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Synthesis and coordination chemistry of aminophosphine derivatives of adenine †

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Received 3rd April 2003, Accepted 19th June 2003
First published as an Advance Article on the web 7th July 2003

Two aminophosphine derivatives of adenine N^9-($N^{2'}$-diphenylphosphinoaminoethyl)adenine **L1** and N^9-($N^{2'}$-diphenylphosphino-$N^{2'}$-*n*-propylaminoethyl)adenine **L2** were synthesized. Oxidation of **L1** and **L2** with H_2O_2, elemental sulfur or elemental selenium led to the corresponding oxidized products **5**–**10**. Both **L1** and **L2** behave as monodentate ligands towards late transition metals. Reaction of compound **L1** or **L2** with [AuCl(tht)], [{RhCl(μ-Cl)(η^5-C_5Me_5)}$_2$], [{IrCl(μ-Cl)(η^5-C_5Me_5)}$_2$], [{Rh(μ-Cl)(cod)}$_2$], [{RuCl(μ-Cl)(η^3:η^3-$C_{10}H_{16}$)}$_2$] and [{RuCl(μ-Cl)(*p*-$MeC_6H_4{}^iPr$)}$_2$] gave the corresponding "dangling" monodentate complexes **11**–**20**, leaving the adenine ring free for complementary hydrogen bonding. Interaction of **L1** and **L2** with [MX_2(cod)] (M = Pt; X = Cl, Me) in 2 : 1 molar ratio also gave monodentate complexes **21** and **22**. All compounds have been fully characterized by microanalysis, IR, ^{31}P-{^{1}H} NMR, ^{1}H NMR and EI/CI/FAB MS spectroscopies. ^{1}H-{^{31}P} NMR, ^{1}H–^{1}H-COSY or ^{1}H–^{13}C correlation experiments were used to confirm the spectral assignments. Four compounds were structurally characterized by crystallographic X-ray analysis.

Introduction

Owing to their resemblance to the structure of adenosine and their broad-spectrum of antiviral or anticancer activity, adenine derivatives substituted at the N^9-position constitute an important class of pharmacologically active compounds.[1] Among them (N^9-[2-(phosphonomethoxy)ethyl]adenine and its analogues have been extensively studied.[2,3] In bioinorganic chemistry, metal complexes capable of forming complementary hydrogen bonds occupy an ever-increasing important position in the development of biochemically active molecules. Houlton *et al.*[4] have prepared some interesting bifunctional complexes which combine the covalent bond-forming capabilities of the metal ion and a ligand surface capable of recognizing nucleotide bases by means of hydrogen bonding. The same group developed the concept of *directed metalation* and reported a series of nucleoside analogues in which the ribose group is replaced by a dimethylene/trimethylene tethered ethylenediamine [5–8] or 1,2-dithioethane.[9] Interaction of such chelate-tethered nucleoside analogues with metal ions gave interesting A-N^3-bound or A-C^8-bound mono- or poly-nuclear complexes. In an approach which combines the antitumour activities of diphosphines and their gold(I) complexes [10,11] and our experience in the synthesis and coordination chemistry of P–N compounds [12–15] we have incorporated the aminophosphine unit into adenine through an aminodimethylene linkage at N^9-position. The adenine analogues prepared in this way possess two functions: excellent coordination tendency towards transition metals and the capacity for base-pair or complementary hydrogen bonding interactions. The new combination of the bioactive adenine and aminophosphine as well as the corresponding complexes may lead to some enhanced biological activities.

Experimental

All solvents and reagents were purchased from Aldrich and Lancaster. Dichloromethane was heated to reflux over powdered calcium hydride and distilled under nitrogen. Diethyl ether and tetrahydrofuran were purified by reflux over sodium/benzophenone and distillation under dinitrogen. Ligand preparations were performed under an oxygen-free nitrogen atmosphere using standard Schlenk techniques. Coordination reactions and work-up were performed in dry solvents. [MX_2(cod)] (M = Pd, Pt; X = Cl; cod = cycloocta-1,5-diene) [16] and [{RuCl(μ-Cl)(η^3:η^3-$C_{10}H_{16}$)}$_2$] [17] were prepared using literature procedures. Preparation of all the compounds apart from the representative **L1** and **11** are available as electronic supplementary information (ESI †).

Infrared spectra were recorded (KBr discs) on a Perkin-Elmer system 2000 spectrometer, ^{1}H NMR spectra (300 MHz) on a Varian Gemini 2000 spectrometer, ^{31}P-{^{1}H} NMR spectra at 121.4 MHz with δ referenced to external 85% H_3PO_4, ^{13}C-{^{1}H} NMR spectra at 67.9 MHz on a JEOL GSX 270 spectrometer, 2D-NMR (COSY, and ^{1}H–^{13}C or ^{1}H–^{13}P heteronuclear correlation) on a Bruker Advance 300. Microanalyses were performed by the University Service within this Department and fast atom bombardment (FAB) or chemical ionization (CI) mass spectra by the EPSRC Mass Spectrometer Service (Swansea, UK). Precious metal salts were provided on loan by Johnson Matthey PLC.

N^9-($N^{2'}$-Diphenylphosphinoaminoethyl)adenine (L1)

N^9-(2′-Aminoethyl)adenine (2.48 g, 13.91 mmol) was dissolved in hot CH_3CN. To this solution was added Et_3N (2.20 cm^3, 14.38 mmol) and Ph_2PCl (2.52 cm^3, 14.04 mmol) in CH_3CN (20 cm^3). The reaction mixture was refluxed for 1 h and cooled to room temperature. The solvent was removed *in vacuo* and H_2O (40 cm^3) was added to remove the salt. The mixture was filtered washing with H_2O (2 × 20 cm^3) and EtOH (2 × 20 cm^3) and Et_2O (2 × 20 cm^3) successively to give 3.40 g of crude product. Recrystallization from CH_3CN gave the pure product as a white solid. Yield: 2.254, 40%. Microanalysis (%): Found (calc.) for $C_{19}H_{19}N_6P$: C, 62.23 (62.98); H, 5.02 (5.28); N, 23.49 (23.19). IR (KBr disc, cm^{-1}): 3384m, 3328m, 3293m, 3142m, 3098w, 3066w, 2934w, 2891w, 2847w, 1655vs, 1598vs, 1575s, 1488m, 1432m, 1416s, 1390w, 1375w, 1359m, 1325m, 1307s, 1238s, 1205w, 1165m, 1125s, 1094m, 1082w, 1057m, 1025w, 1010w, 958w, 941w, 911s, 854w, 797s, 753s, 739s, 695vs, 644m, 588m, 556m, 519s, 482m. CIMS (*m*/*z*): 363 [M + H]$^+$. EIMS (*m*/*z*): 362 [M]$^+$.

