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FULL PAPER

Synthesis, spectroscopy, and theoretical studies of platinum(II) phosphate complexes †

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Received 17th December 2001, Accepted 22nd February 2002
First published as an Advance Article on the web 9th April 2002

A method for the synthesis of $[Pt(dpp)_2(en)]$ (dpp = diphenyl phosphato, en = ethane-1,2-diamine) is reported, and the resulting complex characterised spectroscopically. The synthesis involves displacement of chloride ligands using silver(I), and requires non-aqueous media. Density functional studies suggest typical square-planar coordination geometry, with rather weak Pt–O bonds and very strong N–H ··· O hydrogen bonds. Comparison with model complexes suggests that phosphates are weaker ligands to platinum(II) than nitrates, and are therefore likely to be highly reactive.

Introduction

Since the serendipitous discovery[1] of the biological activity of cisplatin (*cis*-$[PtCl_2(NH_3)_2]$, **1**) (see Fig. 1), platinum-containing

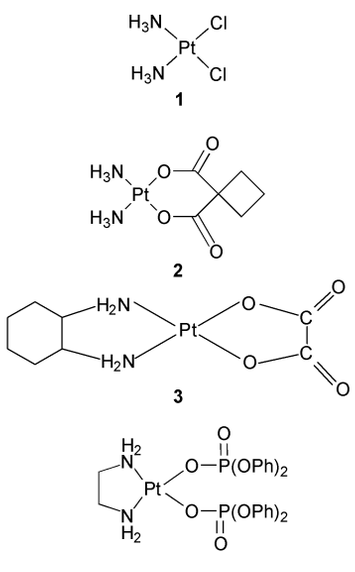

Fig. 1 Molecular structures of cisplatin **1**, carboplatin **2**, oxaliplatin **3** and $[Pt(dpp)_2(en)]$, **4**.

anti-tumour drugs have become the focus of intense chemical, biological, and medicinal research.[2] The "platinums" are one of the two most widely used anti-tumour drugs classes in the world, with proven effectiveness in treating testicular and ovarian cancers as well as activity against several other forms.[2] The accepted mechanism of cisplatin activity involves initial aquation in intra-cellular fluid to give the highly reactive *cis*-$[PtCl(NH_3)_2(OH_2)]^+$ species,[3] followed by binding to nucleophilic sites on DNA, particularly the N7 site of guanine.[4] Cisplatin has several properties that make it less than ideal as a therapeutic agent. It has a limited spectrum of activity against different types of cancer, it can be subject to inherent or acquired resistance to treatment, and is also highly toxic.[2]

Many analogous Pt^{II} complexes have been synthesized and tested as potential drugs, including many direct analogues of the general form *cis*-$[PtX_2A_2]$[5] and more recently Pt^{IV} compounds.[6,7] Many of these adhere to the structure–activity rules devised by Cleare and Hoeschele,[8] which stipulate neutral complexes containing *cis*-leaving groups and inert N–H bearing nitrogen donors. Despite concerted efforts to find improved drugs, only carboplatin (**2**) has found widespread use as an alternative.[9] Other drugs containing oxygen ligands as leaving groups include oxaliplatin (**3**), which is licensed across Europe, and nedaplatin, licensed in Japan.[10] Both show promise in treating cancers not amenable to cisplatin therapy, but are yet to find worldwide approval. There is therefore great interest in developing new compounds that might show different characteristics to known compounds.

