Supramolecular chemistry of organoplatinum(IV) complexes: A syndiotactic polymer with uracil substituents

Michael J Nieradko and Richard J Puddephatt

Abstract

The reaction of RCH₂X with [PtMe₂(DPA)]₂, (DPA = di-2-pyridylamine) has given [PtXMe₂(CH₂R)(DPA)] by cis oxidative addition to give 2a, when R = 6-uracil, X = Cl, or 3a, when R = CO₂H, X = Br, but by a mixture of cis and trans oxidative addition to give 4a/4b when R = 4-C₆H₄CO₂H, X = Br. The unusual cis stereochemistry of oxidative addition is rationalized thermodynamically by the formation of an intramolecular hydrogen bond in 2a and 3a but not 4a, and kinetically by the role of the ligand DPA NH group in hydrogen bonding to halide. Complex 2a in the solid state forms an unusual supramolecular syndiotactic polymer by forming two different intermolecular NH...O=C hydrogen bonds to neighbouring molecules.

Keywords
hydrogen bond, platinum, polymer, supramolecular, syndiotactic, uracil

Date received: 9 May 2022; accepted: 4 July 2022

Introduction

The fields of supramolecular chemistry and organometallic chemistry continue to flourish, and there is increasing interest in the interface of these areas, since the products have potential applications in molecular materials, polymers, catalysis or pharmaceuticals.¹⁻⁷ For example, there are now many platinum complexes that contain substituents with hydrogen bonding properties that can participate in supramolecular self-assembly.⁸⁻¹⁵ The incorporation of nucleobase units in platinum complexes has been a particular area of interest because both have important applications in cancer therapy, either separately or in combination. For example, a combination of 5-fluorouracil and cisplatin is effective against several tumour types.¹⁶⁻¹⁸

Multiple H-bonds
A versatile route to organoplatinum(IV) complexes is by oxidative addition of alkyl halides to electron-rich platinum(II) complexes. These reactions typically occur by the polar SN2 mechanism, leading to trans oxidative addition. The reactions are tolerant of many functional groups. Specifically, hydrogen bonding groups, including carboxylic acids and the nucleobase uracil can be incorporated in this way (Scheme 1). Complexes A and C have been shown to have the structures expected for trans oxidative addition, and they both self-assemble to form supramolecular dimers (Scheme 1). 

This paper describes related chemistry using the chelate ligand di-2-pyridylamine \([HN(2-C_5H_4N)_2, DPA]\) in place of the 4,4'-di-tert-butyl-2,2'-bipyridine (bubipy) ligand of Scheme 1. DPA has an NH group and so there is potential for more extensive hydrogen bonding and self-assembly. Surprisingly, a difference in the stereochemistry of oxidative addition was observed, and the structure of a syndiotactic supramolecular polymer is described. We note the related expertise of Alwyn Davies in the self-association of organometallic compounds. 

Results and discussion

The new organoplatinum complexes are shown in Scheme 2. The complex \([PtMe_2(DPA)]\) (DPA = 2,2'-dipyridylamine), 1, has been reported previously but details of its spectra were not given. In the \(^1H\) NMR spectrum, the methylplatinum groups give a singlet resonance at \(\delta(1H) = 0.58\), with satellites arising from the coupling to \(^{195}\text{Pt}\) with \(2J(\text{PtH}) = 86\) Hz, a typical value for methylplatinum(II) complexes. The NH resonance appeared as a broad singlet at \(\delta(1H) = 0.58\). The organoplatinum(IV) complexes were prepared by oxidative addition of the corresponding alkyl halide to complex 1. Unexpectedly, the oxidative addition of 6-(chloromethyl) uracil and bromoacetic acid gave the products of cis oxidative addition 2a and 3a, in contrast to the trans stereochecmistry observed with the corresponding bubipy complexes (Scheme 1). The oxidative addition of 4-(bromomethyl) benzoic acid gave a mixture of the products of cis and trans oxidative addition, 4a and 4b, in approximately 1:3 ratio (Scheme 2).