† Electronic supplementary information (ESI) available: Preparation of all compounds apart from **L1** and complex **11**; Tables S1–S8: NMR spectral data of all the compounds. See http://www.rsc.org/suppdata/dt/b3/b303715k

DOI: 10.1039/b303715k

Table 1 Details of the X-ray data collections and refinements for compounds **5**, **11**, **15** and **17**

Compound	**5**·1.125$CHCl_3$	**11**·1/2H_2O	**15**·1/4C_4H_4O	**17**·1/2$CHCl_3$
Empirical formula	$C_{20.125}H_{20.125}Cl_{3.375}N_6OP$	$C_{19}H_{20}AuClN_6O_{0.50}P$	$C_{30}H_{35}Cl_2N_6O_{0.25}PRh$	$C_{29.50}H_{34.50}Cl_{3.50}IrN_6P$
M	512.7	603.8	688.4	820.4
Crystal colour, habit	Colorless, block	Colorless, block	Deep red, prism	Orange, prism
Crystal dimensions/mm	0.1 × 0.08 × 0.08	0.2 × 0.1 × 0.03	0.18 × 0.1 × 0.06	0.05 × 0.05 × 0.12
Crystal system	Monoclinic	Monoclinic	Monoclinic	Monoclinic
Space group	$P2_1$	$P2/c$	$P2_1/c$	$P2_1/n$
a/Å	15.8751(18)	18.2826(3)	16.3100(2)	14.8735(11)
b/Å	8.4370(10)	11.9140(2)	9.0989(1)	10.7643(8)
c/Å	20.658(2)	12.7693(2)	22.2647(2)	20.7773(15)
β/°	111.474(2)	106.965(1)	96.689(1)	98.120(2)
U/Å^3	2575	2660	3282	3293
Z	4	4	4	4
D_c/g cm^{-3}	1.322	1.508	1.393	1.655
μ/mm^{-1}	0.480	5.706	0.726	4.417
F(000)	1053	1164	1412	1620
Measured reflections	12999	12619	13837	15660
Independent reflections (R_{int})	7069 (0.0840)	3727 (0.0503)	4659 (0.0274)	4575 (0.1231)
Final *R*1, *wR*2 [$I > 2\sigma(I)$]	0.0780, 0.1722	0.0378, 0.0836	0.0369, 0.0995	0.0486, 0.0695

[Au(Cl)(L1)] (11)

To **L1** (57 mg, 157 μmol) in dichloromethane (30 cm^3) was added [AuCl(tht)] (50 mg, 156 μmol). The mixture was stirred at room temperature for 30 min and then vacuumed to *ca.* 0.5 cm^3. Et_2O was added and the solid was filtered off and washed with Et_2O (3 × 3 cm^3). Yield: 90 mg, 97%. Microanalysis (%): Found (calc.) for $C_{19}H_{19}AuClN_6P$: C, 38.71 (38.37); H, 3.02 (3.22); N, 13.80 (14.13). IR (KBr disc, cm^{-1}): 3327m, 3162m, 2916w, 2864w, 1649vs, 1599s, 1575m, 1481m, 1436s, 1416s, 1359w, 1327w, 1308m, 1242m, 1202w, 1164w, 1108s, 1056m, 998w, 922w, 901w, 798m, 746m, 710w, 694s, 649m, 546m, 491m, 449m. FAB$^+$ (*m*/*z*): 595 [M + H]$^+$, 594 [M]$^+$, 559 [M − Cl]$^+$.

X-Ray crystallography

Table 1 lists details of data collections and refinements for **5**, **11**, **15** and **17**. Data were collected at room temperature using Mo-Kα radiation with a SMART system. Intensities were corrected for Lorentz-polarisation and for absorption. The structures were solved by the heavy atom method or by direct methods. The positions of the hydrogen atoms were idealised. Refinements were by full-matrix least squares based on F^2 using SHELXTL.[18] In **5** there is a total of 1.125$CHCl_3$ solvate molecules. The half occupancy molecule is disordered, its carbon atom was refined isotropically and its hydrogen atom was not included in the final refinement. The NH protons in **5** were refined in idealised positions.

CCDC reference numbers 207487–207490.

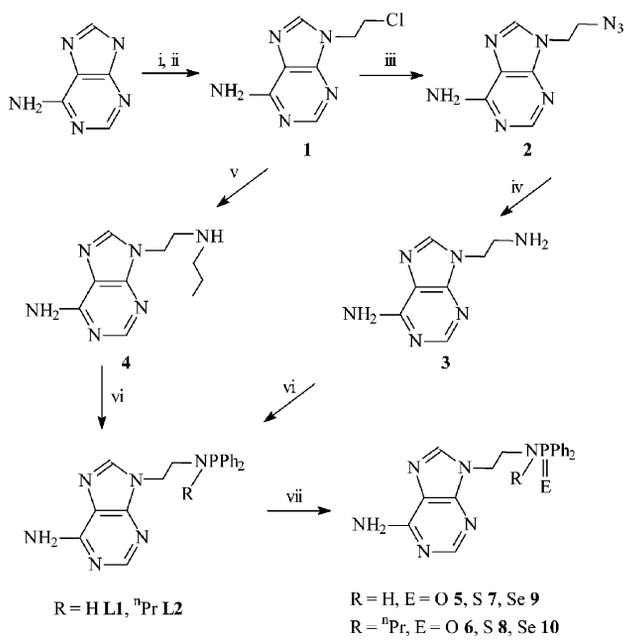
See http://www.rsc.org/suppdata/dt/b3/b303715k/ for crystallographic data in CIF or other electronic format.

Results and discussion

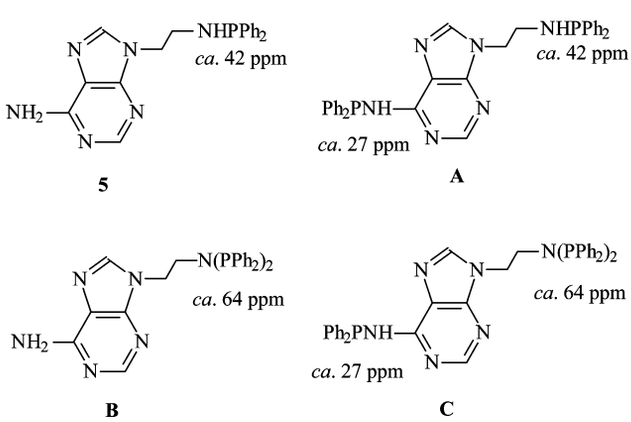
Ligand preparation and oxidation

Scheme 1 shows the synthesis of the ligands **L1** and **L2** and the corresponding oxidised compounds. The precursors **1**[19,20] **2**[21] and **3**[22] were prepared according to literature methods with slight modification. Compound **4** was easily obtained from **1** and much excess neat *n*-propylamine at room temperature in a similar method to the preparation of ethylenediamine-N^9-ethyladenine hydrochloride.[5,7,23] However, according to microanalysis results, we obtained **4** as a free amine rather than a hydrochloride salt.

