Aza[6]helicene Platinum Complexes: Chirality Control of cis-trans Isomerism
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Dedication (optional)

Abstract: It was serendipitously observed that cis-PtCl₂(NCEt)PPh₃ reacted differently with either racemic or enantiopure 4-aza[6]helicene giving respectively cis (racemic) and trans (enantiopure) 4-aza[6]helicene-bis-chloro-triphenylphosphine-platinum(II) complexes. This unexpected reactivity is explained through a dynamic process (crystallization induced diastereoselective transformation) and enables to address a new aspect of reactivity in chiral transition metal complexes.

Square planar (SP-4) Pt(II) complexes of general formula LL′PtX₂ display the usual cis/trans isomerism that is well-known in coordination chemistry. Such isomerism can have important practical implications such as in the famous case of Pt(NH₃)₂Cl₂ whose cis isomer is an efficient antitumor drug, while the trans isomer is ineffective. Therefore the control of the stereochemistry of SP-4 platinum complexes appears to be a pivotal step for the development of efficient drugs as well as innovative molecular materials.

Pure enantiomers and their racemic mixture are known to display different physical properties such as melting points and solubilities. One can take benefit from these different physical properties to optimize, for instance, resolution processes of chiral molecular materials.

In this communication, we show that the stereochemistry of the complexation of 4-aza[6]helicene ligand (2) with PtCl₂(NCEt)PPh₃ depends dramatically on the state of 2: indeed, racemic 2 leads to cis-PtCl₂(2)PPh₃ (cis-3), whilst enantiopure 2 leads to trans-PtCl₂(2)PPh₃ (trans-4). In other words, the cis/trans isomerism is here controlled by the enantiopure or racemic form of the azahelicene ligand. This is, at the best of our knowledge, a brand new aspect of chirality in transition metal complexes.

Helicene derivatives have recently shown potential interest as molecular materials due to their inherent chirality, large magnitude chiroptical properties and π-conjugated electronic structure. Following our work aimed at understanding the impact on the chiroptical properties of a metallic ion upon coordination to a helicene ligand, we studied the complexation of 4-aza[6]helicene 2 as a monodentate N-ligand to a platinum(II) center.

![Scheme 1. Synthesis of cis-isomer 3 and trans-isomer 4 in either racemic or enantiopure forms.](image)

For this purpose, cis-PtCl₂(NCEt)PPh₃ complex (cis-1), a square planar platinum complex bearing a triphenylphosphine ligand and a propionitrile in mutual cis position, was used. In refluxing toluene, it isomerizes to the trans-PtCl₂(NCEt)PPh₃ complex (trans-1), which in turn may give the dimeric form trans-[PtCl₂(cl)(PPh₃)]₂ after releasing EtCN. It is known that by reacting 1 with a pyridine ligand, the trans-PtCl₂(py)PPh₃ complex is formed and it does not isomerize to the cis form, probably due to the trans-effect of PPh₃ ligand. By replacing pyridine with azahelicene as the N donating ligand, an additional stereogenic element is introduced (P/IM helical chirality) to the cis/trans isomerism and diastereoisomers P-cis and P-trans (and their corresponding mirror-images M-cis and M-trans) are expected. 4-Aza[6]helicene 2 was prepared in racemic form according to the well-known photocytolysis process (see SI). The reaction of PtCl₂(NCEt)PPh₃ 1 with a slight excess (1.2 eq.) of (+)-2 in refluxing toluene for one night resulted in the precipitation of a
yellow solid with 74% yield. This precipitate was identified as *cis*-isomeric complex 3 (Scheme 1) by multinuclear NMR spectroscopy, ESI-MS and X-ray crystallography. For instance, in the \(^1\text{H}\) NMR spectrum, a strongly deshielded doublet appears at 9.56 ppm (\(J_{\text{H,H}} = 9.4\) Hz) corresponding to H5 proton and a doublet of doublet at 8.45 ppm (\(J_{\text{H,H}} = 5.4, J_{\text{H,P}} = 1.4\) Hz) corresponding to H3 (see numbering in Scheme 1). Furthermore, the \(^{31}\text{P}\) NMR displays one signal at 6.2 ppm with a \(^{195}\text{Pt}-^{31}\text{P}\) coupling constant of 3860 Hz. Single crystals were grown by slow evaporation of diisopropylether in a CH\(_2\)Cl\(_2\) solution of 3. The latter crystallized in the triclinic P-1 centro-symmetric space group with the presence of \(M\) and \(P\) azahelicenes. Its X-ray crystallographic structure depicted in Figure 1 reveals the square planar geometry around the platinum atom which is coordinated to two chlorine ligands being in a *cis* mutual position, one 4-aza[6]helicene ligand and one PPh\(_3\). A little distortion from ideal angles of 90° is observed (N4PtP and N4PcCl1 angles of 94.8° and 85.2° respectively) presumably due to steric hindrance of ligands. Furthermore, *trans*-influence causes a greater bond length between platinum and the chlorine atom *trans* to phosphine (Pt-C11: 2.357 Å) than the corresponding one with the chlorine *trans* to the nitrogen atom (Pt-C12: 2.291 Å). These values are in agreement with similar complexes.\(^{110}\) Interestingly, weak intramolecular \(\pi-\pi\) interactions take place between one phenyl of the PPh\(_3\) ligand and the pyridyl ring (centroid-centroid distance 3.852 Å). This interaction is only possible in the *cis* geometry complex and fixes the geometry around the platinum. Furthermore, due to the steric hindrance of the helix, the PPh\(_3\) is stacked on one side of the pyridyl ring and therefore planar chirality appears with the pyPtCl2 defining the chiral plane.\(^{110}\) Indeed, torsion angles of -86.16 and -80.93° (pm-chirality) are measured respectively for C3NPtP and C4aNPtC1 in the cis-3 molecule having the M-4-aza[6]helicene ligand, which means that the M-helicity induces a fixed pm-chiral planar sense.\(^{110}\) All four possible stereoisomers (two diastereomeric pairs of enantiomers) are depicted in Figure 1c. This efficient chiral induction from the helix to the planar chirality around the Pt center is also reflected in the chiroptical properties (*vide infra*). Finally, looking more into details the crystal packing of 3 reveals a set of several different intermolecular CH...Cl hydrogen bonds that contribute to the cohesion and the stability of the crystal (Figure 2d). In solution, NOESY experiments performed in CD\(_2\)Cl\(_2\) allow to evidence contacts i) between H1 and H16 atoms belonging to opposite sides of the az[a6]helicene moiety and ii) between Ha protons of the PPh\(_3\) ligand and protons H3 and H5 of the az[a6]helicene (Figure 2a). This indicates that the preferred conformation of racemic *cis*-3 in the solid state is also stable in solution. Overall, these interactions are responsible for the fixed *cis* geometry, stability and low solubility in toluene of the racemic complex 3. Finally, ESI mass spectrometry afforded a peak at \(m/z\) 880.0 corresponding to sodium cationized \([\text{PtCl}_2(\text{P(Ph)Na})]^+\) of elemental composition corresponding to \([\text{C}_{31}\text{H}_{20}\text{NPCl}_3\text{P}Na]^+\) and with an excellent match between the calculated and the experimental isotropic cluster (see SI). Tandem MS experiments were carried out on the monoisotopic ion at \(m/z\) 880.0 isolated in the ion trap and allowed to decompose via collision with He gas. In these conditions, the peak at \(m/z\) 330 was detected, corresponding to protonated 2, thus confirming the presence of the az[a6]helicene ligand in the complex. 