We were not able to grow good single crystals of the carboxylic acid derivatives 3 or 4, but the stereochecmistry was clearly defined by the NMR spectra. Thus, complex 3a and 4a have no symmetry while 4b has effective mirror symmetry (point group C_s). Complex 3a was formed as a single isomer and the \(^1H\) NMR spectrum contained two equal intensity methylplatinum resonances at \(\delta(1H) = 0.87\), \(J(\text{PtH}) = 72\) Hz, and 1.20, \(J(\text{PtH}) = 70\) Hz, and the coupling constants \(J(\text{PtH})\) are typical for platinum(IV).
Nieradko and Puddephatt

Figure 1. Views of the structure of complex 2a: (a) the molecular structure and intramolecular hydrogen bond [graph set $S_1^1(6)$, N(5)-Cl(1) 3.125(5) Å]; (b) intermolecular hydrogen bonds [graph set $R_2^2(20)$, N(2)-O(2B) = O(2)-N(2B) = 2.865(6) Å, symmetry equivalent atoms x,y,z; 2-x, -y, 1-z]; (c) intermolecular hydrogen bonds [graph set $R_2^2(8)$, N(4)-O(1A) = O(1)-N(4A) = 2.789(7) Å, symmetry equivalent atoms x,y,z; 2-x, -1-y, -z]; (d) part of the supramolecular polymer formed by intermolecular hydrogen bonding (opposite enantiomers shown as red and blue).

complexes. The PtCH$_2$ protons are diastereotopic and gave two doublet resonances at $\delta$(H) = 2.42, $^2$J(HH) = 8 Hz, $^3$J(PtH) = 104 Hz, and 2.56, $^3$J(HH) = 8 Hz, $^2$J(PtH) = 102 Hz. Complex 4a gave similar NMR parameters, but the more symmetrical isomer 4b gave a single methylplatinum resonance at $\delta$(1H) = 1.08, $^2$J(PtH) = 70 Hz, and a single PtCH$_2$ resonance at $\delta$(1H) = 3.05, $^2$J(PtH) = 102 Hz. The 1:3 ratio of 4a:4b did not change at temperatures up to 60 °C, above which slow decomposition occurred.

The $^1$H NMR spectrum of complex 2a clearly indicated the stereochemistry arising from cis oxidative addition. Thus, there were two methylplatinum resonances at $\delta$(1H) = 0.84, $^3$J(PtH) = 73 Hz, and 0.87, $^3$J(PtH) = 68 Hz, while the diastereotopic PtCH$_2$ protons gave an $^3$AB' quartet with $\delta$(1H) = 2.53, $^3$J(HH) = 10 Hz, $^3$J(PtH) = 82 Hz, and 3.11, $^2$J(HH) = 10 Hz, $^2$J(PtH) = 114 Hz. In this case, an X-ray structure determination was possible and the interesting features are shown in Figure 1. The complex 2a is chiral but crystallizes as a racemic mixture. The lattice contains equal amounts of the two enantiomers (for octahedral complexes, defined as C, clockwise, or A, anticlockwise). Figure 1(a) shows the molecular structure for one enantiomer, and indicates that there is an intramolecular NH...ClPt hydrogen bond, with distance N(5)-Cl(1) 3.125(5) Å. It is likely that it is the presence of this hydrogen bond that favours the formation of the product of cis oxidative addition 2a. In addition to this intramolecular hydrogen bond, each molecule is connected to a molecule of opposite chirality on either side by formation of complementary, head-to-tail intermolecular NH...O=C hydrogen bonds. On one side, the
hydrogen bond donor is the N(2)H group of the DPA ligand and the acceptor is the uracil carbonyl oxygen atom O(2) of a neighbour related by inversion symmetry (Figure 1(b)), with distances N(2)..O(2B) = O(2B)N(2B) = 2.865(6) Å. On the other side, the hydrogen bond donor is the uracil N(4)H group and the acceptor is the uracil carbonyl oxygen atom O(1) of a second neighbour, also related by inversion symmetry (Figure 1(c)), with distances N(4)..O(1A) = O(1..N(4A) = 2.789(7) Å. In the related complex C (Scheme 1), formed by trans oxidative addition, the interuracil group hydrogen bonding involves the other pair of NH and CO groups.\textsuperscript{21} The combination of the two forms of intermolecular hydrogen bonding results in the formation of a supramolecular syndiotactic polymer, with alternating CACA chirality of the platinum complex components 2a (Figure 1(d)).

