DALTON COMMUNICATION

Molecular recognition of 2,6-diaminopyridine by platinum orotate complexes

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The crystal structure of $\{[Pt(HL)(dppe)]\cdot NC_5H_3(NH_2)_2\text{-}2,6\}_2$ [H_3L = 2,6-dioxo-1,2,3,6-tetrahydropyrimidine-4-carboxylic acid, orotic acid, dppe = 1,2-bis(diphenylphosphino)ethane] has demonstrated that the in-built triple hydrogen-bonding functionality of the co-ordinated orotate is able to recognise at a molecular level 2,6-diaminopyridine, which has complementary hydrogen-bonding groups; this designed complementarity has produced a more efficient hydrogen-bonding arrangement than that possible in [Pt(HL)(dppe)] alone.

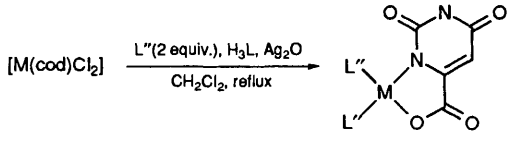
The synthesis and applications of bifunctional metal complexes that combine the covalent bond forming capabilities of a central metal ion with a ligand surface that is capable of recognising a nucleotide base or related complex through complementary hydrogen-bond interactions are of considerable interest.[1-3] Such interactions have potential implications for metallo-drug design and for materials chemistry[4] since triply hydrogen-bonded complementary base pairs have been used for inducing the formation of supramolecular mesophases[5,6] and as the basis for self-assembled nanostructures.[7,8]

In this communication we report the synthesis of bis(mono)- and di-phosphine-platinum and -palladium complexes of orotic acid (2,6-dioxo-1,2,3,6-tetrahydropyrimidine-4-carboxylic acid). Platinum complexes are of interest due to their potential as anti-tumour agents.[9] The phosphine ligands impart solubility in organic solvents to the complexes and give a useful $^{31}P\text{-}\{^1H\}$ NMR structural probe. Orotic acid (vitamin B_{13}, H_3L), which is a minor base component of nucleic acids, is a derivative of uracil [pyrimidin-2,4(1*H*,3*H*)-dione] containing an additional carboxylic acid functionality, and is thus able to co-ordinate to a metal ion as a bidentate dianionic ligand through the carboxylate and deprotonated nitrogen atom. This leaves a potential hydrogen-bond acceptor, hydrogen-bond donor, hydrogen-bond acceptor (ADA) arrangement that is capable of forming hydrogen bonds with a compound such as 2,6-diaminopyridine, which has the complementary DAD arrangement, or with adenine, which has the DA motif and so could utilise only one hydrogen-bond acceptor and donor, in a Watson–Crick manner. Diammine complexes of platinum and palladium with orotic acid[10] and 3-methyl-2,6-dioxo-1,2,3,6-tetrahydropyrimidine-4-carboxylic acid (H_2L')[11] have been reported previously and the anti-tumour properties of [Pd$L'(NH_3)_2$] studied.[11] However, no phosphine-containing complexes have been reported nor have any hydrogen-bonded adducts. The presence of the methyl substituent in the 3-position in [Pd$L'(NH_3)_2$] prevents such derivatives from hydrogen bonding in an analogous manner to that proposed for orotic acid.