With the aim to prepare enantiomerically pure complexes, the \(M\)-(c) and \(P\)-(c)-2 enantiomers were separated by HPLC over a chiral stationary phase (see SI). Then the reaction between 1 and \(P\)-(c)+ was performed in the same conditions as reported for the racemic ligand (see SI). To our surprise, no yellow precipitate was observed and a new compound 4 was isolated in 69 % yield after purification, which displayed different \(^1\text{H}\), \(^{13}\text{C}\) and \(^{31}\text{P}\) NMR spectra from *cis*-3 (see SI).
to the intramolecular NOE theory,\textsuperscript{[11]} the NOE intensity of two H nuclei separated by a distance \( r \) shows \( r^{-6} \) dependency. As a consequence, the threshold of about 5Å for vanishing NOE is commonly accepted. For the sake of clarity, the average calculated distance of H3 with the Ha protons of the phenyl groups of triphenylphosphine were below and above 5Å for isomer cis-3 and trans-4, respectively. Furthermore, coupling constants \( J_{	ext{HH}P} (3.8 \text{ Hz}) \) and \( J_{	ext{HP}} (1.4 \text{ Hz}) \) are observed in complex 4 for H3 and H2 protons respectively in the \( ^1 \text{H} \) NMR spectrum (confirmed by \( ^{31} \text{P} \) decoupling experiments), not observable in the cis-3 isomer. \( J_{	ext{HH}P} \) have been reported for complex trans-\( \text{PtCl}_2(\text{SO}(\text{CH}_3)_2)(\text{PCy}_3) \), (Cy = cyclohexyl)\textsuperscript{[88]} and this further corroborates the hypothesis of a trans-geometry for complex \( P^{(+)}-4 \). Finally, the trans nature of 4 was unambiguously confirmed thanks to a sample prepared by reacting \((\pm)-2\) with pure trans-[\( \text{Pt}(\text{PPh}_3)(\mu-\text{Cl})(\text{Cl})_2])\textsuperscript{[86]} which displayed the same \( ^1 \text{H} \) and \( ^{31} \text{P} \) NMR spectra as \( P^{(+)}-4 \). This compound can only be the racemic trans-complex due to the strong trans effect of PPh\(_3\) (equation 1).

\[
\text{trans-[PtCl}_2(\mu-\text{Cl})(\text{PPh}_3)_2]_2 \overset{\text{rac-2 (2 eq.)}}{\xrightarrow{\text{CD}_2\text{Cl}_2}} \text{trans-isomer rac-4} \quad (1)
\]

