Metal-promoted synthesis of amidines containing the model nucleobases 1-methylcytosine and 9-methyladenine†

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The amidine complexes cis-[L2PtNH≡C(R)(1-MeCy(−2H))]NO3 (R = Me, 1a; Ph, 1b, Me,C, 1c; Ph(C2H5)3, 1d) and cis-[L2PtNH≡C(R)(9-MeAd(−2H))]NO3 (R = Me, 2a; Ph, 2b; Me,C, 2c; Ph(C2H5)3, 2d), are formed when cis-[L2Pt(μ-OH)](NO3)2 (L = PPh3) reacts with 1-methylcytosine (1-MeCy) and 9-methyladenine (9-MeAd) in solution of MeCN, PhCN, Me2CCN and Ph(C2H5)CCN. Reaction of 1a,b and 2a,b with HCl affords the protonated amidines [NH2≡C(R)(1-MeCy(−H))]NO3 (R = Me, 3a; Ph, 3b) and [NH2≡C(R)(9-MeAd(−H))]NO3 (R = Me, 4a; Ph, 4b) and cis-[PPh3]2PtCl2 in quantitative yield. Treatment of 3b and 4b with NaOH allows the isolation of the neutral benzimidamides NH2-C(Ph)(1-MeCy(-2H)) (5b) and NH2-C(Ph)(9-MeAd(-2H)) (6b). In the solid state 3b shows a planar structure with the hydrogen atom on N(4) cytosine position involved in a strong H-bond with the NO3− ion. Intermolecular H-bonds between the oxygen of the cytosine ring and one of the H atoms of the amine-NH2 group allow the dimerization of the molecule. A detailed analysis of the spectra of 3b in DMF- d7 or at −55 °C indicates the presence of an equilibrium between the species [NH2≡C(R)(1-MeCy(−H))]NO3 and [NH2≡C(R)(1-MeCy(−2H))][NO3]2, exchanging with trace amounts of water at 25 °C. [15N,1H]-HMBC experiments for 5b and 6b indicate that the amido tautomer H2N-C(Ph)(nucleobase(-2H)), is the only detectable in solution and such structure has been confirmed in the solid state. The reaction of 5b and 6b with cis-L2Pt(ONO2)2 (L = PPh3), in chlorinated solvents, determines the immediate appearance of a pale yellow colour due to the coordination of the neutral amidine, likely in its imino form HN≡C(Ph){nucleobase(-H)}, to give the adducts cis-[L2PtNH=C(Ph){nucleobase(-H)}]NO3. In fact, addition of “proton sponge” leads to the immediate deprotonation of the amidine ligand with formation of the starting complexes 1b and 2b.

Introduction

Amidines, R−C≡(NH)NH2, their N-monosubstituted and N,N′-disubstituted derivatives are important intermediates in the synthesis of heterocyclic compounds,1 some of which are pharmacologically active molecules.2 The usual synthetic methods proceed through: i) addition of metal amides to nitriles; ii) addition of salt of ammonia or amines to nitriles; iii) transformation of nitriles into imido esters followed by the condensation with NH2 or amines (Pinner synthesis).1,3 In several cases, the preparation needs high temperatures,4 strongly reducing agents,4 highly acidic or alkaline conditions.4

More recently, the activation of nitriles through coordination to a metal centre, increasing the rate of the nucleophilic attack at the carbon atom of the CN group,7 led to the synthesis of several amidine complexes of transition metals, in particular of platinum(t1 and t1v).4 We have recently shown that, if the nucleophile is the nitrogen atom of the NH2-deprotonated 1-methylcytosine (1-MeCy) and 9-methyladenine (9-MeAd) (Chart 1), the azametallic cycle complexes of platinum(t1) cis-[L2PtNH≡C(R)(1-MeCy(-2H))]+ and cis-[L2PtNH≡C(R)(9-MeAd(-2H))]+ (L = PPh3 and PMePh2) are formed.9,10

They contain as an anionic ligand the deprotonated form of the N-monosubstituted amidines R−C≡(NH)NHR’ (R = Me, Ph), in which the NHR’ group is the nucleobase 1-MeCy or 9-MeAd, and are structurally similar to 1,3,5-triazapentadienes recently reviewed by Kopylovich and Pombeiro.11

In this paper we present the synthesis and the structural characterization of these new amidines, in their protonated and neutral forms, [NH2≡C(R){nucleobase(-H)}]NO3, and NH2=C(R){nucleobase(-2H)}, respectively. The ionic species are formed in high yield by protonation of the amidine complexes cis-[L2PtNH=C(R){nucleobase(-2H)}]NO3 (L = PPh3; R = Me, Ph) with aqueous HCl, allowing the quantitative recovery of the
Chart 1 Synthetic procedures for the amidine Platinum(ii) complexes (L = PPh₃, PMePh₂).

Chart 2 Synthetic pathway for the synthesis of amidines and their coordination properties.

metal as cis-(PPh₃)₂PtCl₂, as shown in Chart 2 for the 1-MeCy derivative.

The nitrate salt of N-(1-methyl-2-oxo-1,2-dihydropyrimidin-4-yl)benzimidamide, [NH₂C(Ph){1-MeCy(-H)}]NO₃, has been characterized by single crystal X-ray analysis and in solution by NMR at variable temperature. In the solid state, strong intermolecular H-bonds stabilize a dimeric structure of the cation, which is also maintained in solution of DMSO-d₆ or DMF-d₇.

