Crystal structure of K[PtCl₃(caffeine)] and its interactions with important nitrogen-donor ligands

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ABSTRACT
The crystal structure of K[PtCl₃(caffeine)] was determined. The coordination geometry around platinum is square-planar formed by N9 of the caffeine ligand and three Cl⁻ ions. The bond lengths and angles of K[PtCl₃(caffeine)] were compared with those reported for [PtCl₃(caffeine)]⁻ and K[PtCl₃(theobromine)]. At the level of the statistical significance of the data we have compared, no differences in the bond distances and angles for any of these compounds were noticed. Weak interactions between K⁺ and Cl⁻ are responsible for the formation of 1-D polymeric chains in the crystal structure of the complex. The interactions of K[PtCl₃(caffeine)] with inosine (Ino) and guanosine-5′-monophosphate (5′-GMP) were studied by ¹H NMR spectroscopy at 295 K in D₂O in a molar ratio of 1 : 1. The results indicate formation of the reaction product [PtCl₃(Nu)] (Nu=Ino or 5′-GMP) with the release of caffeine from the coordination sphere of the starting complex. The higher stability of the bond between the Pt(II) ion and Ino or 5′-GMP compared to the stability of the platinum–caffeine bond is confirmed by density functional theory calculations (B3LYP/LANL2DZp) using as models 9-methylhypoxanthine and 9-methylguanine.
1. Introduction

Cisplatin was the first developed cytostatic drug based on a metal ion [1–3], and it is still the most used cytostatic worldwide in the treatment of different types of cancers [1–3]. Regardless of the success of cisplatin, cancer drug resistance continues to be a major impediment in medical oncology [1–6]. The need to develop new complexes with reduced side effects and higher activity has stimulated the synthesis of many new platinum complexes [7–10]. In addition to effective antitumor agents, attention was also focused on finding amplifiers which enhance the effects of known agents. While the mechanism of action of many antitumor agents is their inhibitory effect on DNA and protein biosynthesis, agents which increase DNA damage or inhibit the repair of the DNA damage induced by antitumor agents have much potential as amplifiers [11]. Caffeine (3,7-dihydro-1,3,7-trimethyl-1H-purine-2,6-dione) inhibits post-replication repair of both UV and chemically induced damage in DNA lesions caused by cisplatin [12]. Therefore, interest has continued in potential anticancer active analogs of cisplatin in combination with caffeine, forming platinum–caffeine complexes [13–16]. Thus, the structures of cis-[PtCl(caffeine) (PET$_3$)$_2$BF$_4$] and similar methyl-substituted derivatives of xanthine were known 30 years ago [17, 18]. Cramer and co-workers [19] reported that K[PtCl$_3$(caffeine)] exhibits anticancer activity against lymphocytic leukemia in mice and they also presented the crystal structure of the [MePh$_3$P][PtCl$_3$(caffeine)] complex. In addition, the complexes of other metals such as Ni(II), Cu(II), Zn(II), Cd(II) and Au(III) with caffeine were synthesized [20–24] and some complexes were confirmed with anticancer, antifungal, and antimicrobial activity [25]. Some antitumor agents that damage DNA of tumor cells also damage the DNA of normal cells via the same mechanism [26]. In the same way, drugs which enhance antitumor activity via their inhibition of DNA repair can enhance primary effects and side effects of antitumor agents. The published results indicate that caffeine in combination with adriamycin can enhance its antitumor activity toward a breast cancer cell line in mice, without influence on side effects; caffeine had no effect on the antitumor activity of cisplatin toward the same cancer cell lines [11].

K[PtCl$_3$(caffeine)] is unstable in water, where it is reduced to metallic platinum [15]. Also, this complex can be stabilized in the presence of some nucleosides such as guanosine (Guo) and inosine (Ino) forming [PtCl$_2$(caffeine)(Nu)] (Nu = Guo or Ino). Coordination of both nucleosides to the metal center occurred through N7 [15]. Independently, it was reported that reaction of K[PtCl$_3$(caffeine)] with Guo or 5′-GMP leads to partial or extensive reduction to metallic platinum [14].

We report here our studies on the interactions of K[PtCl$_3$(caffeine)] with Ino and 5′-GMP by $^1$H NMR spectroscopy. The crystal structure of the studied complex is reported as well and density functional calculations to rationalize the favored coordination of Ino and 5′-GMP to the metal center over the coordination of caffeine. The structures of the investigated complex and ligands are shown in figures 1 and 2, respectively.

2. Experimental

2.1. Materials

K$_2$PtCl$_4$ (Strem Chemicals), caffeine (Fisher Chemicals), guanosine-5′-monophosphate sodium salt (5′-GMP) (Acros Organics) and inosine (Ino) (Strem Chemicals) were used without purification. K[PtCl$_3$(caffeine)] was synthesized according to a published procedure [14]. The resulting orange-yellow powder was dissolved in a hot mixture of ethanol/water. By cooling the filtrate overnight in a refrigerator, orange crystals were obtained. The purity of the complex was checked by elemental microanalysis and $^1$H NMR spectroscopy. Yield (77.35 mg, 65%). Anal. Calcd. for K[PtCl$_3$(C$_8$H$_{10}$O$_2$N$_4$)] (%) (FW = 534.35): C, 17.97; H, 1.88; N, 10.48. Found: C, 17.97; H, 1.88; N, 10.48. $^1$H NMR characterization (D$_2$O, 200 MHz). $^1$H NMR (δ, ppm) 8.44 (s, H8), 4.06 (s, 7-CH$_3$), 3.36 (s, 1-CH$_3$), 3.68 (s, 3-CH$_3$) (figure S1).