Due to the low solubility of **3** in common organic solvents at room temperature, its reaction with Ph_2PCl was carried out in CH_3CN at reflux in the presence of Et_3N. Monitoring by ^{31}P-{^1H} NMR indicated that the reaction of **3** and Ph_2PCl in 1 : 1 molar ratio occurred mainly at the dangling alkyl primary amino group to give **L1** though a trace amount of **A** (Scheme 2) was found in the reaction mixture. Work-up by removing the salt from the reaction mixture with water and washing with



Scheme 1 Synthesis of aminophosphine analogues of adenosine. Reagents and conditions: (i) anhydrous DMF, NaH (60% in mineral oil), 2 h; (ii) $ClCH_2CH_2Br$, rt, 36 h; (iii) NaN_3, DMSO, 80 °C, 24 h; (iv) MeOH, H_2, 1 atm, 10% Pd/C; (v) $CH_3CH_2CH_2NH_2$, rt, 4 d: (vi) Ph_2PCl, Et_3N, CH_3CN, reflux, 12 h: (vii) THF, H_2O_2 (30%), 0 °C; or THF, S_8/Se, reflux, 2 h.



Scheme 2 Prdoduct mixture when **3** and Ph_2PCl were reacted in 1 : 2 molar ratio.

EtOH and Et_2O and recrystallization from CH_3CN gave an air- and moisture-stable white solid **L1** in modest yield. The selectivity of P–N bond formation at the dangling amino group rather than the aryl C^6-NH_2 at the purine ring can be attributed to the difference in basicities of the two primary amino groups. The alkyl group at the N^9-dangling chain is more electron-rich than the amino group at the 6-position whose lone pair is highly delocalized in the electron-withdrawing purine ring. Attempts to get N^9-($N^{2'}$,$N^{2'}$-bis(diphenylphosphino)aminoethyladenine **B** proved to be unsuccessful. Reaction of **3** and Ph_2PCl in 1 : 2 molar ratio gave a mixture of compounds shown in Scheme 2 which are difficult to separate. It is obvious that in the secondary substitution, the favorable basicity at the amino nitrogen of dangling chain is compensated by the unfavorable steric effect from the diphenylphosphine group. Therefore no selectivity between the secondary alkyl amino group and the primary aryl amino group at C^6-position was observed in the second substitution.

As a consequence of the *n*-propyl group at the N^9-position, compound **4** is more soluble in organic solvent than **3**. In dichloromethane the reaction of **4** with Ph_2PCl went smoothly at room temperature in the presence of triethylamine to give **L2** in 61% yield. Again the basicities of the secondary alkyl amino group prevailed and the substitution occurred almost exclusively at the "dangling" amino position to give **L2** as an air- and moisture-stable white solid.

Oxidation of **L1** and **L2** with elemental sulfur and selenium proceeded smoothly in THF at reflux within 2 h. However oxidation of these ligands with aqueous H_2O_2 (30%) or H_2O_2–NH_2CONH_2 adduct needs care. The oxidizing agent can only be used stoichiometrically or slight excess, otherwise the oxidation at N^1 position of the purine ring occurs.[24,25] Usually, the urea-hydrogen peroxide adduct is a very convenient reagent for oxidation of P(III).[26] Suspension of the excess H_2O_2–NH_2CONH_2 adduct in the CH_2Cl_2 solution of P(III) compound leads to the stoichiometric conversion of P(III) to P(V), simple work-up with filtration removes most of the excess adduct and the resulting urea. The filtrate can be washed with water to guarantee the absolute removal of the trace urea or adduct and dried over anhydrous magnesium sulfate to give the product. However, in our cases, due to the high polarity of the product and the complementary hydrogen bonding capacity of the adenine moiety, the urea was found to be difficult to remove just by filtration. Washing with water is not efficient, especially with **5** which is more soluble in water than in CH_2Cl_2. The involvement of H_2O (formed or from aqueous H_2O_2 or from washing) and the tendency of hydrogen bonding interactions between H_2O and the adenine moiety make it very hard to get satisfactory microanalysis results with the oxygen oxidized compounds **5** and **6**. Oxidation of **L1** and **L2** by air proved too slow to be useful as a preparative technique. Stirring the solution of **L1** or **L2** in THF in air at room temperature for 4 days only gave *ca.* 30% oxidation of the starting material.

L1, **L2** and compounds **1**–**10** were fully characterized by multiple NMR spectrometry (Tables S1–S3 in ESI †), EI/CI/FAB mass spectrometry, infrared spectroscopy and microanalyses. All the compounds gave reasonable microanalysis results apart from **5** and **6**, which showed slightly lower carbon percentage than the calculated value due to the involvement of H_2O mentioned above. Their mass spectra show the molecular ions and the expected fragmentation pattern with appropriate isotope distributions. The sulfur and selenium species **7**–**10** showed the $[M - S]^+$ and $[M - Se]^+$ fragment ions in their EIMS spectra. The corresponding $[M - O]^+$ were not observed in **5** and **6**, implying that the P=S and P=Se bond are not as stable as the P=O bond. In their IR spectra, all compounds display broad medium intensity ν_{N-H} vibrations, usually two, in some cases several, depending on the different extent of hydrogen bonding and dryness, in the range 3349–3106 cm^{-1}. The N–H bending absorption of NH_2 and NH groups and the stretching absorption of C=N bond of the purine ring were observed at around 1655 and 1598 cm^{-1} as two very strong bands. Compound **3** shows the typical strong $\nu_{N\equiv N}$ band for azide compounds at 2100 cm^{-1}. Compounds **5** and **6** displayed strong $\nu_{P=O}$ at *ca.* 1180 and 1183 cm^{-1}. Since the absorption intensities of $\nu_{P=S}$ and $\nu_{P=Se}$ tend to be medium to weak, it is difficult to assign them unambiguously.

In the ^{31}P-{^1H} NMR spectrum (Table S2 in ESI †), **L1** shows a similar resonance to other aminophosphines derived from equimolar of alkyl primary amines and chlorodiphenylphosphine[27] with δ_P at *ca.* 43.8. **L2** (Table S3 in ESI †) displays a higher frequency phosphorus signal at δ_P 62.8, similar chemical shifts were observed for other aminophosphines[28,29] from secondary alkyl amines and Ph_2PCl. Their oxygen derivatives **5** and **6** show lower frequency shifted signals at δ_P 25.0 and 32.4 compared with the precursors. The chemical shifts of their sulfide compounds **7** and **8** fall in higher frequencies at *ca.* δ_P 60.7 and 70.5. The selenium compounds **9** and **10** also show singlets at higher frequencies than the **L1** and **L2** at δ_P 57.0 and 69.3 with the selenium satellites. The coupling constants $^1J_{PSe}$ = 755 and $^1J_{PSe}$ = 753 Hz are typical for one bond P–Se couplings[30] (Tables S2 and S3 in ESI †).