The neutral species, of which the amino and the imino tautomeric forms are expected [NH₂C(R){nucleobase(-H)}] and NH⁻C(R){nucleobase(-2H)}, respectively (Chart 2), have been obtained in the amino form, namely NH₂C(Ph){1-MeCy(-2H)} and NH₂C(Ph){9-MeAd(-2H)}, and this isomer is the preferred one, as confirmed by the structural characterization in the solid state and in solution. The stabilization of the imino tautomer through metal coordination has been also investigated by reacting these amidines with the complex cis-L₂Pt(NO₃)₂(L = PPh₃) containing the labile nitrate ligands. The adducts, tentatively formulated as cis-[L₂PtNH-C(Ph){nucleobase(-H)}]NO₃, quantitatively convert into cis-[L₂PtNH-C(Ph){nucleobase(-2H)}]NO₃, by addition of a “proton sponge”.

The single crystal X-ray analysis of the cytosine derivative cis-[PPh₃]₂PtNH-C(Ph){1-MeCy(-2H)}]NO₃ confirms the coordination features of the anionic ligand previously described for the PMePh₂ analogue and allows the examination of the structural differences between the free and the coordinated benzimidamides. Finally, the reactivity of Me₃C–CN and Ph₂(H)C–CN has been explored, showing that the insertion of these hindered nitriles into the platinum–nucleobase bond is incomplete in the case of 9-MeAd, while the amidine complexes cis-[PPh₃]₂PtNH-C(C)(R) {1-MeCy(-2H)}]NO₃ [R = Me₃C and Ph₂(H)C] can be isolated in high yield. They are structurally analogous to the acetonitrile and benzonitrile derivatives, suggesting that the use of appropriate nitriles can lead to a variety of metallacycle complexes from which new amidines can be prepared.

Experimental section

Instrumentation and materials

¹H, ¹³C and ³¹P NMR experiments were recorded on a Bruker AVANCE 300 MHz operating at 300.13, 121.49 and 100.61 MHz, respectively. ¹⁵N NMR with Bruker 400 AMX-WB spectrometer (operating at 40.6 MHz). The ¹H and ¹³C chemical shifts were referenced to the residual impurity of the solvent and to TMS. The external references were H₃PO₄ (85% w/w in D₂O) for ³¹P and CH₃NO₂ (in CDCl₃ at 50% w/w) for ¹⁵N. Inverse detected spectra were obtained through heteronuclear multiple bond correlation.
(HMBC) experiments, using parameters similar to those previously reported. IR spectra were recorded on a JASCO FT/IR-4100 type A Fourier Transform Infrared Spectrometer using Nujol mulls between KBr discs.

All the solvents (CHCl₃, MeOH, PhCN, CDCl₃, D₂O, DMSO-d₆, DMF-d₇), HCl, NaOH, Ph,C(H)CN, (CH₃)CCN and CH(OCH₃)₃ are Aldrich products. 9-MeAd, cis-[P(Ph₃)₂Pt(N=CMe)(-2H)]NO₃ (R = Me, 1a; Ph, 1b) and cis-[P(Ph₃)₂Pt(N=CMe)(9MeAd)(-2H)]NO₃ (R = Me, 2a; Ph, 2b) were synthesized as previously reported. Synthetic work:

1. cis-[P(Ph₃)₂PtNH=CC(C₆Me₅)(-2H)]NO₃, 1c. A suspension of cis-[P(Ph₃)₂Pt(μ-OH)](NO₃) (32 mg, 2.0 × 10⁻² mmol) and 1-MeCy (5.2 mg, 4.0 × 10⁻² mmol) in CH₂Cl₂ (2 mL) and CH₃Cl (4 mL) was stirred at r.t. for 2 h. Addition of Et₂O to the resulting yellow solution afforded the precipitation of a pale yellow solid, which was recovered by filtration, washed several times with Et₂O, and dried under vacuum. The yield of 1c was 32 mg, 80%. Elemental analysis calcd (%) for C₄₆H₄₅N₅O₄: C 62.96, H 5.05, N 24.38. 1H NMR in CDCl₃ (δ, ppm): 8.79 (s, 1H, H2); 8.36 (s, 1H, H8); 8.87 (s, 1H, H2); 8.68 (s, 1H, H1); 7.91–7.77 (c.m., 5H, Ph); 3.90 (s, 3H, N(9CH)); 1.89 (s, 9H, CMe₃). 1H NMR in D₂O (δ, ppm): 8.13 (d, JHH = 7.1 Hz, 1H, H6); 7.81–7.59 (c.m., 5H, Ph); 6.50 (d, JHH = 7.1 Hz, 1H, H5); 3.53 (s, 3H, N(1CH₃)); 1.39 (s, 9H, CMe₃). 13C [¹H] NMR in D₂O (δ, ppm): 166.8 (C₂); 158.3 (C2); 153.8 (C8); 135.0 (C13); 130.2 (C₆); 129.3 (C₇); 128.1 (C₅); 99.2 (C5); 39.1 (N(1CH₃)). 1H NMR in DMSO-d₆ (δ, ppm): 12.12 (br s, 1H, NH); 11.87 (br s, 1H, NH); 9.81 (br s, 1H, NH); 8.26 (d, JHH = 7.5 Hz, 1H, H6); 7.97–7.88 (c.m., 5H, Ph); 6.48 (d, JHH = 7.5 Hz, 1H, H5); 3.44 (s, 3H, N(1CH₃)). IR: νNH = 3458 and 3282 cm⁻¹; νCO = 1651 cm⁻¹. Suitable crystals for X-ray analysis were obtained from slow diffusion of Et₂O vapors into a MeOH solution of 3b, at r.t. With the same procedure, 3a was obtained starting from cis-[P(Ph₃)₂PtNH=CC(Me)(-2H)]NO₃ (yield 75%). Elemental analysis calcd (%) for 3a: C₄₆H₄₅N₅O₄; C 63.68, H 4.85, N 30.54; found C 63.40, H 4.70, N 30.85. 1H NMR in D₂O (δ, ppm): 8.13 (d, JHH = 7.05 Hz, 1H, H6); 6.40 (d, JHH = 7.05 Hz, 1H, H5); 3.57 (s, 3H, N(1CH₃)); 2.48 (s, 3H, CMe₃). 1H NMR in DMSO-d₆ (δ, ppm): 11.22 (br s, 1H, NH); 11.12 (br s, 1H, NH); 8.24 (d, JHH = 6.51 Hz, 1H, H6); 6.22 (d, JHH = 6.51 Hz, 1H, H5); 3.51 (s, 3H, N(1CH₃)). 2.64 (s, 3H, CCH₃).