The complexes [M(HL)(L″)$_2$] [M = Pt, L″ = PPh_3 **1**, PMe_2Ph **2**, PBu_3 **3** or PEt_3 **4**; L″$_2$ = 1,2-bis(diphenylphosphino)ethane (dppe) **5**; M = Pd, L″$_2$ = dppe **6**] were prepared by an adaptation of the method of Kemmitt *et al.*[12] Two equivalents of the phosphine (or 1 equivalent of dppe), [M(cod)Cl_2] (cod = cycloocta-1,5-diene), an excess of H_3L and an excess of silver(I) oxide were refluxed in dichloromethane (see Scheme 1). The resulting colourless (**1**–**5**) or pale yellow (**6**) solutions were filtered and taken to dryness under reduced pressure and the crude products were recrystallised from dichloromethane–hexane. Satisfactory microanalyses and fast-atom bombardment (FAB) mass spectra were obtained for all complexes (see Table 1). The $^{31}P\text{-}\{^1H\}$ NMR spectra of complexes **1**–**5** show AX-spin patterns with corresponding ^{195}Pt satellites indicating the presence of two inequivalent phosphorus environments. In all cases the phosphorus *trans* to the carboxylate oxygen experiences a larger $^1J(^{31}P,^{195}Pt)$ coupling constant than the phosphorus lying *trans* to nitrogen. The $^{31}P\text{-}\{^1H\}$ NMR spectrum of complex **6** shows an AB system due to the relative similarities of $^2J(^{31}P,^{31}P)$ and the chemical-shift difference between the signals. In the ^1H NMR spectra, the N–H chemical shift is concentration dependent, suggesting dimerisation of [M(HL)(L″)$_2$] through hydrogen bonding in $CDCl_3$.

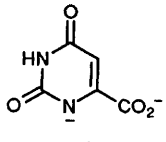
Single crystals of complex **5*** were obtained by the slow diffusion of hexane into a dichloromethane solution. The crystal structure confirmed that orotate behaves as a bidentate dianionic ligand (Fig. 1). The unit cell contains two crystallographically independent molecules, both of which are linked *via* two hydrogen bonds with their centrosymmetrically related counterparts to form 'dimer pairs'. The N···O separations of 2.89(2) and 2.91(2) Å are longer than the analogous hydrogen bonding distances in [Pt(HL)$(NH_3)_2$] (2.77 Å).[10]

The crystallographically independent pairs of hydrogen-bonded dimers are cross-linked *via* weak C–H···O hydrogen bonds between one of the ethylene C–H hydrogen atoms from diametrically opposite dppe fragments within one dimer and the carbonyl oxygen atom involved in hydrogen-bonded dimer-pair formation in the other. The C···O, H···O distances are 3.42



	M	L″		M	L″$_2$
1	Pt	PPh_3	**5**	Pt	dppe
2	Pt	PMe_2Ph	**6**	Pd	dppe
3	Pt	PBu_3			
4	Pt	PEt_3			

Scheme 1



HL^{2-}

Table 1 FAB mass, $^{31}P-\{^1H\}$ NMR and IR spectroscopic data for complexes **1–6**

Complex	$(M + H)^+$ (%)	$\delta(P^1)$	$\delta(P^2)$	$^2J(P^1,P^2)$	$^1J(P^1,Pt)$	$^1J(P^2,Pt)$	ν(CO)	ν(NH)
1	874 (93)	12.1	3.6	26	3499	3811	1680s, 1673s, 1660s	3225m
2	626 (100)	−13.9	−23.0	27	3344	3627	1667s, 1637s	3153m
3	754 (98)	−0.3	−6.1	26	3323	3579	1682s, 1669s, 1654s	3199m
4	586 (100)	7.3	1.5	26	3313	3575	1677s, 1670s, 1650s	3154m
5	748 (100)	39.8	33.2	14	3323	3780	1664s (br)	3160m
6	659 (100)	62.3	62.1	27	—	—	1656s, 1635s	3158m

and 2.46 Å and the C–H · · · O angle is 172°. The combined effect of these weak C–H · · · O interactions is to form weakly linked tapes that extend in the 110 direction as shown in Fig. 2.

The geometries around both independent platinum atoms are distorted square-planar with the bite angles of the chelating ligands being less than 90°; the O–Pt–N angles are, at 78.9(5) and 80.1(6)°, somewhat smaller than the equivalent angles in $[Pt(HL)(NH_3)_2]$ (82.3°).[10] There is a notable departure from planarity of the atoms in the co-ordination plane in one of the complexes with the phosphorus *trans* to oxygen lying 0.27 Å out of plane, *cf.* 0.07 Å in the other independent complex.