^1H NMR spectra of **1**,[31] **2**[32] and **3**[33] and the ^{13}C NMR spectrum of **2**[20] have been reported in DMSO or DMSO-d_6–D_2O. To compare the ^1H NMR spectra of the precursors and the aminophosphines **L1** and **L2**, the same solvent should be employed. However catalytic oxidation (with either catalyst or irradiation) of P(III) compounds by DMSO have been reported,[34–36] and we did observe the gradual oxidation of aminophosphine compounds in DMSO-d_6 during spectral acquisition, therefore employing DMSO-d_6 for **L1** and **L2** was precluded. Fortunately, **L1** and **L2** are readily soluble in $CDCl_3$ and CD_2Cl_2.

For comparative purposes, in addition to the spectra in DMSO-d_6, ^1H NMR data of **1**–**4** in $CDCl_3$ containing a few drops of DMSO-d_6 were also collected and are listed (Table S1 in ESI †).. It was found that in the ^1H NMR spectra the chemical shifts of the C^6-NH_2 group and one of the CH groups of the purine ring (C^2 or C^8) varies with solvent ($CDCl_3$, DMSO-d_6 or $CDCl_3$–DMSO-d_6). On the other hand, in the ^{13}C-{^1H} NMR spectra, the resonance frequencies of the carbons on the purine ring of compounds **1**–**4** showed little variation in different solvents, these data are in accord with the ^{13}C-{^1H} NMR spectra of other analogues of adenine.[37] To assign the C^2-H and C^8-H unambiguously, ^1H–^{13}C correlation experiments (^1H–^{13}C HMQC) were performed. It turned out that the C^8-H appeared in lower frequency at around δ_H 7.8 in $CDCl_3$ or $CDCl_3$–DMSO-d_6, while in DMSO-d_6, it appeared close to the C^2-H resonance at around δ_H 8.2. The C^6–NH_2 resonance in $CDCl_3$ or $CDCl_3$–DMSO-d_6 was observed at around δ_H 5.6, in DMSO-d_6 at around δ_H 7.2.

Based on the above observation, we assign the higher frequency singlet at *ca.* δ_H 8.2 to C^2–H and the lower frequency sinlget at *ca.* δ_H 7.8 to C^8 in the ^1H NMR spectra of **L1**, **L2** and **5**–**10** (Tables S2 and S3 in ESI †). The assignments were confirmed by ^1H–^{13}C correlation experiments. In the ^1H NMR spectra, the broad singlet of C^6-NH_2 appeared at around δ_H 6 and can be confirmed by H/D exchange experiment. Again in the ^{13}C-{^1H} NMR spectra, these compounds show closely similar carbon signals of the purine ring (Tables S2 and S3 in ESI †).

Compounds **L1** and **5**, **7** and **9** (Table S2 in ESI †) show a triplet at *ca.* δ_H 4.3 and a multiplet at *ca.* δ_H 3.3. The multiplet was attributed to the multiple spin–spin couplings between CHCH, CHNH and PNCH and thus was assigned to $AdeCH_2CH_2$, the triplets to the $AdeCH_2CH_2$. In addition, the NH resonances of **L1**, **5**, **7** and **9** were observed as slightly broad pseudo-quartet or doublet of triplet due to the multiple coupling $^3J_{CHNH}$ and $^2J_{NHP}$ and were confirmed by H/D exchange experiment. The fact that in the oxidized compounds

the NH signal fell to higher frequency at δ_H 4.4–4.6 than the NH at δ_H 2.2 in the P(III) compound **L1** is in agreement with our former observation.[12]

In the ^{1}H NMR spectra of **L2** and **6**, **8**, **10** (Table S3 in ESI †), the triplet at *ca.* δ_H 4.3 can be easily assigned to AdeCH_2CH$_2$, the sextet at *ca.* δ_H 1.5 to NHCH$_2$CH_2CH$_3$, the triplet at *ca*. δ_H 0.7 to NHCH$_2$CH$_2$CH_3 respectively. However, it is not straight forward to assign the doublets of triplets at *ca.* δ_H 3.3 and the multiplet at *ca.* δ_H 3.0. ^{1}H–^{1}H COSY spectra reveals the relationship of the signals and the doublets of triplets δ_H 3.3 was assigned to AdeCH$_2$CH_2 and the multiplets at *ca.* δ_H 3.0 to NCH_2CH$_2$CH$_3$. It is still not clear why the latter appeared as multiplets rather than doublets of triplets as AdeCH$_2$CH_2. Maybe one of the phenyl rings of the Ph_2P group at the N atom blocks the free rotation of the N–C bond and makes the two protons of the NCH_2CH$_2$CH$_3$ group inequivalent. The ^{1}H-{^{31}P} NMR spectra were collected and the NCH_2CH$_2$CH$_3$ signal was simplified as a pseudo-triplet, however, no more information was obtained.

In the ^{13}C-{^{1}H} NMR spectra of **L1** and **5**, **7** and **9** (Table S2 in ESI †) the signals for the two methylene carbons could not be assigned directly. The ^{1}H–^{13}C correlation experiment reveals that the doublet at higher frequency between δ_C 46.2–43.9 belongs to AdeCH_2CH$_2$, the lower frequency doublet or singlet between δ_C 45.9–40.4 to the AdeCH$_2$CH_2. This is in accord with the proton signals order in the ^{1}H NMR spectra, the AdeCH_2CH$_2$ appearing at higher frequency and AdeCH$_2$-CH_2 at a lower frequency. Interestingly, though in **L1** the two-bond P–C coupling $^2J_{PC}$ = 17 Hz is bigger than the three-bond C–P coupling $^3J_{PC}$ = 6 Hz, no $^2J_{PC}$ coupling was observed in its oxidized compounds **5**, **7** and **9**.

However, in the ^{13}C-{^{1}H} NMR spectra of **L2**, **6**, **8** and **10** (Table S3 in ESI †), as revealed by the ^{1}H-^{13}C correlation experiments, the carbon signals in the alkyl carbon region for AdeCH$_2$CH$_2$NCH$_2$CH$_2$CH$_3$ are not in the same order as that of proton signals. The chemical shifts δ_C appeared as the following order: NCH$_2$CH$_2$CH$_3$ > AdeCH$_2$$CH_2$ > Ade$C$H$_2$CH$_2$. Herein both $^2J_{CP}$ and $^3J_{CP}$ were observed for Ade$C$H$_2$$CH_2$ and NCH$_2$$CH_2CH_3$.