2. cis-[P(Ph₃)₂PtNH=(CH₂Ph₃)(-2H)]NO₃, 1d. A suspension of cis-[P(Ph₃)₂Pt(μ-OH)](NO₃) (502 mg, 3.1 × 10⁻¹ mmol), 1-MeCy (79.2 mg, 6.5 × 10⁻¹ mmol) and Ph₂C(H)CN (128 mg, 6.6 × 10⁻³ mmol) in CH₂Cl₂ (5.0 mL) was stirred at ca 25 °C for 3 days. A trace amount of solid was eliminated by filtration and Et₂O (20 mL) was then added to the resulting yellow solution. The powdered precipitate was recovered by filtration, washed several times with Et₂O, and dried under vacuum, to give a yellow solid. The yield of 1d was 585 mg, 92%. Elemental analysis calcd (%) for C₉₁H₇₃N₅O₃P₄PtPt. CH₂Cl₂: C 56.81, H 4.18, N 5.91; found C 56.49, H 4.21, N 6.09. 1H NMR in CDCl₃ (δ, ppm): 7.62–6.86 (c.m., 41H, Ph and H6); 6.07 (br s, 1H, NH); 5.93 (dd, JHH = 7.1 Hz, JHP = 1.2 Hz, 1H, H5); 5.18 (s, 1H, CH); 2.68 (s, 3H, N(1CH₃)); 13C [¹H] NMR in DMSO-d₆ (δ, ppm): 7.71 (JPP = 3523 Hz); 7.27 (JPP = 3402 Hz); JPP = 25.3 Hz. 1H NMR in DMSO-d₆ (δ, ppm): 7.75–6.75 (c.m., 41, H, Ph and H6); 6.28 (br s, 1H, NH); 5.86 (dd, JHH = 7.1 Hz, JHP = 1.2 Hz, 1H, H5); 5.28 (s, 1H, CH); 3.35 (3H, N(1CH₃)). 3. [NH₂=C(Ph)(-2H)]NO₃, 3b. To a solution of 1b (215 mg, 2.1 × 10⁻¹ mmol) in CH₂Cl₂ (10 mL), a solution of HCl 0.05 M (8.53 mL, 4.3 × 10⁻¹ mmol) was slowly added and the mixture let stir for 2 h at r.t. The aqueous phase was then separated through a separating funnel and the solvent evaporated under vacuum at ambient temperature. The resulting white solid 3b was 54.4 mg (yield 89%). Elemental analysis calcd (%) for 3b: C₁₂H₁₃NO₇; C 49.48, H 4.51, N 24.03; found C 49.30, H 4.68, N 23.85. 1H NMR in D₂O (δ, ppm): 8.13 (d, JHH = 7.1 Hz, 1H, H6); 7.81–7.59 (c.m., 5H, Ph); 6.50 (d, JHH = 7.1 Hz, 1H, H5); 3.53 (s, 3H, N(1CH₃)). 13C [¹H] NMR in D₂O (δ, ppm): 173.0 (C₆); 165.1 (C₄); 157.6 (C₂); 146.0 (C₆); 135.3 (C₁); 131.0 (C₅); 128.5 (C₆); 127.8 (C₃); 105.1 (C₅); 38.3 (N(1CH₃)). 1H NMR in DMSO-d₆ (δ, ppm): 11.11 (br s, 1H, NH); 9.14 (br s, 1H, NH); 8.03–7.57 (c.m., 5H, Ph); 7.87 (d, JHH = 7.0 Hz, 1H, H6); 6.06 (d, JHH = 7.0 Hz, 1H, H5); 3.32 (s, 3H, N(1CH₃)). IR: νNH = 3444 and 3183 cm⁻¹.
6. \( \text{H}_2\text{N-C(Ph)}\text{(9-MeAd-2H)} \), 6b. To a solution of 4b (184 mg, 5.8 \times 10^{-3} \text{ mmol}) in \text{H}_2\text{O} (6 \text{ mL}) a solution of \text{NaOH} 0.1 \text{ M} (5.90 \text{ mL}) was slowly added. The white precipitate immediately formed was recovered by filtration, washed with \text{H}_2\text{O} and dried under vacuum. The yield of 6b was 97 mg, 66%. Elemental analysis calcld (%) for 6b: C_{31}\text{H}_{21}\text{N}_6\text{O}_4\text{Pt} 62.40, H 4.52, N 33.08. 1H NMR in DMSO-
{\ce{d6}} (600 MHz, ppm): 6.87 (s, 1H, H2); 8.11–7.45 (c.m., 6 H, Ph and H8); 7.99 (br s, 1H, NH); 8.63 (s, 1H, H8); 8.28 (s, 1H, H7). 