To gain further insight into the molecular stereochemistry of the complexes, DFT calculations were carried out for both products of cis and trans oxidative addition (see experimental for details).\textsuperscript{29} The calculated structures and relative energies are shown in Figure 2. The calculations successfully predict the greater relative stability of 2a over 2b, by 11 kJ mol\textsuperscript{-1}, and 3a over 3b, by 21 kJ mol\textsuperscript{-1}. This is consistent with the presence of an intramolecular hydrogen bond, NH..Cl in 2a and OH..Br in 3a, only in the products of cis oxidative addition. The geometry of 4a (Figure 2(c)) does not allow formation of an intramolecular OH..Br hydrogen bond and, in this situation, the product of trans oxidative addition 4b is predicted to be more stable (by 20 kJ mol\textsuperscript{-1}). In related complexes [PtXMe\textsubscript{2}R(NN)], X = halogen, NN = diamine ligand, it is generally found that the bulkier alkyl group R prefers the axial coordination site trans to X, so complex 4 behaves in the expected way with 4b preferred over 4a when hydrogen bonding is not present.\textsuperscript{19,20,30} The DFT calculations do not consider intermolecular interactions, so the quantitative aspects should be considered with caution, but the predictions do support the experimental observations in a qualitative way.

**Conclusion**

The prediction that the platinum(IV) complexes with DPA ligand might give different structures compared to the bubipy complexes of Scheme 1 has been upheld.
The observation of much faster cis-trans isomerism of the DPA complexes was not predicted but can be rationalized according to Scheme 3. The easy flexing of the 6-membered Pt(DPA) ring can allow the NH group to hydrogen bond to the leaving halide ion in the first step of the SN₂ oxidative addition to give 5-coordinate intermediate D. The hydrogen bonding may then slow the transfer of the halide ion to platinum to give the typical product of trans oxidative addition, F. This slower coordination step can give time for the isomerization step from D to give E, and then halide transfer to platinum to give the product of cis oxidative addition G can occur. The hydrogen bonding might also facilitate the halide dissociation from F or G and so allow further isomerization steps by way of D or E (Scheme 3).

The most interesting case was the oxidative addition of 6-(chloromethyl)uracil to give the chiral complex 2a (Scheme 2 and Figure 1). Compared with the bupy derivative C of Scheme 1, complex 2a is formed by cis rather than trans oxidative addition, it has an intramolecular NH...Cl hydrogen bond, it uses the NH/C=O groups at the 3/4 positions rather than the 1/2 positions of the uracil group in forming the intermolecular complementary head-to-tail NH...O=C hydrogen bonds between uracil groups, and it contains extra intermolecular complementary head-to-tail NH...O=C hydrogen bonds using the NH group of the DPA ligand and the carbonyl group at the 2-position of the uracil group. The overall result is to form a supramolecular, syndiotactic polymer (Figure 1), whereas C forms a supramolecular dimer (Scheme 1). The supramolecular self-assembly is becoming an important component of the toolbox for synthesis of functional organometallic polymers.