In **5**, the complex can only utilise two of its three hydrogen-bond donors and acceptors. Thus, it is to be expected that the complex would interact more efficiently with a substrate providing a DAD match for its ADA triple hydrogen-bonding potential. This is supported by downfield shifts observed in the ^1H NMR spectra of complexes **1–6** in $CDCl_3$ with 2,6-diaminopyridine, which has the complementary DAD hydrogen-bonding site arrangement, suggesting the presence in solution of hydrogen-bonded adducts. Single co-crystals were obtained from a dichloromethane solution containing equimolar amounts of **5** and 2,6-diaminopyridine. The crystal structure of the resulting adduct **7*** confirmed that the two component molecules are indeed linked *via* three hydrogen bonds. Further hydrogen bonds between an NH_2 proton on the 2,6-diaminopyridine molecule and a carbonyl oxygen atom of an adjacent complex are also present and link these 1 + 1 adducts into 2 + 2 dimers, as shown in Fig. 3.

Bond lengths and angles around the platinum atom and within the pyrimidine ring show no significant differences to those observed for **5**. Indeed, the conformation of the platinum complex as a whole does not undergo any significant change on adduct formation. A notable feature of the triple hydrogen-

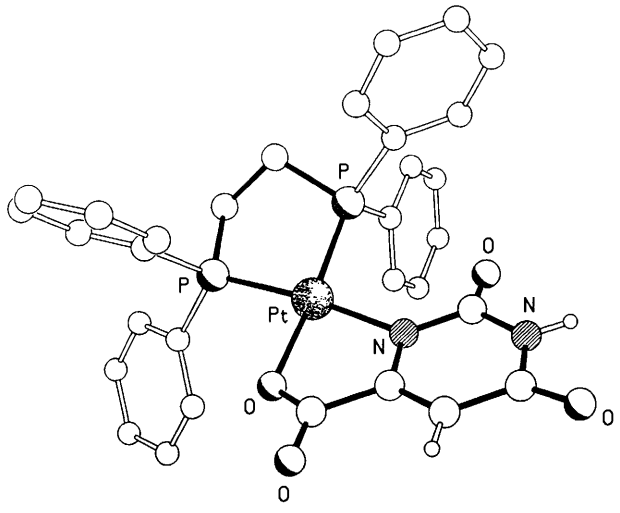


Fig. 1 Molecular structure of one of the crystallographically independent complexes present in the crystal structure of [Pt(HL)-(dppe)] **5**

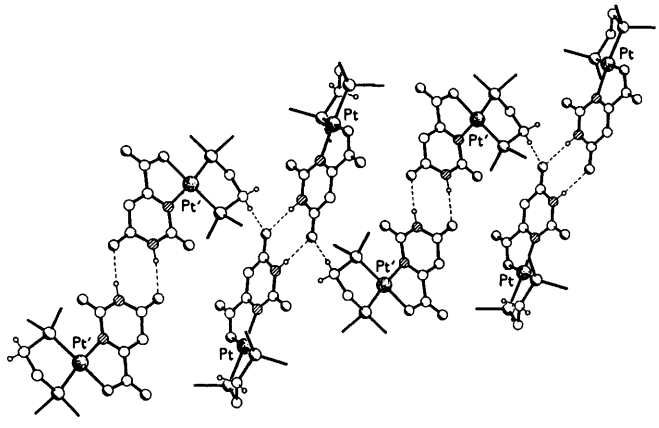


Fig. 2 Part of one of the tapes of weakly C–H · · · O linked by hydrogen-bonded dimer pairs in the crystal structure of **5**

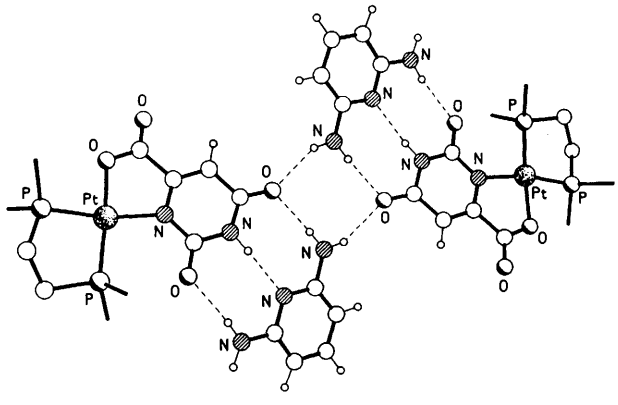


Fig. 3 The hydrogen-bonded 2 + 2 adduct formed between **5** and 2,6-diaminopyridine