Suitable crystals for X-ray analyses of 5b and 6b were obtained from slow evaporation at r.t. of a solution in CDCl3 into a NMR tube.

7. Relative stability of the amidine complexes. i) 18.5 mg of cis-[(\text{PPh}_3)_2\text{Pt(\mu-\text{OH})}]_2(\text{NO}_3)_2 (1.2 \times 10^{-2} \text{ mmol}) and 1-MeCy (3.0 mg, 2.4 \times 10^{-2} \text{ mmol}) were rapidly dissolved in 0.8 mL of DMSO-\text{d}_6 solution containing equimolar amounts of Me_3CCN (39 mg), Ph_3CHCN (93 mg) and CH_3CN (20 mg) in order to have Pt/each nitrile ratio 1/20. On the base of 31P NMR spectra, 1a and 1d were in a ratio of 9 : 0 : 1, after 24 h the corresponding ratio was 7 : 1 : 2 and after 5 days at r.t. it became 2 : 1 : 7. ii) 21.2 mg of 2a (184 mg, 5.8 \times 10^{-3} \text{ mmol}) was dissolved in a mixture of 0.3 mL of CH_3CN and PhCN, to give quantitatively the azametallacycles 1b, 1c, 1e and 1d in a ratio of 9 : 0 : 1, after 24 h the corresponding ratio was 7 : 1 : 2 and after 5 days at r.t. it became 2 : 1 : 7. We have recently shown that the dinuclear hydroxo complex cis-[(\text{PPh}_3)_2\text{Pt(\mu-\text{OH})}]_2(\text{NO}_3)_2 reacts with 1-MeCy or 9-MeAd, in CH_3CN or PhCN, to give quantitatively the azametallacycles cis-[(\text{PPh}_3)_2\text{Pt(\mu-\text{OH})}]_2(\text{NO}_3)_2 and 1b and 1c and 1d were in a ratio of 9 : 0 : 1, after 24 h the corresponding ratio was 7 : 1 : 2 and after 5 days at r.t. it became 2 : 1 : 7. We have recently shown that the dinuclear hydroxo complex cis-[(\text{PPh}_3)_2\text{Pt(\mu-\text{OH})}]_2(\text{NO}_3)_2 reacts with 1-MeCy or 9-MeAd, in CH_3CN or PhCN, to give quantitatively the azametallacycles cis-[(\text{PPh}_3)_2\text{Pt(\mu-\text{OH})}]_2(\text{NO}_3)_2 and 1b and 1c and 1d were in a ratio of 9 : 0 : 1, after 24 h the corresponding ratio was 7 : 1 : 2 and after 5 days at r.t. it became 2 : 1 : 7. We have recently shown that the dinuclear hydroxo complex cis-[(\text{PPh}_3)_2\text{Pt(\mu-\text{OH})}]_2(\text{NO}_3)_2 reacts with 1-MeCy or 9-MeAd, in CH_3CN or PhCN, to give quantitatively the azametallacycles cis-[(\text{PPh}_3)_2\text{Pt(\mu-\text{OH})}]_2(\text{NO}_3)_2 and 1b and 1c and 1d were in a ratio of 9 : 0 : 1, after 24 h the corresponding ratio was 7 : 1 : 2 and after 5 days at r.t. it became 2 : 1 : 7.

X-ray structure determination

Crystal data and details of data collections and refinements for the structures reported are summarized in Table 1. Intensity data of compounds 1b, 3b, and 5b were collected at room temperature (293(2) K) on a Nonius DIP-1030H system (Mo-Kα radiation, λ = 0.71073 Å), those of 6b on a Nonius FR591 rotating anode (Cu-Kα, λ = 1.54178 Å), equipped with Kappa CCD imaging plate. Cell refinement, indexing and scaling for the data sets were performed by using Denzo and Scalepack programs. All the structures were solved by direct methods and subsequent Fourier analyses and refined by the full-matrix least-squares method based on F^2 with all observed reflections. A molecule of diethyl ether was detected in the AF map of 1b. Hydrogen atoms were positioned in calculated positions except those of amine group in 3b, 5b, and 6b. All the calculations were performed using the WinGX System, Ver 1.80.05.

Crystallographic data for this paper is available in the ESI, CCDC numbers 811783–811786.†

Results and discussion

Syntheses of the amidine complexes cis-[(\text{PPh}_3)_2\text{PtNH=C(R)\{nucleobase(-2H)\}]_2\text{NO}_3]

