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Control of the platinum(II) ligating properties of rigid 1,2-diamines: the case of *trans*-2,3-diaminonorbornane

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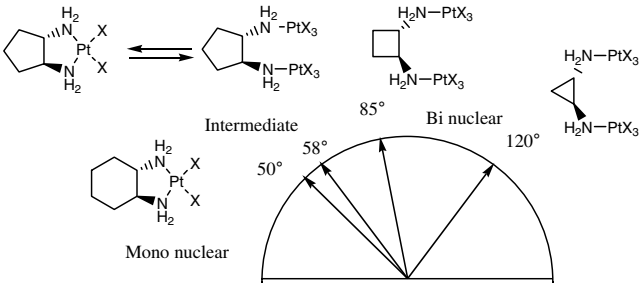
Abstract—Guided by a simple predictive model, a norbornane-based *trans*-1,2-diamine was identified as a potential bridging ligand for di-nuclear platinum complex formation; efficient synthesis and product characterization confirmed this hypothesis.

Polyfunctional ligands serve as convenient molecular scaffolds for the preparation of multinuclear transition metal complexes. From Farrell's pioneering work, interest has emerged for di and trinuclear platinum(II) complexes, featuring flexible aliphatic 1,ω-diamines as bridging ligands, that exhibit cytotoxicity and overcome the resistance phenomena often encountered with cisplatin.[1] Another class of di-nuclear platinum compounds, based on 1,2-azole ligands have been introduced recently by Komeda, Reedijk and co-workers.[2] By a fine tuning of the inter-platinum distance, ligation occurs with a minimum kink of the DNA, rendering the enzymatic repair processes inefficient. The distance between the metal centres is of a paramount importance for directing intra- or inter-strand ligation.

The N–C–C–N dihedral angle of a 1,2-diamine determines the formation of a mono- or a di-nuclear complex, according to Scheme 1.[3] Two domains are established: at a low dihedral angle, chelation occurs and a 1:1 ligand:metal stoichiometry is observed, whereas at a high dihedral angle, bridging behaviour and a 1:2 stoichiometry predominate. The transition from mono to di-nuclear domains is located somewhere between 60° and 80°.

To extend the suite of fixed dihedral angle ligands for fine tuning of platinum complex formation, here we consider the bicyclo[2.2.1]heptane (norbornane) skeleton,



Scheme 1. Relationship between ligand bite angle and behaviour.

which can dispose four different vicinal diamines motifs (Scheme 2).

Quantum screening at the HF/6-31G level (Gaussian, gas phase)[4a] indicated that among the four structures depicted in Scheme 2, only **1** (or its dihydrochloride salt **1**·2HCl) possesses an appropriate dihedral angle for forming a di-nuclear platinum complex. Reinvestigation at B3LYP/6-31G^{++} (water)[4] level indicates the following angles: for **1**, N_1–C_1–C_2–N_2: 104° and H_1–C_1–C_2–H_2: 125° for **1**·2HCl, N_1–C_1–C_2–N_2: 112° and H_1–C_1–C_2–H_2: 125°. The bite angle depends to a certain extent on whether the nitrogen lone pairs are involved in bonding.

After consulting the literature precedents,[5] we devised a more convenient synthesis of **1** (Scheme 3). Evans aziridination of norbornene **5** afforded **6** as expected.[6] The challenging step consisted of the aziridine ring opening of **6** by nitrogen nucleophile attack on the *endo* face.[7]