**Experimental**

The complex [Pt₂Me₂(μ-SMe₂)] was prepared according to the literature method. NMR spectra were recorded by using a Varian Mercury 400 NMR or Varian Inova 600 NMR spectrometer. ¹H chemical shifts are reported relative to TMS and assignments were aided by ¹H-¹H NOESY and ¹H-¹H gCOSY experiments. The NMR labels are shown in Chart 1. IR spectra were recorded using a Bruker Vector spectrometer by ATR. X-ray data were collected at 150 K using a Nonius Kappa CCD diffractometer with graphite-monochromated Mo-Kα radiation (λ = 0.71073 Å). A suitable crystal of 2a, grown from DMSO/methanol/ether solution, was coated in Paratone oil and mounted on a glass fibre loop. Unit cell parameters were calculated and refined from the full data set. The structure was solved by direct methods and refined by full-matrix least-squares techniques using the SHELX suite of crystallographic software. The hydrogen atoms were placed in calculated positions and refined using the riding model. There was a disordered solvent molecule in the lattice which could not be modelled so the program SQUEEZE was used to account for the electron density. Details of the structure are given in the Supplementary cif file (CCDC 2168906). The DFT calculations were carried out using the BLYP functional, with double-zeta basis set and first-order scalar relativistic corrections, with solvation modelled for dichloromethane solution by using COSMO, all as implemented in ADF-2020. Details of the calculated ground state structures are given in the Supporting Information.

**Scheme 3.** A likely mechanism of cis-trans isomerization for the DPA complexes.

**Chart 1.** NMR labels.
[PtClMe₂(CH₂C₄H₄N₄O₂)(DPA)], 2a
To a solution of [PtMe₂(DPA)], 1 (0.100 g, 0.25 mmol) in acetone (5 mL) was added a solution of 6-(chloromethyl) uracil (0.050 g, 0.31 mmol) in THF (5 mL). The mixture was stirred for 3 h, the solvent was removed under vacuum, and the product was recrystallized from MeCN/MeOH/ Et₂O to give colourless crystals. Yield 0.095 g, 68%.

NMR in DMSO-d₆: δ(H) = 0.84 (s, 3H), δ(PtH) = 73 Hz, PtMe), 0.87 (s, 3H), δ(PtH) = 68 Hz, PtMe), 2.53 (d, 1H, 3J(HH) = 10 Hz, 3J(PtH) = 82 Hz, CH₃), 3.11 (d, 1H, 3J(HH) = 10 Hz, 3J(PtH) = 114 Hz, CH₃), 5.19 (s, 1H, uracil CH); 7.16 (dd, 1H, 3J(HH) = 6 Hz, 3J(HH) = 7 Hz, H₆), 7.18 (dd, 1H, 3J(HH) = 6 Hz, 3J(HH) = 7 Hz, H₅); 7.29 (d, 1H, 3J(HH) = 8 Hz, H₆); 7.30 (d, 1H, 3J(HH) = 8 Hz, H₅); 7.92 (m, 2H, 2J(PtH) = 82 Hz, CH₂), 8.25 (m, 2H, 2J(PtH) = 6 Hz, H₆); 8.40 (d, 1H, 3J(HH) = 6 Hz, H₅), 9.84 (s, 1H, uracil NH); 10.66 (s, 1H, uracil NH); 10.71 (s, 1H, NH); IR (cm⁻¹): 1715, 1612 [ν(NH)]. Anal. calcd for C₁₂H₁₅N₃Pt: C 36.4, H 3.8, N 10.6. Found: C 36.2, H 3.6, N 12.6%.

Supporting information
Calculated atomic coordinates from the DFT calculations. Details of the X-ray structure determination are given in the cif file and have been deposited at the Cambridge Crystallographic Data Centre (CCDC 2168906).