We have recently shown that the dinuclear hydroxo complex cis-[(\text{PPh}_3)_2\text{Pt(\mu-\text{OH})}]_2(\text{NO}_3)_2 reacts with 1-MeCy or 9-MeAd, in CH_3CN or PhCN, to give quantitatively the azametallacycles cis-[(\text{PPh}_3)_2\text{Pt(\mu-\text{OH})}]_2(\text{NO}_3)_2 and 1b, 1c, 1e and 1d were in a ratio of 9 : 0 : 1, after 24 h the corresponding ratio was 7 : 1 : 2 and after 5 days at r.t. it became 2 : 1 : 7.
shown that the formation of cis-\([\text{PPh}_3\text{PtNH}=\text{C}(\text{R})\{1-\text{MeCy}(-2\text{H})\}]\)NO\(_3\) (R = Me, 1a; Ph, 1b) occurs at ambient temperature and no intermediates are detectable. In contrast, 9-MeAd undergoes deprotonation, giving initially the chelated \(N^1,N^2\) adenine complex cis-\([\text{PPh}_3\text{Pt}\{9-\text{MeAd}(-H),N^1,N^2\}\}]\)NO\(_3\),\(^19\) which reacts with a solvent molecule only after several hours at room temperature, affording quantitatively the insertion products cis-\([\text{PPh}_3\text{PtNH}==\text{C}(\text{R})\{9-\text{MeAd}(-2\text{H})\}]\)NO\(_3\) (R = Me, 2a; Ph, 2b). A similar reaction pattern is observed when the deprotonation of 1-MeCy occurs in solution of CH\(_2\)Cl\(_2\) in the presence of the substituted acetonitriles Me\(_2\)CCN or Ph\(_2\)CH(CN) and the amidines cis-\([\text{PPh}_3\text{PtNH}==\text{C}(\text{R})\{1-\text{MeCy}(-2\text{H})\}]\)NO\(_3\) (R = Me, C, 1c; Ph\(_2\)H)\(_2\)CN, 1d) are formed in quantitative yield (by \(^{31}\)P NMR). The products 1c and 1d have been isolated as pure compounds and characterized by multinuclear NMR spectroscopy in CDCl\(_3\) and DMSO-\(d_6\). In both the solvents, the compounds exhibit features similar to those of the CH\(_2\)CN and Ph\(_2\)CH(CN) analogues (1a and 1b), as shown in Table T1 (ESI†) where the \(^{31}\)P and selected \(^1\)H NMR data are collected. As previously observed for 1a, complexes 1c and 1d in solution of DMSO-\(d_6\) appear stable while in chlorinated solvents they slowly (a few days at 25 °C) decompose to give the free nitrile and uncharacterized platinum complexes. The reaction is reversible as indicated by the immediate and quantitative formation of the amidine complexes 1c and 1d upon addition of an excess of Me\(_2\)CCN or Ph\(_2\)CH(CN), respectively. The relative thermodynamic stability of the amidinic complexes 1a–1b was investigated by reacting the hydroxo complex and 1-MeCy in mixture of CH\(_2\)CN and Ph\(_2\)CH(CN) (see experimental). 1a and 1b are rapidly formed in a molar ratio ca. 3:2 and the composition of the reaction mixture slowly changed, leading to the quantitative presence of 1b in few days at r.t. The effect of the stabilization due to the presence of phenyl rings in the nitrile molecule is confirmed in another experiment where it has been observed that, carrying out the condensation reaction in DMSO-\(d_6\) with an equimolar mixture of CH\(_2\)CN, Me\(_2\)CCN and Ph\(_2\)CH(CN), the relative concentration of 1a, 1c and 1d, at the equilibrium (after 5 days at 25 °C) was 2:1:7. As previously seen for CH\(_2\)CN and Ph\(_2\)CH(CN),\(^9,10\) the reaction of cis-\([\text{PPh}_3\text{Pt}(\mu-\text{OH})\}]\)NO\(_3\), with 9-MeAd in CH\(_2\)Cl\(_2\), in the presence of an excess of Me\(_2\)CCN or Ph\(_2\)CH(CN), rapidly affords the intermediate cis-\([\text{PPh}_3\text{Pt}\{9-\text{MeAd}(-H),N^1,N^2\}\}]\)NO\(_3\), which slowly reacts with the nitrile to give the amidines cis-\([\text{PPh}_3\text{PtNH}==\text{C}(\text{R})\{9-\text{MeAd}(-2\text{H})\}]\)NO\(_3\) (R = Me, C, 2c; Ph\(_2\)H)\(_2\)CN, 2d). However the insertion of the nitrile molecule into the Pt-N(6) bond is not quantitative, even in the presence of a large excess of nitrile. As an example, the \(^{31}\)P NMR spectrum of a mixture of cis-\([\text{PPh}_3\text{Pt}(\mu-\text{OH})\}]\)NO\(_3\), 9-MeAd and Ph\(_2\)CH(CN), in molar ratio 1:2:20, is shown in Fig. S1 (ESI†). The AB pattern detected in the fresh prepared solution (Fig. S1a, ESI†), at \(\delta\ 8.78\) (\(J_{PP} = 3860\) Hz) and 6.16 ppm (\(J_{PP} = 3100\) Hz; \(J_{PP} = 20\) Hz), is attributable to the \(N^1,N^2\) -chelated adeninate complex, and its relative concentration is about 40% after 8 days (Fig. S1b, ESI†). These results reflect the relatively high thermodynamic stability of the five membered \(N^6,N^7\)-chelated adenine complex with respect to the amidine derivative 2d. Although 2c and 2d were not isolated as pure compounds, their \(^{31}\)P NMR in CDCl\(_3\) parameters are included in Table T1 (ESI†). The chemical shift and coupling constant values for these compounds also suggest a structure similar to those of 2a and 2b, previously characterized.\(^9,10\)

**Syntheses and characterization of the amidines [NH\(_2\)==\text{C}(\text{R})\{\text{nucleobase(-H)}\}]\)NO\(_3\) and NH\(_2\)==\text{C}(\text{R})\{\text{nucleobase(-2H)}\])**

Addition of two equivalents of aqueous HCl to CH\(_2\)Cl\(_2\) solutions of 1a, b and 2a, b leads to the immediate and quantitative protonation of the amidine ligands, released as nitrate salts [NH\(_2\)==\text{C}(\text{R})\{\text{nucleobase(-H)}\}]\)NO\(_3\) (nucleobase: 1-MeCy, R = Me, 3a; Ph, 3b; 9-MeAd, R = Me, 4a; Ph, 4b), and the concomitant coordination of the chloride ions to the metal centre (Chart 2). The platinum containing product, cis-\([\text{PPh}_3\text{PtCl}_2\], dissolved in the chlorinated solvent, can be quantitatively separated from the reaction mixture.