The phenyl protons in the phosphorus species **L1, L2, 5**–**10** appeared as complicated multiplets due to the H–P coupling in the ^{1}H NMR spectra. The phenyl carbons, however, display well-resolved signals in their ^{13}C-{^{1}H} NMR spectra (Tables S2 and S3 in ESI †). In the P(III) compounds **L1** and **L2**, the coupling between the *ipso*-carbon and the phosphorus is unobservable or relatively small, $^1J_{PC}$ = 14 Hz, the coupling between the phosphorus and the *ortho*-carbons or *meso*-carbons is relatively large, $^2J_{PC}$ = 20 Hz, $^3J_{PC}$ = 25 Hz, and the coupling between the *para*-carbon and the phosphorus is not observed. In contrast, the coupling between the *ipso*-carbon and phosphorus in the oxidized P(V) compounds is huge, $^1J_{PC} \approx$ 128, 100 and 90 Hz, respectively, corresponding to O, S, Se oxidized species, the small coupling $^4J_{CP}$ = 3 Hz between the phosphorus and the *para*-carbon is also observed. The P–C^o coupling $^2J_{PC} \approx$ 10 Hz and P–C^m coupling $^3J_{PC} \approx$ 12 Hz were smaller than that in the P(III) compounds.

Comparing the proton signals and carbon signals of the two methylene groups of AdeCH$_2$CH$_2$ moiety between compounds **L1**, **L2** and **5**–**10** (Tables S2 and S3 in ESI †), we found that the proton signal of AdeCH_2CH$_2$ always appeared at higher frequency at around δ_H 4.3 and that of AdeCH$_2$CH_2 always at the lower frequency around δ_H 3.5. However the carbon signals do not necessarily follow this order. This made us reconsider the assignment of proton and carbon resonances of AdeCH$_2$CH$_2$ of **1**, **2** and **3**.[20,31–33] In terms of the general tendency of the **L1**, **L2** and **5**–**10**, we assign the higher frequency proton signal at *ca.* δ_H 4.3 to AdeCH_2CH$_2$, the lower frequency signal at around δ_H 3.5 to AdeCH$_2$CH_2. The carbon resonances were assigned through ^{1}H–^{13}C correlation spectra as listed in Table S4 in ESI. † The assignment of the carbon signals for Ade$C$H$_2$CH$_2$ and AdeCH$_2$$CH_2$ in **2** was found to be contrary to the assignment in the reference.[20]

As for compound **4**, ^{1}H–^{1}H COSY and ^{1}H–^{13}C correlation spectra reveal a similar tendency in chemical shifts to its phosphorus species, with the triplets of protons in the order of AdeCH_2CH$_2$ (δ_H 4.30) > AdeCH$_2$CH_2 (δ_H 3.08) > NCH_2-CH$_2$CH$_3$ (δ_H 2.60), while the carbon singlets in an reversed order of Ade$C$H$_2$CH$_2$ (δ_C 44.35) < AdeCH$_2$$CH_2$ (δ_C 49.04) < NCH$_2$CH$_2$CH$_3$ (δ_C 51.64) (Table S1 in ESI †).

Compound **5** was also characterized by X-ray crystallography (Fig. 1, Table S5 in ESI †). As shown in Fig. 1(b), hydrogen bonding plays a predominant role in the stabilization of the structure. Various types of intermolecular hydrogen bonds occur between adjacent molecules, including the Hoogsteen type between one N(6)–H and N(7) [N(6)–H(6A) ··· N(37A): d(D ··· A) = 3.088(14) Å, d(H ··· A) = 2.14 Å, ∠(DHA) 161.5°; N(36A)–H(36A) ··· N(7): d(D ··· A) = 3.094(13) Å, d(H ··· A) = 2.12 Å, ∠(DHA) = 171.8°], the Watson–Crick type [N(6)–H(6B) ··· N(31B): d(D ··· A) = 3.045(16) Å, d(H ··· A) = 2.09 Å, ∠(DHA) = 164.3°; N(36)–H(36B) ··· N(1B): d(D ··· A) = 3.093(15) Å, d(H ··· A) = 2.14 Å, ∠(DHA) = 162.5°] in the adenine moiety and that between the N–H and the P=O groups (and *vice versa*) of the dangling chain [N(12)–H(12A) ··· O(31): d(D ··· A) = 2.822(12) Å, d(H ··· A) = 2.14 Å, ∠(DHA) = 125.1°; N(42)–H(42) ··· O(1): d(D ··· A) = 2.811(12) Å, d(H ··· A) = 2.20 Å, ∠(DHA) = 119.3°].

Coordination chemistry of L1 and L2

Attempts to get chelate complexes **D** shown in Scheme 3 from **L1** and **L2** were not very successful. Reaction of [PdX$_2$(cod)] (X= Cl, Br) and **L1** or **L2** (in both 1 : 1 and 1 : 2 molar ratio) led to the immediate precipitation of a yellow solid which did not dissolve in any solvent (not even in DMSO and DMF), the insolubility makes the characterization very difficult. Interaction of **L1** and [Pt(CH$_3$)$_2$(cod)] in 1 : 1 molar ratio gave a mixture of **20** (DMSO-d$_6$, δ_P 60.6, $^1J_{PtP}$ = 2160 Hz) and the proposed eight-membered chelate complex (δ_P 61.18, $^1J_{PtP}$ = 2184 Hz) in *ca.* 3 : 4 ratio based on integration of ^{31}P-{^{1}H} NMR. ^{1}H NMR spectrum of this mixture also displayed two sets of signals, in which one set was in agreement with that of **20**. Further characterization of the chelate complex was impossible because of the failure in separation. However, **L1** and **L2** proved to be excellent monodentate ligand towards transition metals. Reaction of **L1** and **L2** with [Au(tht)Cl] and Rh(I), Rh(III), Ir(III), Ru(II) and Ru(IV) gave monodentate complexes **11**–**20**. Two molar equivalents of **L1** or **L2** reacted with [PtX$_2$-(cod)] (X = CH$_3$ or Cl) also gave monodentate complexes **21** and **22**. The complexes gave reasonable microanalysis results. Like ligands **L1** and **L2**, the IR spectra of the complexes display the typical medium ν_{NH} stretching bands at around 3300 and 3150 cm^{-1}, the ν_{NH} bending and C=N stretching were observed as very strong bands at *ca.* 1640 and 1590 cm^{-1}. Their FAB MS spectra show the molecular ions and the expected fragmentation ions with appropriate isotope distributions.