* Crystal data for **5**. $C_{31}H_{26}N_2O_4P_2Pt{\cdot}0.25CH_2Cl_2$, M = 768.8, colourless plates, crystal dimensions 0.38 × 0.32 × 0.02 mm, monoclinic, space group $P2_1/n$, a = 17.981(3), b = 10.147(2), c = 35.279(6) Å, β = 94.46(1)°, U = 6417(2) Å^3, Z = 8 (2 crystallographically independent molecules), D_c = 1.592 g cm^{-3}, μ(Mo-Kα) = 4.55 mm^{-1}, $F(000)$ = 3012. 7867 Independent data ($2\theta \leqslant 50°$) were collected on a Siemens P4/PC diffractometer using Mo-Kα radiation (λ = 0.710 73 Å), graphite monochromator, ω scans, and of these 4836 had $|F_o| > 4\sigma(|F_o|)$ and were considered to be observed. The structure was solved using the heavy-atom method and the non-hydrogen atoms were refined anisotropically (SHELXTL[13]) by full-matrix least squares based on F^2 using absorption-corrected data to give R_1 = 0.068 and wR_2 = 0.149 for the observed data and 638 parameters. Crystal data for **7**. $C_{36}H_{33}N_5O_4P_2Pt{\cdot}CH_2Cl_2$, M = 941.6, yellow prisms, crystal dimensions 0.33 × 0.18 × 0.15 mm, monoclinic, space group $P2_1/n$, a = 13.303(2), b = 22.726(3), c = 13.575(2) Å, β = 104.59(2)°, U = 3971.7(7) Å^3, Z = 4, D_c = 1.575 g cm^{-3}, μ(Mo-Kα) = 3.79 mm^{-1}, $F(000)$ = 1864. 5036 Independent data ($2\theta \leqslant 45°$) were collected as for complex **5** and of these 4121 had $|F_o| > 4\sigma(|F_o|)$ and were considered to be observed. The structure was solved as for complex **5**, with the anisotropic refinement (SHELXTL[13]) of the non-hydrogen atoms based on F using absorption-corrected data to give R = 0.045 and R' = 0.048 for the observed data and 483 parameters. Complete atomic coordinates, thermal parameters and bond lengths and angles have been deposited at the Cambridge Crystallographic Data Centre. See Instructions for Authors, *J. Chem. Soc., Dalton Trans.*, 1996, Issue 1.

bonding motif between the orotate and the diaminopyridine is the non-equivalence of the N–H · · · O hydrogen-bond distances, with that involving the amino group associated with 2 + 2 dimer formation being significantly shorter [2.88(1), *cf.* 3.04(1) Å; N–H · · · N 3.02(1) Å]. This asymmetry is the more surprising since the carbonyl involved in the stronger hydrogen bond is also involved in a second hydrogen-bonding interaction to form the 2 + 2 adduct [N · · · O 3.02(1) Å]. Another feature of the triply hydrogen-bonded motif is a non-coplanarity of the pyrimidine and diaminopyridine rings. There is a fold angle of 27° about an axis coincident to the N · · · N · · · N direction within the diaminopyridine. Further oligomerisation of the 2 + 2 adduct is prevented by the presence of the platinum diphosphine moiety which acts as a blocking group. Such intermediate molecular-weight aggregates are of potential in the development of nanometer-scale structures.[7,14] There is however, in the solid state, a secondary intercomplex C–H · · · O interaction between an *m*-phenylene C–H hydrogen atom and the non-co-ordinated carboxylate oxygen (C · · · O 3.22, H · · · O 2.47 Å, C–H · · · O 135°).

The orotate complexes described in this communication demonstrate the bifunctionality of the orotate ligand, which enables it to form a supramolecular building block for the molecular recognition of organic molecules having complementary hydrogen-bonding groups.

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