All these organic compounds are insoluble in chlorinated solvents whereas they easily dissolve in H\(_2\)O, DMSO and DMF. Compounds 3a and 4a, unlike the benzonitrile derivatives 3b and 4b, slowly decompose in water (a few days, at room temperature) with formation of CH\(_2\)CN and of the protonated nuclobases [1-MeCyH\(_2\)NO\(_3\)] and [9-MeAdH\(_2\)NO\(_3\)]. Therefore, only 3b and 4b have been further characterized as neutral species, according to Chart 2.

Aqueous solutions of 3b and 4b, upon addition of stoichiometric amounts of NaOH, afford white precipitates of the neutral amidines NH\(_2\)==\text{C}(\text{Ph})\{1-\text{MeCy}(-2\text{H})\} (5b) and NH\(_2\)==\text{C}(\text{Ph})\{9-\text{MeAd}(-2\text{H})\} (6b) which have been characterized in solution by multinuclear NMR spectroscopy and in the solid state by single crystal X-ray analysis. These neutral species, insoluble in H\(_2\)O, dissolve in CDCl\(_3\), and DMSO-\(d_6\), where they appear indefinitely stable. The \(^1\)H NMR spectra of 5b and 6b exhibit well-resolved doublets for the cytosine H5 and H6 protons and very sharp singlets for H2 and H8 adenine signals. The NH resonances are observed as two broad singlets having the same relative intensities, with very different chemical shift values (\(\Delta\delta\ 4.4\) and 5.1 ppm for 5b and 6b, respectively, in CDCl\(_3\)). \(^1\)H,\(^{15}\)N HMOC experiments (Fig. S2, ESI†) of 5b indicate that both the NH signals at \(\delta\ 11.56\) and 7.14 ppm correlate with the same \(^{15}\)N nucleus (at \(\delta\ 266\) ppm), in agreement with the presence of two hydrogen atoms bound to the same nitrogen. Of the two possible tautomers of these amidines (Chart 2), the \(\text{amino}\) form appears to be the only one detectable in solution, as predicted by Prevorsek.\(^26\) The large chemical shift difference for the NH protons can be accounted for by the presence of relatively strong \(\text{intermolecular}\) hydrogen bonds, as detected in the solid state structure of 5b and 6b and discussed in the next section (Fig. S3 and S4, ESI†).

A more complex \(^1\)H NMR pattern was observed in the case of the protonated amidines 3b. In fact, whereas in D\(_2\)O the endocyclic protons H(6) and H(5) are observed as sharp doublets, with \(J_{HH} = 7.07\) Hz, they occur as poorly resolved doublets in DMSO-\(d_6\). This unprecedented behaviour prompted us to study the system in DMF-\(d_7\) at variable temperature. In this medium, at 25 °C, H5 and H6 show very broad singlets at 7.4 and 9.0 ppm, respectively, and a sharp singlet at 3.57 ppm for the N(1) methyl group. The NH proton resonances, undetectable in D\(_2\)O, are observed as very broad singlets, with the same relative intensities, at 13.4, 12.9 and 12.6 ppm in DMF-\(d_7\). Decreasing the temperature to \(-55\) °C, a sharpening of all the NH resonances is observed, with the concomitant progressive merging of those at higher field, to give a single resonance at 13.8 ppm, as shown in Fig. 1. A similar trend with the temperature is observed for
Fig. 1  Temperature dependence of the equilibrium between the monomer 3b and the dimer 3b’ in DMF-d7. Only selected temperatures are shown.

the H5 and H6 signals, which become sharp doublets at low temperature.

NMR investigation of the H-bonded monomer–dimer equilibrium of 3b

Inspection of Fig. 5 reveals in 3b the presence of dimeric species formed via H-bonding between the iminium protons at N2 and the carbonylic oxygen O2. In addition, the aminic proton N4 and one nitrate oxygen are at H-bonding distance. These features are almost exactly reproduced in solution of DMF-d7, as revealed by the 1H NMR spectra monitored at different temperatures (Fig. 1). The dynamic behaviour in solution discloses other relevant features.

In the 1H NMR spectrum recorded at -50 °C, three major broad peaks are observed between 12.2 and 13.2 ppm, i.e. within the typical H-bonding resonance range, beside three minor peaks: one in the H-bonding resonance range (δ = 13.8 ppm), the last two are somehow more shielded (δ = 10.75 and 10.42 ppm). These are NH resonances which can be accounted for due to the dimer–monomer equilibrium illustrated in Chart 3.

On the basis of this scheme, two major resonances, in the H-bond region and assigned to the NH protons of the iminium moiety, account for the formation of the dimer 3b’. The minor resonances in the more shielded region are again the NH resonances of the iminium moiety in the “free” monomer 3b, and the last major and minor resonances in the H-bond region pertain to the aminic proton of the dimer and of the monomer, respectively, that are H-bonded to the nitrate anion. The presence of H-bonds in solution between aminic protons and inorganic anions is documented.21 This case is somehow different from the picture given by the X-ray diffraction analysis reported in Fig. 5, which highlights the presence of a dimer 3b” with only two different H-bond interactions: of the aminic proton with the nitrate anion, and of only one iminium proton with carbonylic oxygen. This may be a situation dictated by packing requirements of the crystalline state.

The presence of the three major resonances in the H-bond region may be accounted for due to the dimeric structure of 3b’. Alternatively, the equilibrium, fast at room temperature, between the dimeric strucure 3b” and 3b”’ can be proposed. However, this situation would lead to an averaged NH resonance in a more shielded region. Thus the arrangement 3b’ that is to be preferred, would require the slow proton exchange between water (always present) and the aminium an iminium centers, and also the low rotation around the CN double bond.