Although phosphates are ubiquitous in the human body, and are an integral part of DNA, there has been little interest in investigating platinum phosphato complexes for anti-tumour activity. Bose and colleagues[11] have investigated the kinetics of formation of phosphonato- and phosphato-platinum(II) complexes using ^{31}P NMR. Appleton and co-workers[12] have also investigated a variety of platinum phosphato complexes. In these studies, the platinum complexes had the ability to either chelate or form dimeric species with the phosphato ligands, the formation of the complexes being highly dependent on pH. Kozelka and Barre[13] have studied the binding of nuclear bases to platinum(II) through both N and P=O groups using ^{31}P NMR, reporting that phosphate groups do indeed show some affinity for Pt^{II}. In order to minimise the possibility of oligomeric binding we have chosen to use phosphato diester ligands, and embarked on synthetic and theoretical studies of platinum(II) phosphato complexes, to investigate their chemical, spectroscopic, structural, and electronic properties. In this study, we report the results of such investigations on $[Pt(dpp)_2(en)]$, where dpp = diphenyl phosphato and en = ethane-1,2-diamine, along with theoretical studies of several

† Electronic supplementary information (ESI) available: B3LYP optimised Cartesian coordinates of $[Pt(dmp)_2(en)]$. See http://www.rsc.org/suppdata/dt/b1/b111460n/

 DOI: 10.1039/b111460n

analogous compounds. Of particular interest here is the strength of the Pt–O bond in phosphato complexes, which is implicated in the rate of *in vivo* aquation and hence is related to biological activity. We envisage that "hard" phosphate ligands such as dpp might interact relatively weakly with the softer Pt^{II} centre, resulting in faster aquation and possibly greater activity (and toxicity).

Experimental

Synthesis of $[Pt(dpp)_2(en)]$ (**4**) is in part based on the method described by Kemmitt *et al.*[14] for the synthesis of platinum(II) phosphonato and arsonato complexes. $[PtCl_2(en)]$ (0.21 g, 0.64 mmol) was suspended in 10 mL of DMF. Diphenyl phosphate (0.32 g, 1.28 mmol) and silver(I) oxide (0.18 g, 0.78 mmol) were added to this suspension, the reaction being protected from light and stirred at room temperature overnight. The black colour imparted from the silver(I) oxide was replaced by the pale yellow silver(I) chloride. The suspension was passed through Celite, affording a pale yellow, clear filtrate. The solvent was removed under reduced pressure and the resulting oily solid, now containing some black material, was once again dissolved in the minimum volume of DMF and filtered. Dichloromethane was introduced to the pale yellow filtrate and the solution was placed in a freezer at −18 °C overnight. Over this time a white, crystalline solid precipitated. This solid was collected at the pump, washed with dichloromethane and air-dried. Yield of $[Pt(dpp)_2(en)]$ 0.32 g, 0.425 mmol, 66%, IR/cm^{-1} ν(NH) 3265m, ν(CH) 3058m, ν(PO) 1200s, δ(NH) 1592m, ν(Pt–O) 532m.[15] Microanalysis: Calculated for $[Pt(dpp)_2(en)]$ C 41.44%, H 3.76%, N 3.72%. Found C 41.45%, H 3.57%, N 3.85%.

Diffuse reflectance infrared Fourier transform spectra (DRIFTS) of $[Pt(dpp)_2(en)]$ were obtained on a Bio-Rad FTS-7 spectrophotometer over the range 400–4000 cm^{-1} using a KBr background and matrix. A Bio-Rad FTS-40 spectrophotometer was used over the range 200–400 cm^{-1} with polyethylene as the background and matrix. ^1H NMR spectroscopy was carried out using a Bruker AC 200 MHz spectrometer. ^{31}P, ^{13}C, and ^1H (where necessary) were carried out on a Bruker AMX 400 MHz spectrometer. Solvents used were of at least 99.6% purity and were available commercially.

All theoretical calculations were carried out using Gaussian 98[16] running on a Compaq XP1000 workstation. Initial HF/LANL2DZ[17] optimisations were performed assuming no symmetry: harmonic frequency calculations at this level confirmed each species as a true minimum, and gave estimates of the vibrational contributions to binding energies. Subsequent B3LYP[18] optimisations employed the Stuttgart–Dresden[19] basis set and effective core potential on platinum, with the all-electron 6-31+G* basis[20] on all other atoms. In the cases of $[PtCl_2(en)]$, [Pt(ox)(en)], $[Pt(OH)_2(en)]$ and $[Pt(en)(OH_2)_2]^{2+}$, initial optimisations converged to C_2 symmetry — this was enforced during subsequent optimisations. Atomic partial charges were calculated using the natural bonding orbital (NBO) scheme,[21] which has been widely used in the study of transition metal complexes.[22]