In the ^{31}P-{^{1}H} NMR spectra (Tables S6 and S7 in ESI †), apart from complexes **17**, **18** and **22** all the complexes show the chemical shifts at higher frequencies than **L1** and **L2**. The rhodium species exhibited the expected doublets with appropriate coupling constants ($^1J_{RhP}$ = 149–161 Hz). The platinum complex **21** shows a singlet at δ_P 60.6 with platinum satellites $^1J_{PtP}$ = 2106 Hz. The coupling constant is typical for a phosphine ligand *trans* to the methyl group. The chemical shift of complex **22**, like other aminophosphine complexes from [PtCl$_2$(cod)], falls in a lower frequency at δ_P 59.9 than the free ligand.[27] The magnitude of the $^1J_{PtP}$ = 3983 Hz is typical for a phosphine ligand *trans* to chloride and thus in agreement with the *cis* geometry. The lower frequency-shift of the iridium complexes **17** (δ_P 34.7) and **18** (δ_P 49.0) compared with **L1** (δ_P 43.8) and **L2**

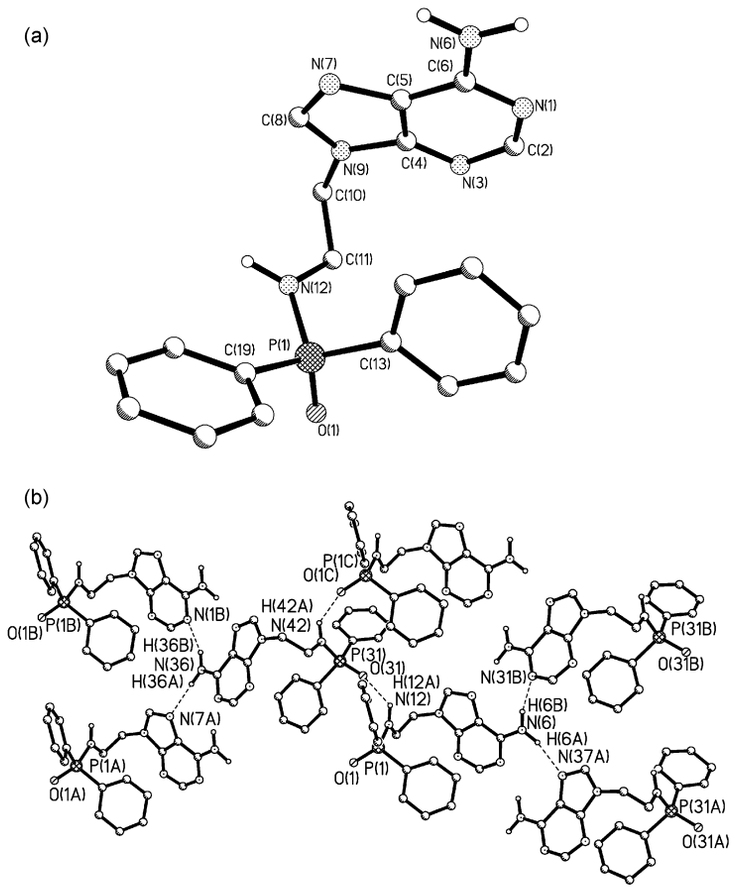
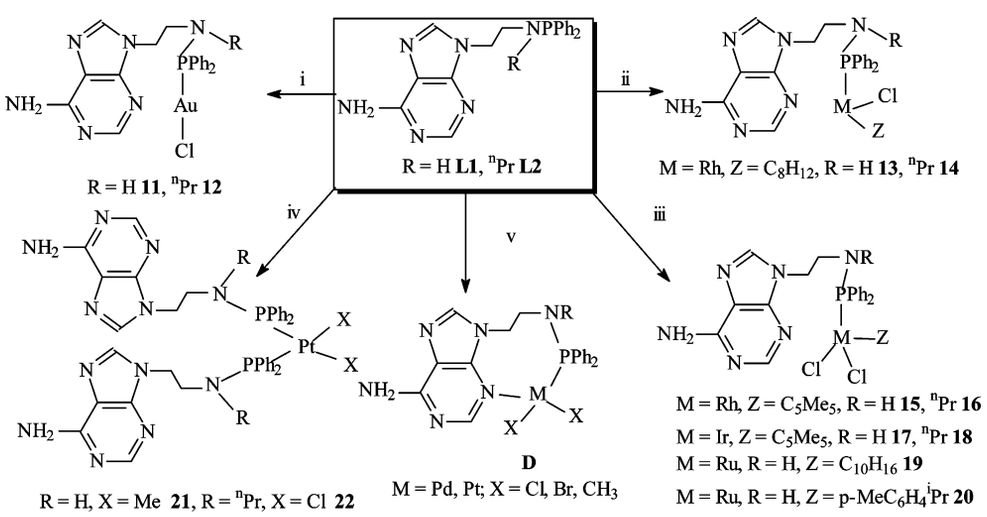


Fig. 1 (a) The crystal structure of compound **5**. (b) The crystal structure of compound **5** showing part of hydrogen bonding.



Scheme 3 Coordination chemistry of **L1** and **L2**. Reagents and conditions: (i) [AuCl(tht)], CH_2Cl_2, rt, 2 h; (ii) [{Rh(μ-Cl)(cod)}$_2$], THF, rt, 2 h; (iii) 0.5 [{RhCl(μ-Cl)(η^5-C_5Me_5)}$_2$], [{IrCl(μ-Cl)(η^5-C_5Me_5)}$_2$], 0.5 [{RuCl(μ-Cl)(η^3:η^3-$C_{10}H_{16}$)}$_2$] or [{RuCl(μ-Cl)(*p*-$MeC_6H_4{}^{i}$Pr)}$_2$]; (iv) 0.5 [$PtCl_2$-(cod)] or Pt(cod)Me_2; (v) [PdX_2(cod)] (X = Cl, Br, Me), CH_2Cl_2.

(δ_P 62.8) was also observed in other iridium complex of aminophosphine.[38]

The ^{1}H NMR spectra of the complexes are closely similar to the free ligand, in spite of the fact that in some cases the signals of $AdeCH_2CH_2$ and $NCH_2CH_2CH_3$ are broadened. Comparison of the ^{1}H NMR data of **L1** (Table S2 in ESI †) with its complexes in Table S6 in ESI † shows that the NH signals of the dangling chain are shifted to higher frequency on coordination, from δ_H 2.2 to δ_H 3.6–3.8. In the case of **11**, even further higher frequency shift (δ_H 4.86) was observed because of the involvement of DMSO-d_6. In order to identify the NH signal, to simplify the coupling system of $AdeCH_2CH_2$ and to measure the coupling constants $^3J_{CHNH}$ and $^2J_{PNH}$, D_2O was added to the $CDCl_3$ or $CDCl_3$–DMSO-d_6 solution of the complexes, if necessary, ^{1}H-{^{31}P} NMR spectra were also collected. Interestingly, while the C^6-NH_2 signal on the purine ring at around δ_H 5.7 disappeared immediately after shaking the solution vigorously for all the compounds, the signal for NH on the dangling chain lingered for 0.5–2 h before vanishing in **L1**, **5**, **7** and **9**. For the complexes in Table S6 in ESI, † it is very difficult to get spectra free of the NH signal. Standing the sample for two days with D_2O added to $CDCl_3$ solution with shaking or sonication from time to time led to ^{1}H NMR spectra with the NH signal decreased and $AdeCH_2CH_2$ signal simplified to some extent. The sluggish H/D exchange may be mainly attributed to the steric effect and the hydrophobic properties of

both the diphenylphosphine group and other moiety introduced together with the metal.