At higher temperatures, the increasing exchange rates for the monomer–dimer equilibrium bring about the broadening and the final collapse of the NH resonances present in equivalent positions. This dynamic behaviour can be monitored and quantified in terms of equilibrium constants (see below) up to about 0 °C; at higher temperatures contaminations by other phenomena (rotations and proton exchanges) will interfere.

The thermodynamic behaviour can be monitored from other resonances of the monomer-dimer system, which therefore must be exactly attributed. Proton 5 and 6 of the 2-oxopyrimidine ring are in the form of doublets, in both structures, and therefore easily recognized, but not singularly assigned. The attribution procedure occurs via a NOESY experiment that at -55 °C is ambiguous: both the monomer and the dimer are in the “negative” NOE region, and the dipolar interactions are indistinguishable from exchange interactions. At 20 °C the resonances of the 2-oxopyrimidine ring collapse into two broad singlets. In the NOESY spectrum in Fig. S5 (ESI†), the deshielded singlet at 8.60 ppm belonging to proton 6 gives dipolar interaction with the methyl signal at 3.75 ppm. The shielded singlet at 7.02 ppm gives a dipolar interaction with the
intense water signal at 3.95 ppm, denouncing the proximity to the aminic proton (which exchanges fast with water protons): this is the signal of proton 5 (See Fig. S5, ESI†).

At low temperatures, the resonances of protons 5 and 6 split into two pairs of doublets. The doublets of protons 6 resonate in a free region and will be utilized for a quantitative evaluation of the thermodynamics via the van’ Hoff analysis of the monomer–dimer interconversion.

Van’t Hoff plot

The integration of NMR peaks is, among the NMR parameters, the one measured with the least accuracy, also because of the limits of the instrumental numeric procedure. We therefore adopted the strategy of fitting the peaks into a combination of Gaussian and Lorentzian functions, followed by the analytical integration of these. The fitting is computationally accomplished with the Levenberg–Marquardt method. Accurate integration values can be acquired between –55 and 15 °C, i.e. just below the coalescence temperature. The equilibrium constant $K$ for the process is defined by:

$$2 \text{ monomer } 3b \xrightleftharpoons{\text{K}_{\text{md}}}{\text{K}_{\text{dm}}} \text{ dimer } 3b'$$

where $K = \frac{[\text{dimer } 3b']}{[\text{monomer } 3b]^2}$ and $2[\text{dimer } 3b'] + [\text{monomer } 3b] = 0.011 \text{ mol L}^{-1}$.

This is a non-equimolar equilibrium, and therefore the concentration of $3b$ in DMF-$d_7$ must be determined with utmost accuracy, more for a correct evaluation of the equilibrium entropy $\Delta S^\circ$ than for the evaluation of the equilibrium enthalpy $\Delta H^\circ$. The monomer $3b$ and DMF-$d_7$ were weighed in the NMR tube, and the concentration was checked after the measurement session by the further addition of a weighed amount of a substance with relevant molecular weight and one small $1H$ peak resonating in a free region: the choice was triethyl orthoformate.

From the Van’t Hoff plot, the thermodynamic parameters $\Delta H^\circ = -1.58 \text{ kcal L mol}^{-1}$ and $\Delta S^\circ = 9.01 \text{ cal K}^{-1} \text{ L mol}^{-1}$ are determined.
The positive entropy change for a dimerization process is unexpected so we then verified the accuracy of the results with the analytical integration of other signals, the NH and the methyl resonances, retrieving very similar positive values. Some comments on this point are necessary. Positive entropy changes for dimerization processes promoted by intermolecular H-bonding are not common, and are invariably associated with condensed phase experiments run in highly polar solvents. A rationalization has been offered. Since the molecular dipole vectors of two molecules such as 3b mutually cancel upon the formation of a H-bonded dimer, the latter species possesses no molecular dipole vector. Highly polar solvent molecules are heavily organized around the monomer with relevant dipole vector, but to a relevantly minor extent around a dimer lacking a molecular dipole vector.

X-ray structural studies

The X-ray structural determination of complex 1b shows the insertion of the benzonitrile molecule into the cytosine Pt-N(4) bond with formation of a six-membered ring, as depicted in Fig. 2. Selected bond distances and angles are collected in Table 2.

Fig. 2 ORTEP drawing (35% probability ellipsoids) of the cation of 1b.

The platinum is bound to the nucleobase donor site N3, the inserted benzonitrile nitrogen N2, and completes the square planar coordination through phosphorus donors. The Pt–N3 and Pt–N2 bond distances are of 2.074(4) and 2.052(4) Å. The former bond length appears slightly shorter, the other longer with respect to the values measured in complexes cis-[(PMePh3)2PtNH═C(R)]([1-MeCy(-H)]+ with R = Me (2.097(4) and 2.036(4) Å, respectively) and Ph (2.112(7) and 2.043(6) Å). The Pt–P bond distances are 2.2955(12) and 2.2898(13) Å. The N2P2 donors show a slight tetrahedral distortion in 1b, with deviations up to ±0.22 Å from their mean plane. The amidine fragment results bowed with the cytosine and phenyl from the benzonitrile that formed an angle of 15.0(1)°, while the nucleobase ring forms a dihedral angle of 49.2(1)° with the mean coordination plane N3P4. Inside the six-membered ring fragment, the geometrical parameters indicate an electron delocalization. The molecule shows a π–π stacking between the cytosine and PPh3 phenyl ring C(19) and a slightly stronger interaction between the phenyl rings C(25) and C(31) of the two PPh3 (distance between ring centroids of 3.69 and 3.47 Å, dihedral angle 20.34° and 8.38°, respectively).