For two compounds with published X-ray crystallographic structures, namely $[PtCl_2(en)]$[23] and [Pt(ox)(en)],[24] the above method resulted in Pt–N bond lengths that were on average 0.07 Å too long, Pt–O lengths 0.02 Å too short, and Pt–Cl lengths 0.01 Å too long. Similar overestimations of Pt–N bond lengths have been reported in a recent study of cisplatin,[25] such that this appears to be a systematic effect in DFT calculations. Comparison of the properties of the free ligands supports the use of dimethyl phosphate (dmp) as a model for diphenyl phosphate: charges on O and P (not shown) differ by less than 5%, or around 0.05 electrons, while the geometry about P is almost identical.

Results and discussion

a) Synthesis

Silver salts such as silver nitrate and silver sulfate have been extensively used for the conversion of platinum(II)-halo complexes into the complex of choice, *via* the highly reactive diaquaplatinum(II) complex which is formed. Initial attempts to prepare $[Pt(dpp)_2(en)]$ (**4**) in water using this method were unsuccessful. $[Pt(OH)(en)(OH_2)]^+$ was introduced to a solution of diphenyl phosphate (dppH) in water at a pH of 1 and stirred at room temperature overnight, after which time no reaction had occurred. While it was not expected that the high acidity would prevent ligation of the diphenyl phosphato ligand to platinum, the sodium salt of diphenyl phosphate was nevertheless prepared and the procedure was repeated. Once again, this was unsuccessful, the diaquaplatinum(II) salt being formed. A further attempt using triethylamine to increase the pH to 7 also failed to yield the desired phosphato complex.

It was expected that this method would be successful in preparing $[Pt(dpp)_2(en)]$ as it is successful in preparing other platinum(II) complexes containing oxygen donors such as carboxylato ligands.[26] For example, oxalato-platinum(II) species can be prepared successfully by this method. However, despite several attempts using different reaction conditions and pH values the conversion of $[PtCl_2(en)]$ to $[Pt(dpp)_2(en)]$ was not successful. The starting complex, $[PtCl_2(en)]$ is insoluble in most organic solvents, and only slightly soluble in water. However, due to the high solubility of diphenyl phosphate and moderate solubility of $[PtCl_2(en)]$ in DMF, the reaction was carried out in this solvent. Silver nitrate effectively removes halo ligands from platinum complexes in DMF,[27] but silver(I) oxide was chosen as the agent to remove the halo ligands from the platinum(II) complexes as (1) it is a moderate base and hence will deprotonate dppH, which can then bind to the platinum, and (2) there is no counter ion to act as a potential competing ligand, as is the case with nitrate. Using these conditions, the complex $[Pt(dpp)_2(en)]$ could be synthesised in moderate yield. This represents the first successful preparation of a platinum(II) bisphosphato-diester complex, with no evidence for dimeric or oligomeric binding.

b) Characterization

As solvent peaks from DMF occur at 8.01 (broad), 2.91 and 2.74 ppm in the ^1H NMR spectrum, d_6-DMSO was chosen as the NMR solvent, showing a solvent peak at 2.49 ppm only. Due to the strongly coordinating nature of DMSO, the spectrum was acquired within 30 minutes of dissolution of the compound. The region of the proton NMR spectrum between 6.2 and 7.6 ppm is shown in Fig. 2. The signal due to the phenyl protons occurs as expected in the region 7.3 to 6.9 ppm. The peak at 6.93 ppm corresponds to the *para* proton on the phenyl carbon and is half the intensity of the peaks at 7.23 and 7.11