The ^{1}H NMR spectrum of **12** (Table S7 in ESI †) shows a closely similar spectrum to **L2**, with the $NCH_2CH_2CH_3$ signal appearing as complicated multiplets, which is simplified as a pseudo-triplet in the ^{1}H-{^{31}P} NMR spectrum. The complexity of $NCH_2CH_2CH_3$ of other complexes of **L2** was less clear because of the slight broadness of the signal. Surprisingly, though complex **18** gave a sharp singlet in the ^{31}P-{^{1}H} NMR spectrum, the ^{1}H NMR signals are extremely broad except that of C^2-H, C^8-H, C^6-NH_2 on the purine ring and the CH_3 of the pentylmethylcyclopentadienyl ring. The broadening of the signals of the dangling moiety at N^9 including the phenyl protons suggests that there may be some conformational exchange around the nitrogen atom. The conformations may arise from the interaction of the large C_5Me_5 group and the purine ring and thus may block the free conversion of the chiral N center. Low-temperature spectra obtained at −30 and −55 °C look even more complicated with the signals splitting into two sets of broad peaks, suggesting that the exchange between the two conformations slow down to some extent, but not slow enough to give two sets of sharp signals. A spectrum collected at 50 °C exhibited slightly narrower and more intensified peaks, however, only the $NCH_2CH_2CH_3$ resonance looked like a triplet, all other peaks remained as broad singlets. The reaction of **L2** and $[\{RhCl(\mu\text{-}Cl)(\eta^5\text{-}C_5Me_5)\}_2]$ in 1 : 1 molar ratio was also tested to give **16**. The ^{31}P-{^{1}H} NMR spectrum showed a broad doublet at δ_P 80.3 with $^1J_{RhP}$ = 152 Hz. The ^{1}H NMR at room temperature is as broad and complicated (appearing like two sets of signals) as that of **18** at low temperature, implying that there are two conformations for this compound in the $CDCl_3$ solution.

Among the above complexes, single crystals suitable for X-ray analysis of compound **11**, **15** and **17** were obtained. These crystals show two common features: the co-crystallisation of some solvate molecules (Table 1) and the presence of a variety of hydrogen bonds. For clarity the solvate molecules are omitted in the structures (Fig. 2(a)–(c), Fig. 3(a) and (b), Fig. 4(a)) except the solvent involved in hydrogen bonding (Fig. 4(b)). The comparative bond lengths and angles are listed in Table S8 in ESI. †

Complex **11** (Fig. 2(a), (b)) co-crystallised with one half molecule of water. The coordination around the Au(1) adopts the typical linear geometry [P(1)–Au(1)–Cl(1) 176.62(8)°] for gold(I) complexes. There are three types of intermolecular hydrogen bonding observed in this structure, including the typical common and reversed Watson–Crick type N(6)–H(6) ··· N(1A) and N(6A)–H(6) ··· N(1) [d(D ··· A) = 2.997(8) Å, d(H ··· A) = 2.02 Å, ∠(DHA) = 172.0°], the weak and less common H-bond N(6)–H(6) ··· N(3B) or N(3) ··· H(6C)–N(6C) [d(D ··· A) = 3.124(8) Å, d(H ··· A) = 2.40 Å, ∠(DHA) = 130.6°] and the Hoogsteen type between N(7) and the dangling N–H of an adjacent molecule [N(12)–H(12) ··· N(7C): d(D ··· A) = 2.989(7) Å, d(H ··· A) = 2.08 Å, ∠(DHA) = 154(6)°]. Different from **5**, **15** and **17**, the structure of **11** displays intramolecular π–π-stacking interaction (Fig. 2(c)). One of the phenyl ring of the phosphine moiety stacks approximately parallel (α = 12°) with the six-membered ring of the adenine. The inter-planar centroid–centroid separation between the stacked rings is of 3.7 Å. No intermolecular π–π-stacking was observed.

Single molecules of **15** and **17** are similar to each other (Fig. 3(a), Fig. 4(a)). The geometry around the Rh(1) or Ir(1) can be viewed as a three-legged 'piano stool' with the two chlorides and the phosphorus P(1) supporting the pentamethylcyclopentadienyl top. The bond angles between the 'legs' are approximately 90°. An intramolecular five-membered-ring hydrogen bond between one of the chloride atoms and the NH group of the aminophosphine moiety is observed in both compounds [N(12)–H(12) ··· Cl(1): d(D ··· A) = 3.149(3) Å, d(H ··· A) = 2.49(4) Å, ∠(DHA) = 124(3)° for **15**, and correspondingly 3.396(2), 2.73(2) Å, 125.8(1)° for **17**]. However the two compounds co-crystallise with various solvent molecules, a quarter of THF for **15** and a half of $CHCl_3$ for **17**. The structures of **15** and **17** also adopt different types of intermolecular hydrogen bonds. Two molecules in **15** pair with each other by Hoogsteen type hydrogen bonds between the N(7) and one N(6)–H [N(6)–H(6A) ··· N(7A) and N(6A)–H(6AA) ··· N(7): d(H ··· A) = 2.13(2) Å, ∠(DHA) = 157(4)°] and one additional intermolecular hydrogen bond between the other

