2b** and **2c** in chloroform or acetonitrile (Figure 3). This implies that the couplet is only related to the dimer formation. In addition, the CD spectrum of a **2a** and **2c** mixture (1:1) in dichloromethane is the sum of the individual **2a** and **2c** spectra, implying that the species do not interfere (Figure S41), which underlines the self-recognition property of **2a**. Variable concentration measurements in dichloromethane showed a linear relationship of the CD intensity and **2a** concentration (Figure S31) as low as 7 µM, suggesting a very high dimerization constant (the least estimate, K ≈ 10^{7} M^{-1}), as would be expected for a molecular associate held by 16 hydrogen bonds.

In support to the CD, the UV-Vis measurements in chloroform or acetonitrile gave different spectra for the *cis*- and *trans*-isomers (Figure 4), in accordance with the ^{31}P NMR data herein and UV literature data of bis-triphenylphosphine $PdCl_2$ complexes.[18] All spectra exhibit absorption maxima at ≈ 345 nm,

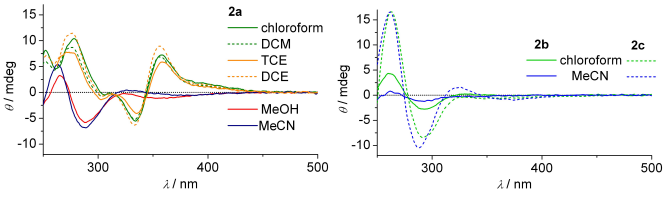

Figure 3. CD spectra of the complexes (15 µM, 1 cm path length). Strong bisignate Cotton effect around 350 nm is indicative of dimer formation. 1,2-dichloroethane and 1,1,2,2-tetrachloroethane are abbreviated as DCE and TCE, respectively.

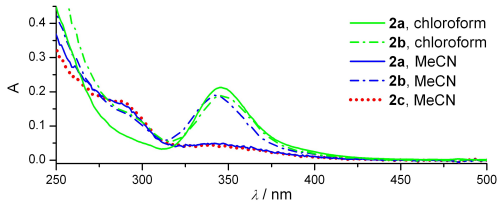

Figure 4. UV-Vis spectra of palladium complexes in different solvents, 15 μM.

assigned as the ligand to metal charge transfer[18] (p_π(Cl)→4d(Pd)). The lack of a red shift when comparing **2a** and **2b**, excludes the possibility of Pd···Pd interactions in **2a** dimer.[3c,d] In cases of the *cis*-isomer presence, additional absorption at ≈ 290 nm is visible. Predominance of the *cis*-isomer is indicated for **2a** and **2c** in acetonitrile, as confirmed by the NMR spectra.

Next, we investigated how addition of solvents that facilitate the formation of *cis*-isomer (i.e. acetonitrile and methanol), influences the chirooptical properties of **2a**. Interestingly, when acetonitrile was added (20 %) to the chloroform solution of **2a**, the exciton couplet gradually disappeared within 60 min period at 25 °C (Figure 5a), also accompanied by the changes in the UV spectra. Likewise, if methanol was added (10 %), the couplet immediately vanished. The resulting spectra are very similar to the spectra in pure acetonitrile (Figure S32), suggesting that trans-cis isomerization reaction occurred. If lesser quantities of the added solvent were used (10 or 1 %), the couplet did not reduce completely.

The slow isomerisation reaction allowed us to monitor the disassembly process shown to have first order kinetics in dimer concentration (Figure 5b). Furthermore, by heating a 1,2-dichloroethane solution of **2a** (70 °C, 3 min), the exciton couplet was substantially reduced (Figure 5c), and the resulting spectra were also indicative of trans-cis isomerization. Upon standing at room temperature, partial formation of the couplet was observed after three days. If higher concentration of **2a** was used, the couplet reformed almost quantitatively (Figure S34).

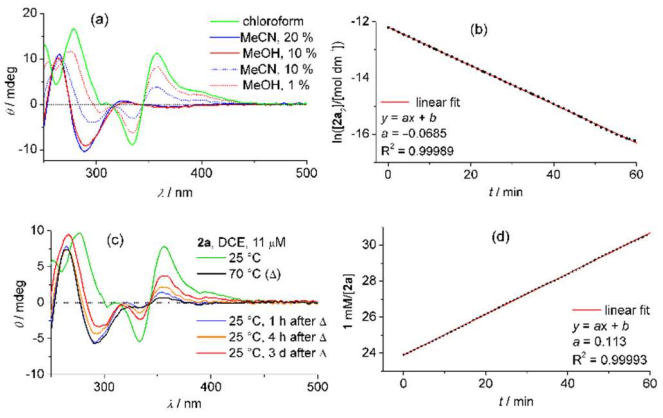

Figure 5. (a) CD spectra recorded after 60 min of solvent mixing (or 3 min for 10 % methanol), indicating dimer disassembly (15 μM); (b) time vs. logarithm of dimer concentration, indicating first order reaction for dimer disassembly; (c) temperature induced disassembly of **2a** dimer and subsequent reassembly upon cooling to 25 °C; (d) time vs. reciprocal monomer concentration (c_{tot} = 0.1 mM), indicating a second order reaction for dimer reassembly. Smoothed concentration data (see ESI) were used as input, for numerical consistency reasons.