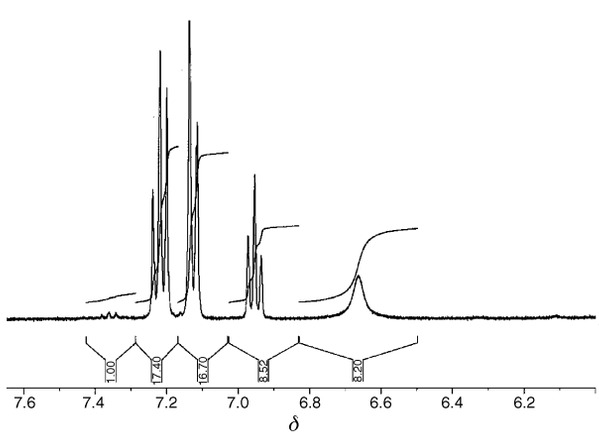

Fig. 2 ^1H NMR spectrum of **4** in the region 6.2–7.6 ppm.

Table 1 Selected geometrical parameters of [Pt(dmp)$_2$(en)]

Bond lengths/Å		Bond angles/°		Torsion angles/°	
Pt–N	2.062	N–Pt–N	83.7	Pt–N–C–C	38.8
Pt–O	2.064	O–Pt–O	88.5	N–C–C–N	−50.9
N–C	1.490	N–Pt–O	93.9	N–Pt–O–P	−45.5
C–C	1.530	Pt–N–C	109.2		
O–P	1.554	N–C–C	108.4		
O=P	1.510	Pt–O–P	119.8		
O ··· H	1.796	N–H ··· O	148.4		
O ··· N	2.747	P=O ··· H	110.8		

ppm corresponding to the equivalent protons on the two *ortho* and *meta* positions respectively. The amine protons are present as a broad peak at 6.63 ppm; the broadness of this peak in a non-exchanging solvent such as DMSO appears to support our theoretical assignment of strong N–H ··· O=P intramolecular hydrogen bonding (see below). Outside the range of Fig. 2, the methylene protons are present at 2.51 ppm, while peaks at 2.01, 2.91 and 3.28 ppm are due to trace acetone, DMF and water respectively. Due to the C_2 axis in the complex, the ^{13}C spectrum shows only five peaks corresponding to the carbon atoms. The peak at 153 ppm is the carbon directly attached to the oxygen, while peaks at 119, 129 and 122 ppm are the carbons *ortho* and *meta* and *para* to the phosphate group, respectively. The aliphatic carbon atoms are present at 48 ppm, along with solvent at 40 ppm.

To further characterise the complex, the ^{31}P NMR spectrum was measured. The compound was initially dissolved in DMSO and was allowed to stand before a NMR spectrum was obtained. The spectrum showed two peaks, due to partial ligand exchange of the phosphate with DMSO, hence a saturated solution of the compound was prepared in CD_2Cl_2 and showed a singlet at −2.54 ppm, indicating phosphate binding to the platinum (diphenyl phosphate in CD_2Cl_2 shows a singlet at −8.64 ppm). Despite several attempts using different solvents and methods, crystals suitable for X-ray diffraction were not forthcoming, the complex persistently forming feathers.

c) Theoretical studies

B3LYP optimisation of *cis*-[Pt(dmp)$_2$(en)] resulted in the expected square-planar geometry about Pt, with Pt–N bond lengths of 2.062 Å and Pt–O lengths of 2.064 Å. Comparison with X-ray coordinates above suggest these lengths might be overestimated by around 0.03 Å. However, there is no doubt that Pt^{II} forms stable complexes with η^1-phosphato ligands, and hence the postulated molecular structure of **4** is a reasonable one. The optimised structure of [Pt(dmp)$_2$(en)] is shown in Fig. 3, with selected geometrical parameters in Table 1.