The molecular structures of the protonated and neutral benzimidamide[NH2═C(Ph){1-MeCy(-H)}]NO3 (3b) and NH2–C(Ph){1-MeCy(-2H)} (5b) are depicted in Figs. 3 and 4 respectively. The

![Fig. 3 ORTEP drawing (35% probability ellipsoids) of compound 3b.](image)

![Fig. 4 ORTEP drawing (35% probability ellipsoids) of compound 5b.](image)
Table 3 Comparison of bond lengths (Å) and angles (°) of the amidine fragment in complexes cis-[(MePh3P)2PtNH=CC(Me)MeCy(-2H)]NO3 (∆ ref [10], cis′-[MePh3P)2PtNH=CC(Me)MeCy(-2H)]NO3 (∆ ref [10]), 1b and in the free ligands 3b and 5b.

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<th>∆α ref [10]</th>
<th>∆β ref [10]</th>
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<td>1.302(10)</td>
<td>1.342(6)</td>
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<tr>
<td>C(3)–C(7)</td>
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<td>1.488(10)</td>
<td>1.507(6)</td>
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Fig. 6 ORTEP drawing (35% probability ellipsoids) of the two independent molecules of 6b.
change of the $^{31}$P NMR spectrum, shown in Fig. 7, in which the singlet at $\delta$ 3.50 ($\Delta_J = 4018$ Hz) of the nitrate complex is completely replaced by an AB multiplet at 4.80 ($\Delta_J = 3504$ Hz) and 6.58 ppm ($\Delta_J = 25.1$ Hz), attributable to the adduct cis-$\{$(PPh$_3)_2$Pt$(\text{ONO}_2)$\}(C(Ph)=[1-MeC$_2$(2H)]) (7b). The values of coupling constants $^{31}$P-$^{195}$Pt, slightly increased (an average of 72 Hz) with respect to those of the strictly related species cis-$\{$(PPh$_3)_2$Pt$(\text{OH})$\}(C(Ph)=[1-MeC$_2$(2H)]) are presented in Table 7b, strongly support the presence in 7 of the neutral amide acting as a N,N-chelating ligand.

Moreover, addition of “proton sponge” to the CDC$_1$$_3$ solution of 7b causes the immediate deprotonation of the imino ligand, with the quantitative formation of complex 1b, as shown in Fig. 7c. In the same experimental conditions, a more complex $^{31}$P NMR spectrum was observed when 6b was reacted with cis-$\{$(PPh$_3)_2$Pt$(\text{ONO}_2)$\}. In addition to the strong AB pattern at 7.73 ($\Delta_J = 3467$ Hz) and 8.01 ppm ($\Delta_J = 24.5$ Hz), attributed to the adduct cis-$\{$(PPh$_3)_2$Pt$\text{NH}$$\equiv$C(Ph)[9-MeAd(-2H)]) (8b), several weak signals in the range 4–16 ppm were also detected. However, addition of a “proton sponge” caused the immediate disappearance of all these signals, quantitatively replaced by those of the AB multiplet of cis-$\{$(PPh$_3)_2$Pt$(\text{OH})$\}(C(Ph)=[1-MeC$_2$(2H)]) (2b). We are currently trying to crystallize complexes 7b and 8b for a complete characterization in solution and in the solid state. It is interesting to note that the related species 2a.b together with the analogs 1a.b exhibit interesting cytotoxic properties toward several human tumour cell lines.35

Conclusions

The synthesis and structural characterization of the substituted amidines (Z)-N-(1-methyl-2-oxo-1,2-dihydropyrimidin-4-yl)benzimidamide (5b) and (Z)-N-(9-methyl-9H-purin-6-yl)benzimidamide (6b) and their nitrate salts 3b and 4b, are described. The compounds are formed by protonation with HCl of the metallacalix cycles cis-$\{$(PPh$_3)_2$Pt$\text{NH}$$\equiv$C(Ph)[nucleobase(-2H)])$, which are quantitatively obtained by formal insertion of a molecule of PhCN molecule into the Pt-N(4) or Pt–N(6) bond of a platinum–cytosine or adenine complex, respectively. The high affinity of the chloride ions toward the Pt(II) centre, with formation of cis-$\{$(PPh$_3)_2$PtCl$_2$), allows the quantitative recovery of the metal.

The planar structure of 3b in the solid state is stabilized by a strong H-bond between the NO$_3^\text{-}$ ion and the hydrogen atom on N(4) cytosine, whereas intermolecular H-bonds between the oxygen of the cytosine ring and one of the H atoms of the amidine-NH$_2$ group lead to the dimerization of the molecule. The analysis of the proton spectrum of 3b in DMF-d$_7$ shows the presence of an equilibrium between the monomer and the dimer, both exchanging with trace amounts of water, at room temperature.

In addition to MeCN and PhCN, the nucleophylic attack of the NH$_2$-deprotonated nucleobase occurs to the metal-activated nitriles MeCCN and Ph$_2$C(=CN)CN and the nitrato complexes cis-$\{$(PPh$_3)_2$Pt$(\text{NR}_2)$\}(C(Ph)=[nucleobase(-2H)])$\text{NO}_3$, isolated in high yield for the 1-methylcytosine derivative. The method of synthesis here reported for the benzimidamides 5a and 6b can therefore be applied for the preparation of new amidines of type RC(=NH)NHR where the NHR fragment is the model nucleobase 1-methylcytosine or 9-methyladenine.

Acknowledgements

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References