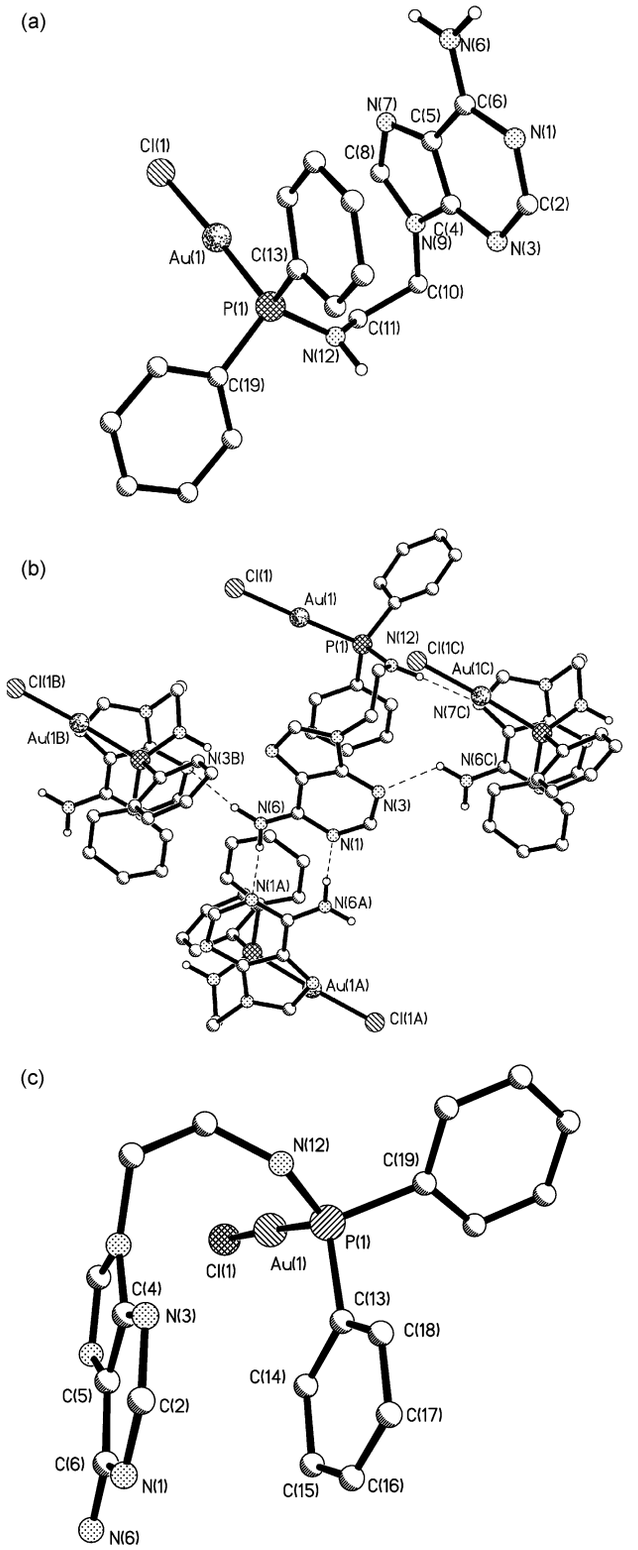


Fig. 2 (a) The crystal structure of complex **11**. (b) The crystal structure of complex **11** showing hydrogen bonding. (c) The crystal structure of complex **11** showing π–π-stacking effect.

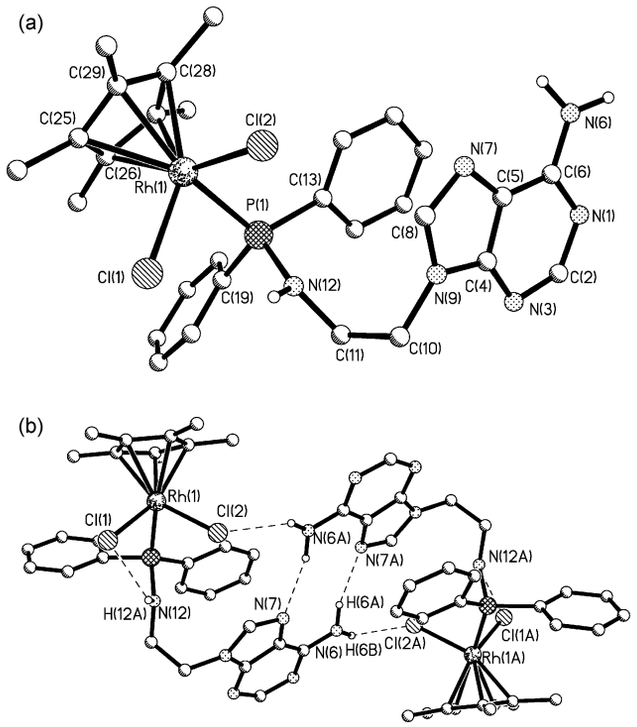


Fig. 3 (a) The crystal structure of complex **15**. (b) The crystal structure of complex **15** showing the hydrogen bonding.

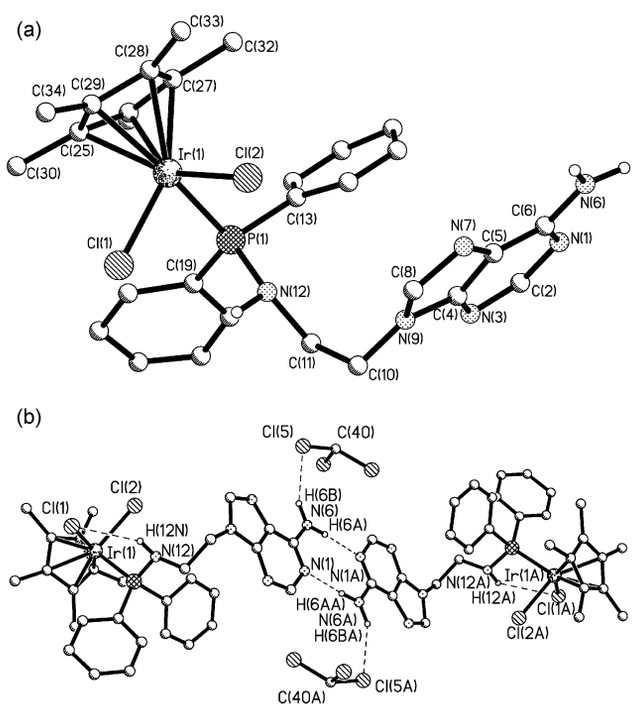


Fig. 4 (a) The crystal structure of complex **17**. (b) The crystal structure of complex **17** showing hydrogen bonding.

N(6)–H and chloride atom Cl(2) on the metal [N(6)–H(6B) ··· Cl(2) and N(6A)–H(6AB) ··· Cl(2B): d(D ··· A) = 3.348(4) Å, d(H ··· A) = 2.52(3) Å, ∠(DHA) = 143(3)°]. In compound **17**, however, two molecules couple with each other only through the Watson–Crick type of hydrogen bondings between N(6)–H and N(1) [N(6)–H(6A) ··· N(1A) and N(6A)–H(6AA) ··· N(1): d(D ··· A) = 3.073(7) Å, d(H ··· A) = 2.09 Å, ∠(DHA) = 175.7°]. The other N(6)–H proton forms an H-bond with one of the chlorides of the solvate $CHCl_3$. Since there are two more hydrogen bonds between two molecules, the structure of **15** is more compact than that of the long spread-eagled **17**.

In conclusion, we describe two aminophosphine analogues of adenine **L1** an **L2** and their chalcogenide derivatives. **L1** and **L2** proved to be good monodentate ligands towards late transition metals to give a series of monodentate complexes. All the compounds retain a free adenine moiety for complementary hydrogen bonding. Further studies on the interaction of these compounds with DNA and bioactivities are undergoing.

Acknowledgements

We wish to thank the JREI for equipment grants and Johnson Matthey plc for loan of precious metals and Dr Andrew Houlton for his inspiration of this work. Qingzhi Zhang is indebted to St Andrews University for financial support. We also appreciate Dr Stephen M Aucott and Mrs. Joanna Wheatley in this lab for the kind donation of some of the metal precursors and Dr Petr Kilian for help in low-temperature NMR.

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