There are several features of this structure worthy of note: firstly, two intramolecular hydrogen bonds are evident between the N–H of the en ligand and the (formally sp^2 hybridised) phosphate oxygen. This contact is very short (O ··· H = 1.796 Å, O ··· N = 2.747 Å) and is also relatively linear, as measured by the O ··· H–N angle of 148.4°. The 'angle of attack' of H-bonding to the O=P bond is similar to a value of 131.5° found recently for a complex of trimethyl phosphate with H–F.[28] We surmise that the hydrogen bonds in this structure are rather strong, and must contribute substantially to the binding of the phosphate ligands to the Pt(en) fragment — we will return to this point below. Evidence for these intramolecular hydrogen bonds is also seen in the IR spectrum of the complex. The ν(N–H) stretch at 3265 cm^{-1} is broader and less intense than that seen for [PtCl$_2$(en)], and is most likely a consequence of these hydrogen bonds. Also, the crystal structure of [Pt(5′-CMP)(en)]$_2$, where CMP = 5′-cytidine monophosphate), determined by Louie and Bau[29] shows a strong hydrogen bond between a phosphato oxygen and the ethane-1,2-diamine nitrogen, the O–N distance being 2.75 Å which is in good agreement with the analogous distance seen in our calculated structure. Further evidence for strong P=O ··· H–N hydrogen bonding comes from Appleton *et al.*,[12b] who inferred their presence from broad peaks in the ^{31}P NMR spectra of *cis*-[Pt(NH$_3$)$_2$(PO$_4$H$_2$)(H$_2$O)]$^+$.

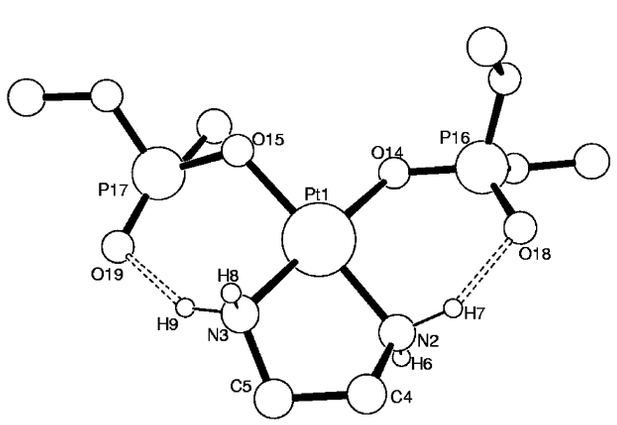

Fig. 3 B3LYP optimised geometry of [Pt(dmp)$_2$(en)] (all H's except NH removed for clarity).

The optimum conformation found contains hydrogen bonds on either side of the coordination plane in a '*trans*' arrangement. A second conformation was identified at the Hartree–Fock level, in which the phosphates form hydrogen bonds on the same side of the coordination plane. However, this was 6.2 kJ mol^{-1} less stable than that shown for the *trans* form, and was not pursued further. The energy difference between these forms, and the likely barrier to interconversion, is so small that at room temperature all four hydrogens would appear equivalent.

Another feature of note is that the phosphate ligand shows some evidence of localisation. The shortest P–O bond is that involved in H-bonding, while the O coordinated to Pt has a longer bond to P, and bonds to OMe groups are longer still. Thus, it seems that the presence of Pt^{II} effectively localises the negative charge on the anion on to a single oxygen. The optimised structure also shows substantial deviation from square planarity, with N–Pt–N = 83.7° and O–Pt–O somewhat larger at 88.5°. The ethane-1,2-diamine fragment lies out of the coordination plane, such that the Pt–N–C–C torsion angle is 38.8°, similar to previously published values[23,24] of 37.1 and 32.2°.

Finally, the conformations adopted by the phosphato ligands appear to be driven by attempts to minimise steric repulsions whilst maintaining the stabilising N–H ··· O H-bonds. Each phosphate ligand has one methoxy group approximately 'equatorial' (*i.e.* roughly in the coordination place) and one 'axial'. These axial methoxy groups are sited roughly above and below the Pt, *i.e.* the positions one would expect axial ligands to be placed in the analogous Pt^{IV} complex. The small size of the methoxy groups used in this model compound mean the axial sites are not particularly crowded, but this crowding would certainly be exacerbated with the larger phenyl groups used in **4**. This may have implications for the reactivity and redox chemistry of such complexes — this will be investigated in subsequent studies.