References
1. Haiduc I and Edelmann FT. Supramolecular organometallic chemistry. Weinheim: Wiley-VCH, 1999.
2. Braga D, Giaffreda SL, Grepioni F, et al. Coord Chem Rev 2006; 250: 1267–1285.
3. Desiraju GR. J Chem Soc Dalton Trans 2000; 3745–3751.
4. Braga D, Grepioni F and Desiraju GR. Chem Rev 1998; 98: 1375–1405.
5. Branner L. Dalton Trans 2003; 3145–3157.
6. Davies PJ, Veldman N, Grove DM, et al. Angew Chem Int Ed 1996; 35: 1959–1961.
7. Grotjahn DB. Pure Appl Chem 2010; 82: 635–647.
8. Rizzato S, Berges J, Mason SA, et al. Angew Chem Int Ed 2010; 49: 7440–7443.
9. Ai Y, Li Y, Fu HLK, et al. Chem Eur J 2019; 25: 5251–5258.
10. McCready MS and Puddephatt RJ. ACS Omega 2018; 3: 13621–13629.
11. Yan X, Li S, Pollock JB, et al. Proc Nat Acad Sci 2013; 110: 15585–15590.
12. Burrows AD, Chan CW, Chowdhry MM, et al. Chem Soc Rev 1995; 24: 329–339.
13. Gianneschi NC, Tieckink ERT and Rendina LM. J Am Chem Soc 2000; 122: 8474–8479.

Supporting information
Calculated atomic coordinates from the DFT calculations. Details of the X-ray structure determination are given in the cif file and have been deposited at the Cambridge Crystallographic Data Centre (CCDC 2168906).
14. Lippert B and Miguel PJS. *Coord Chem Rev* 2016; 327: 333–348.
15. Zhang F, Jennings MC and Puddephatt RJ. *Chem Commun* 2007: 1496–1497.
16. Ravera M, Gabano E, McGlinchey MJ, et al. *Dalton Trans* 2022; 51: 2121–2134.
17. Lippert B. *J Biol Inorg Chem* 2022; 27: 215–219.
18. Esaki T, Nakano S, Tatsumoto T, et al. *Cancer Res* 1992; 52: 6501–6506.
19. Rendina LM and Puddephatt RJ. *Chem Rev* 1997; 97: 1735–1754.
20. Crespo M, Martinez M, Nabavizadeh SM, et al. *Coord Chem Rev* 2014; 279: 115–140.
21. Fraser CSA, Jenkins HA, Jennings MC, et al. *Organometallics* 2000; 19: 1635–1642.
22. Fraser CSA, Eisler DJ, Jennings MC, et al. *Chem Commun* 2001: 1310–1311.
23. Au RHW, Jennings MC and Puddephatt RJ. *Dalton Trans* 2009; 3519–3525.
24. Puddephatt RJ. *Dalton Trans* 2022; 51: 7011–7024.
25. Zhang F, Prokopchuk EM, Broczkowski ME, et al. *Organometallics* 2006; 25: 1583–1591.
26. Davies AG. *Organotin chemistry*. Weinheim: Wiley-VCH, 2004.
27. Brown JM, Chapman AC, Harper R, et al. *J Chem Soc Dalton* 1972; 338–341.
28. Connelly NG and Damhus T. *Nomenclature of inorganic chemistry, IUPAC recommendations*, 2005. Cambridge: RSC Publishing, 2005, pp. 187–190.
29. SCM. *ADF 2020*. Amsterdam: Vrije Universiteit Amsterdam, http://www.scm.com
30. Puddephatt RJ. *Can J Chem* 2019; 97: 529–537.
31. Portalone G, Bencivenni L, Colapietro M, et al. *Acta Chem Scand* 1999; 53: 57–68.
32. Manners I. *Synthetic metal-containing polymers*. Weinheim: Wiley-VCH, 2004.
33. Brammer L. *Chem Soc Rev* 2004; 33: 476–489.
34. Long NJ and Williams CK. *Angew Chem Int Ed* 2003; 42: 2586–2617.
35. Puddephatt RJ. *Coord Chem Rev* 2022; 454: 214342.
36. Scott JD and Puddephatt RJ. *Organometallics* 1983; 2: 1643–1648.
37. Hill GS, Irwin MJ, Levy CJ, et al. *Inorg Synth* 1998; 32: 149–153.
38. Sheldrick GM. *Acta Cryst* 2008; A64: 112.
39. Sheldrick GM. *Acta Cryst* 2015; C71: 3–8.
40. Spek AL. *Acta Cryst* 2015; C71: 9–18.