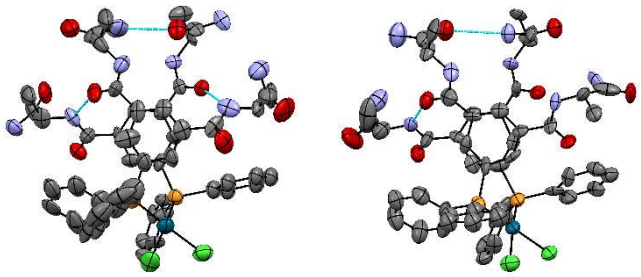

Figure 6. Molecular structures of two different conformers in the *cis*-**2c** single crystal structure ($P2_12_12_1$). Hydrogen atoms are omitted for clarity.

By monitoring the increase in couplet intensity after heating, dimer re-assembly was determined to have second order kinetics in monomer concentration (Figure 5d), as expected.

Single crystals of *cis*-configured **2c** were obtained upon standing of the acetonitrile solution. Two distinct conformers are found in the structure (Figure 6), forming a flattened infinite *P*-helical pattern (Figure S45) through amino acid hydrogen bonding, expanding to a 3D array through chloride hydrogen bonding. Eight symmetrically independent phenylalanines form a complex hydrogen bonded pattern.

Due to the high symmetry of **2a** dimer, strongly indicated by the NMR measurements in chloroform-d_1, a D_2-symmetric structure is proposed, based on two dimensional NOESY experiments, and optimized by DFT calculations (Figure 7). The structure exhibits *P*-helical chirality,[19] indicated by the experimental and calculated CD spectra (Figure 8) showing a positive exciton couplet. The size of the optimised structure is in an excellent agreement with the DOSY data (Table S2).

It is clear that the main driving force for dimer (dis)assembly is the trans-cis isomerization of palladium. This can be rationalised in terms of different equilibria (Scheme 2), where polar solvents favour the formation of *cis*-isomer, with partially "locked" intramolecular hydrogen bonding. Once *trans*-isomer is formed, the complex is "opened" for molecular association. The extent of dimerization can be tuned by varying temperature, concentration, or adding polar solvents. It is interesting to note that when *cis*-configured, monodentate ligands can also be considered as supramolecular bidentate ligands,[20] adding to the stability of the *cis*-isomer.

In summary, we have shown that the square-planar dichloropalladium complex with monodentate phosphine phenylalanineamide ligands, **2a**, forms non-covalent dimers in

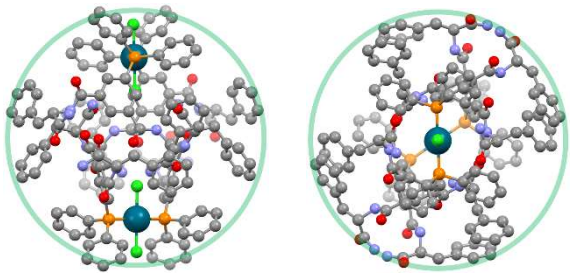

Figure 7. Side and top view of a DFT optimised dimeric structure of **2a** (chloroform), in accordance with NOESY measurements. Hydrogen atoms are omitted for clarity. The circle represents the calculated size (sphere approximation) obtained from DOSY measurements in chloroform-d_1.

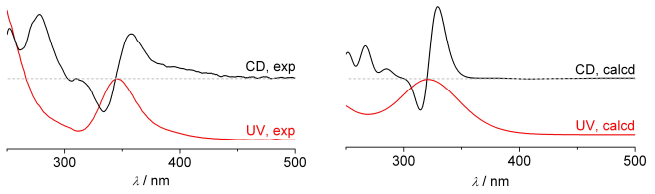

Figure 8. Qualitative comparison of the experimental and TD-DFT calculated UV and CD spectra of **2a** dimer in chloroform, strongly supporting the proposed solution structure.

chlorinated solvents through orthogonal interactions. The complex exhibits distinct chirooptical properties, directly related to the dimer formation which could easily be regulated through external stimuli. Gaining control over the assembly processes is of great importance for designing novel functional systems. The system described herein utilizes controllable supramolecular (dis)assembly, in essence a H-bond ON/OFF switch (in terms of non-covalent association), and offers valuable insight for further investigations, especially in the field of self-assembly and molecular recognition.

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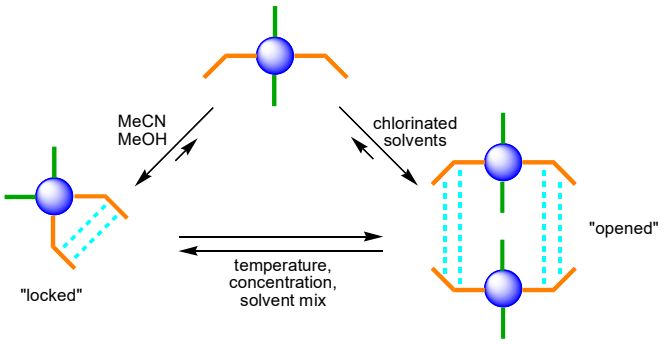

Scheme 2. Representation of different *cis*- and *trans*-**2a** relationships.

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Table of contents entry: "Self-assembly of a chiral complex dimer held by 16 hydrogen bonds was controlled through configurational isomerization of the metal center."