The difficulties encountered in attempts to synthesise **4** in aqueous media suggests that the Pt–O bond to phosphate is relatively weak, such that the ligand is rather labile and easily displaced by nucleophiles. We have explored the strength of Pt–ligand bonds by considering the simple dissociation process [PtL$_2$(en)] ⟶ Pt(en)$^{2+}$ + 2L$^-$ for a total of seven complexes. The resulting estimates of Pt–ligand bond energies are reported in Table 2, and appear to support the hypothesis that phosphates make rather weak ligands. Our model ligand dmp yields the second lowest bond energies of all the anionic ligands considered with a Pt–O bond energy of 838.8 kJ mol^{-1}. Only neutral H$_2$O and nitrate are weaker ligands — several studies have

Table 2 DFT calculated properties of [Pt(dmp)$_2$(en)] and some analogues

	Total energy/au	Pt–O energy[a]/kJ mol^{-1}	Pt–O length/Å	μ/D	q_{NBO} Pt	q_{NBO} en	q_{NBO} ligand
[Pt(dmp)$_2$(en)]	−1754.33724	838.8	2.064	6.0	0.786	0.563	−0.675
[Pt(OH)$_2$(en)]	−461.59821	1018.8	2.001	9.2	0.720	0.426	−0.573
[Pt(ac)$_2$(en)]	−766.98733	894.0	2.047	6.8	0.757	0.509	−0.633
[PtCl$_2$(en)]	−1230.42481	853.3	2.331	13.0	0.533	0.489	−0.511
[Pt(ox)(en)]	−687.10913	1013.5[b]	2.005	18.2	0.724	0.480	−1.205
[Pt(NO$_3$)$_2$(en)]	−870.59894	800.5	2.050	13.6	0.765	0.554	−0.659
[Pt(OH$_2$)$_2$(en)]	−462.23181	207.1	2.132	0.3	0.815	0.823	0.181

[a] Including a scaled (0.89) vibrational energy correction from HF/LANL2DZ harmonic frequency calculation. [b] Calculated as half the Pt(en)oxalate $\longrightarrow$ Pt(en)$^{2+}$ + oxalate^{2-} energy.

shown that nitrates form very reactive/toxic complexes and are easily displaced by many reagents.[8] Carboxylate groups (acetato and oxalato) form much stronger complexes, while chlorides are intermediate between these extremes. It should be noted that these values take no account of desolvation or entropic effects, such that their absolute values are unlikely to be accurate. However, it is a reasonable assumption that these effects are approximately constant across the range of complexes considered and hence that trends can be drawn from these data. The main apparent trend in Table 2 is that phosphates form rather weak bonds to Pt^{II}. There also appears to be a rough inverse correlation (R^2 = 0.91) between Pt–O bond energy and bond length, such that the strongest bound complexes, *i.e.* the hydroxo and oxalato complexes, have the shortest bonds.

This conclusion appears to be in accordance with various experimental observations. Appleton and co-workers[12b] have examined the reactions between *cis*-[Pt(NH$_3$)$_2$(OH$_2$)$_2$]$^{2+}$ and a variety of O-donor ligands, including nitrato, carboxylato and phosphato. Acetate was found to react more rapidly than phosphate (under nitrogen) with the diaqua species, however in the presence of oxygen addition of the phosphate to the diaqua species resulted in the rapid formation of blue solutions, attributed to be oligomers of platinum(III). A further study[12a] compared the reaction between amp, (amp = (aminomethyl-)phosphonic acid) and the above platinum complex, as well as *cis*-[Pt(OH)$_2$(NH$_3$)$_2$]. The ligand was found to react much more readily with the aqua species than the hydroxo species, which may indicate that the hydroxo species is more resistant to attack from the ligand. In a recent publication, Davies *et al.*[30] showed that phosphate buffer at a concentration of 9 mM did not interfere with the rate of aquation of cisplatin, further indicating the weak donor ability of phosphate to platinum(II).