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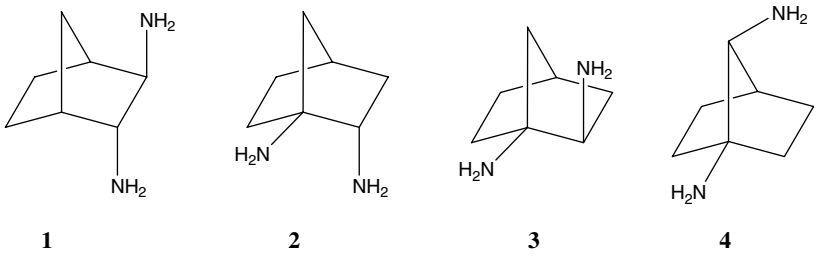
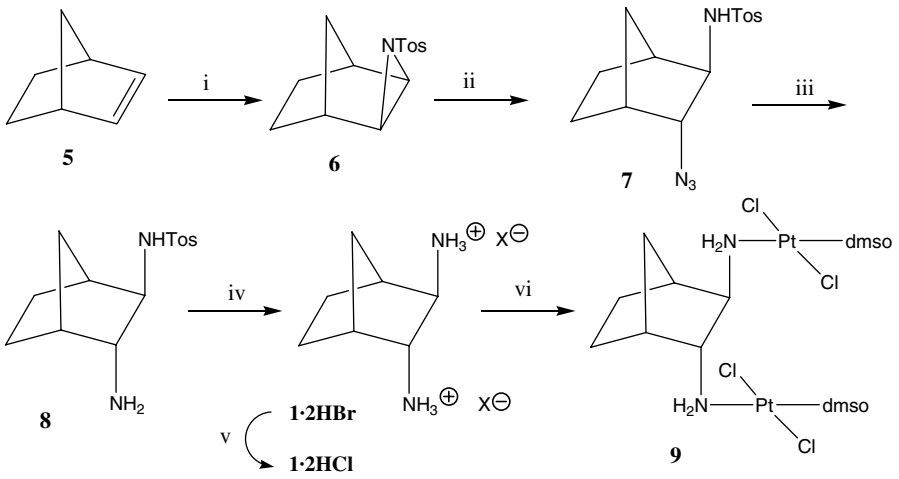


Scheme 2. Different norbornane-based 1,2-diamines envisaged.



Scheme 3. Reagents and conditions: (i) PhINTos, $Cu(Acac)_2$ (5 mol %), MeCN, 66%; (ii) NaN_3, Bu_4NBr (15 mol %), DMF, 125 °C, 21 h, 88%; (iii) H_2, Pd/C, MeOH, 95%; (iv) HBr/AcOH (32%), 100 °C, 82%; (v) Dowex marathon 11, 98%; (vi) $KPtCl_3$(DMSO), KOH (2.0 equiv), H_2O, 84%.

To our satisfaction, sodium azide and a catalytic amount of TBAB in hot DMF provided azide **7** smoothly.[8] This compound was easily hydrogenated to amine **8** in a 95% yield. Deprotection was achieved using HBr/AcOH (82%) followed by an anion exchange to yield dihydrochloride **1**·2HCl. Overall, this new synthesis provided a rapid and secure access to **1** in 67% from the published aziridine **6**. The H_1–C–C–H_2 dihedral angle was determined on the intermediate dihydrobromide **1**·2HBr with the aid of the Diez–Altona–Donders (DAD) Karplus type equation,[9] which is more accurate than the classical version and takes into account the solvent effect, the nature of the substituents and their spatial relationship. The measured $J^3(^1H–^1H)$ value was 3.80 Hz; application of the DAD equation gives a dihedral angle of 124.7°, a value very close to our predicted value of 125°.

Hatano and Saito reported that a single enantiomer of 2,3-diamino[2.2.1]heptane, **1**, reacted with $PtCl_2$(en) to give a di-nuclear complex of formula $[Pt_2(en)_2\mathbf{1}_2]$ featuring two μ-**1** ligands; only limited structural support was presented however.[10] This preliminary observation was encouraging but such a structure does not form the basis for useful interactions with DNA since (a) no room is left for the modulation of leaving groups on the Pt centres, and (b) a double-bridging structure imposes excessively severe constraints on the relative dispositions of the two square planar Pt centres. It was thus important to demonstrate access to a di-nuclear species with a single μ-**1** ligand.

Kukushkin's salt, $KPtCl_3$(DMSO), is an ideal partner for the formation of a 1:2 ligand:Pt bridging complex.[11,3] The reaction of **1**·2HCl with 2 equiv of this reagent led to the formation of a pale yellow solid within a few minutes, isolated by filtration (84% yield).[12] The structure of the complex was confirmed as **9** from ^{195}Pt NMR (resonance at δ −3115 ppm, characteristic of an N_2SCl coordination set[13]), electrospray mass spectroscopy and elemental analysis.

In conclusion, we have demonstrated a new access to diamine **1**, which behaves appropriately for the preparation of single μ-ligand di-nuclear platinum(II) structures. Further work is now in progress to extend this approach to the preparation of other platinum complexes for cytotoxicity evaluation.

Acknowledgement

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