It is worth of mention that it was impossible to observe any \( P^- \) or \( M^-\text{cis}-\text{isomer 3 from the reaction mixture with enantiomerically pure ligand 2, even by performing the reaction at } -50^\circ \text{ C. Furthermore, heating pure samples of 3 or 4 did not result in any changes, suggesting that 3 and 4 are not in equilibrium. However, deeper inspection of the crude mixture from the reaction of rac-2 with 1 revealed the presence of small quantities (\( <5\% \)) of the racemic trans-4 (\( ^1 \text{H} \)- and \( ^{31} \text{P} \) NMR spectra in SI). As a consequence, the formation of large quantities of trans-4 is prevented by the spontaneous precipitation of cis-3 in refluxing toluene which displaces the 1/1’ equilibrium (see Scheme 1). This process corresponds to a crystallization induced diastereoselective transformation\textsuperscript{[13]} and originates from the cis/trans lability of the starting material.

Finally, the mirror-imaged trans-\( M^-\text{(--)}-4 \) complex was obtained starting from \( M^-\text{(--)}-2 \). On the other hand, the enantiopure \( P^{(+)} \) and \( M^-\text{cis} \) complexes 3 were separated by HPLC over a chiral stationary phase (see SI). This nicely illustrates how the chirality of the ligand (racemic vs. enantiopure) can be used to obtain the all set of cis and trans isomeric Pt complexes in either racemic or enantiopure forms.

The chiroptical properties (electronic circular dichroism ECD and molar rotations MR) of \( P^{(+)}/M^{-\text{cis-}} \) enantiomers of ligand 2 and cis and trans isomeric complexes 3 and 4 were then examined (Figure 3). Ligand \( P^-\text{2} \) displays a strong negative CD-activity at 258 nm (\( \Delta\varepsilon = -110 \text{ M}^{-1}\text{cm}^{-1} \)) and strong positive bands at 310, 325 and 348 nm (+46, +150, +66 \text{ M}^{-1}\text{cm}^{-1} \)). Complex \( P^-\text{3} \) displays the same strong negative band of similar intensity (260 nm, \( \Delta\varepsilon = -120 \text{ M}^{-1}\text{cm}^{-1} \)) and strong positive bands at 319, 337, 351 nm that are red-shifted and of lower intensities (50, 78, 82 \text{ M}^{-1}\text{cm}^{-1} \)) compared to \( P^-\text{2} \). The CD spectrum of complex \( P^-\text{4} \) shows the same overall shape as \( P^-\text{3} \) but with lower intensity (\( \Delta\varepsilon = -57 \text{ M}^{-1}\text{cm}^{-1} \)) at 258 nm, and 32, 50, 54 \text{ M}^{-1}\text{cm}^{-1} \) at 317, 336, 348 nm respectively). Two additional weakly CD-active bands at 398 and 420 nm are present in the three compounds. Similarly, lower molar rotation values were measured for \( P^-\text{4} \) as compared to \( P^-\text{3} \) (5870 vs. 8215 (\( \pm 5\% \)), \( \text{CH}_2\text{Cl}_2, C 0.7-0.4 \)) while ligand \( P^-\text{2} \) displays values comparable to similar azal[6]helicene derivatives (7735 (\( \pm 5\% \)), \( \text{CH}_2\text{Cl}_2, C 1.7\text{.} \))\textsuperscript{[78]} The bigger chiroptical properties of cis-3 compared to trans-4 may be explained by the fixed planar chirality present in cis-3 that furnishes additional contributions to the ECD and MR values.

In conclusion, the enantiopurity of the starting helicenic ligand (racemic vs. enantiopure) triggers its reactivity vs. cis/trans isomers formation, thus allowing us to prepare the all set of four \( P^{(+)}/M^-\text{cis} \) and \( P^{(+)}/M^-\text{trans} \) isomeric (4-aza[6]helicene)-bis-chlorotriphenylphosphate-platinum(II) complexes and finally to examine their chiroptical properties in relation with their helical/planar chirality. To our knowledge, this is an unprecedented use of chirality in transition metal complexes, which combines the different solubilities between cis/trans stereoisomers with the configurational lability of the starting materials. We think that this can be often encountered in transition metal complexes and should be more accurately examined when geometrical isomerism (cis/trans, fac/mer)\textsuperscript{[810]} is combined with chirality (RIS, \( \Delta A, MIP \)).

![Figure 2. Selected, long-range NOEs (dashed lines) detected in a) cis-PtCl2(2)(PPha) 3 and b) in trans-PtCl2(2)(PPha) 4. The structures of both isomers are based on DFT calculations (the crystal structure coordinates were taken as starting geometry for 3 only).](image)
Keywords: Helicenes•Chirality•Complexation•Cis/trans isomerism•Platinum


[3] These differences are well-represented by their phase diagram which defines if a chiral molecule is either a conglomerate, a racemic mixture or a solid solution. See: J. Jacques, A. Collet, S. H. Wilen, Enantiomers, Racemates, & Resolutions, J. Wiley & Sons, New York, 1981.