The estimate of Pt–O bond energy in Table 2 inevitably contains a contribution from the strong N–H ⋯ O hydrogen bonds noted above, since separating the ligand from the Pt(en) fragment breaks both interactions. It is not a simple matter to decompose the overall figure of 838.8 kJ mol^{-1} into values for Pt–O and N–H ⋯ O interactions. However, we can obtain an estimate of the strength of such hydrogen bonds from consideration of model systems. The simple model system of cisplatin (*cis*-[PtCl$_2$(NH$_3$)$_2$]) complexed with the phosphate anion $H_2PO_4^-$ gives a hydrogen bond energy of 123.7 kJ mol^{-1} with the same functional and basis set as used above. This is reduced to 119.3 kJ mol^{-1} when corrected for basis set superposition error (BSSE) and changes in zero point energy (ZPE). This complex could equally be described as a hydrogen bond or an ion–molecule complex, but the conformation found here is very similar to that described above, with H ⋯ O = 1.765 Å and N–H ⋯ O = 158.8°. The value of 119 kJ mol^{-1} is probably an overestimate of the value in [Pt(dmp)$_2$(en)], since our intermolecular model system can fully relax without the constraints imposed by coordination to Pt. Despite this, it seems certain that the hydrogen bonds in [Pt(dmp)$_2$(en)] contribute at least 100 kJ mol^{-1} to the stabilisation of the complex, and thus that the 'true' Pt–O bond energy is very low indeed, in the region of 720–750 kJ mol^{-1}. This estimate is further supported by calculation of the tetramethylethane-1,2-diamine (tmeda) analogue [Pt(dmp)$_2$(tmeda)] Pt–O bond energy, which is found to be 737 kJ mol^{-1} using the same methods. Although these weak Pt–O bonds suggest high activity, the diphenyl phosphato complex is not stable with respect to aquation and in biological media will yield the diaqua complex. This complex is known to be highly anticancer active but is too toxic for systemic administration.[31] However, lipophilic complexes such as **4** may have application in local delivery: subsequent studies will attempt to address this possibility.

Insight into these weak Pt–phosphate bonds is gained from the NBO charge information also reported in Table 2. For clarity, these charges have been summed into values for metal, ethane-1,2-diamine, and ligand fragments. It is apparent that the phosphato complex has larger charges (in absolute terms) than all other neutral complexes — the Pt(en) fragment here carries a charge of +1.37, compared with just +1.02 in [PtCl$_2$(en)], +1.15 in [Pt(OH)$_2$(en)], +1.27 in [Pt(ac)$_2$(en)], and +1.32 in [Pt(NO$_3$)$_2$(en)]. We interpret this charge separation as evidence of the 'hardness' of the phosphato ligand — unlike carboxylate or hydroxyl groups, phosphate does not share electron density with metals, but instead simply has electrostatic attraction for the positive metal centre. Nitrate is almost as hard as phosphate by this measure, which accords with its known reactivity and low calculated bond strength.

Conclusions

We have shown that *cis*-[Pt(dpp)$_2$(en)] can be synthesised from [PtCl$_2$(en)] by using a combination of diphenyl phosphato and silver(I) oxide in non-aqueous solvents. It has also been established that the "standard" method of preparation, involving direct replacement of aqua ligands by phosphate fails in this case. The complex has been characterised through infrared and ^{1}H, ^{13}C, and ^{31}P NMR spectroscopy, which reveals that the molecule has C_2 symmetry. Analysis of the model complex *cis*-[Pt(dmp)$_2$(en)] using density functional methods indicates a typical square-planar arrangement, with pronounced hydrogen bonding between N–H of the en ligand and O=P of the phosphate. Comparison with several model complexes indicates that the Pt–O bonds in this complex are very weak, less stable even than those formed in Pt-nitrato complexes. Population analysis suggests that this is due to the hardness of the phosphato ligand, which prevents any significant sharing of electron density.

Acknowledgements

A. R. B. would like to thank the Australian Research Council for a studentship. J. A. P. thanks the Royal Society for a travel grant.

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