Deuteriumoxide (99.9% Deutero GmbH) is commercially available and was used as received. All other chemicals were of the highest purity commercially available and used without purification.
2.2. Instrumental methods

Chemical analysis was performed on a Carlo Erba Elemental Analyzer 1106. $^1$H NMR spectra were acquired on a Varian Gemini 2000, 200 MHz NMR spectrometer at 295 K. The measurements were performed with a commercial 5-mm Bruker broadband probe. All chemical shifts are referenced to TSP (trimethylsilylpropionic acid).

2.3. X-ray crystallography

A single crystal of K[PtCl$_3$(caffeine)] was selected and mounted on a glass fiber. Diffraction data were collected using the Oxford Diffraction Gemini S four-circle goniometer equipped with a Sapphire CCD detector. The crystal to detector distance was 45.0 mm and graphite-monochromated MoKα ($\lambda = 0.7107$ Å) radiation was used. The data reductions were performed with CrysAlis PRO [27]. The space group determination was based on an analysis of the Laue class and the systematically absent reflections. Analytical numeric absorption correction using a multifaceted crystal model was applied [28], and the data were corrected for Lorentz, polarization, and background effects. Structure solution and refinement were carried out with SHeLXT and SHeLXL-2014/6, respectively [29]. ORTEP-3 for Windows [30] was employed for molecular graphics and the software used to prepare material for publication was WinGX [31]. Full-matrix least-squares refinement was carried out by minimizing $(F_o^2 - F_c^2)$. All nonhydrogen atoms were refined anisotropically and the refinement was carried out without geometric or ADP’s restraints. Hydrogens attached to carbon in methyl groups were placed in geometrically idealized positions and refined as riding on their parent atoms with $U_{iso}(H) = 1.5 U_{eq}(C)$. The position of hydrogens

![Figure 1. The structure of K[PtCl$_3$(caffeine)].](image1)

![Figure 2. The structures of ligands.](image2)
in the methine group was found from inspection of the different Fourier maps. K[PtCl3(caffeine)] had contributions from disordered solvent molecules which were removed by the SQUEEZE routine (PLATON) [32] and the output from the SQUEEZE calculations is attached to the CIF file.

2.4. 1H NMR measurements

1H NMR measurements of K[PtCl3(caffeine)] with 5′-GMP and Ino were studied at pD 5.45 (pD = pH + 0.45) [33] on a freshly prepared sample of the reactants. A 10 mmol L⁻¹ solution of the complex and the same concentration of the ligand solution were prepared separately in 300 μL of D2O, prior to the start of the experiment. No buffer was used to prevent increased activation of the complexes due to coordination of phosphate or interfering signals in the observed peak area.

2.5. Quantum chemical calculations

We performed B3LYP/LANL2DZp hybrid density functional calculations, i.e. with pseudo-potentials on the heavy elements and the valence basis set augmented with polarization functions [34, 35]. While optimizing the structures, no other constraints than symmetry were applied. The resulting structures were characterized as minima by computation of vibrational frequencies. The relative energies were corrected for zero-point vibrational energies (ZPE) throughout. The GAUSSIAN 09 suite of programs was used [36]. The influence of the bulk solvent was evaluated via single-point calculations using the CPCM formalism (as implemented in GAUSSIAN 09) for water as the solvent, i.e. B3LYP(CPCM)/LANL2DZp//B3LYP/LANL2DZp + ZPE(B3LYP/LANL2DZp), and additionally B3LYP(CPCM)/Def2-TZVP [37]// B3LYP/LANL2DZp + ZPE(B3LYP/ LANL2DZp) [38]. To probe the aromaticity in the investigated systems, we performed NICS calculations [39] at the B3LYP/Def2-TZVP level of theory.

| Table 1. Crystallographic data and refinement parameters. |
|---------------------------------------------------------|
| K[PtCl3(caffeine)]                                      |
| Chemical formula                                        |
| C16H20Cl6KNO4Pt2                                        |
| M                                                     |
| 1030.38                                                |
| Crystal system, space group                             |
| Monoclinic, C2/c                                        |
| Temperature (K)                                         |
| 293                                                    |
| a, b, c (Å)                                            |
| 22.0397(8), 13.9616(6), 10.3265(4)                      |
| β (°)                                                  |
| 92.129 (3)                                             |
| V (Å³)                                                 |
| 3175.4 (2)                                             |
| Z                                                      |
| 4                                                      |
| F(0 0 0)                                                |
| 1924                                                   |
| No. of reflections for cell measurement                 |
| 2440                                                   |
| θ range (°) for cell measurement                       |
| 3.5–28.4                                               |
| μ (mm⁻¹)                                               |
| 9.47                                                   |
| Crystal size (mm)                                      |
| 0.61×0.45×0.21                                         |
| Absorption correction                                  |
| Analytical                                             |
| Tₘᵣₑₜ, Tₘₐₓ                                       |
| 0.043, 0.163                                           |
| No. of measured, independent, and observed [I > 2σ(I)] |
| 5799, 2802, 2327                                        |
| Rₑᵣ, Rₑᵣ                                            |
| 0.029                                                  |
| Range of h, k, l                                       |
| h = −26→20, k = −16→16, l = −9→12                      |
| wR(F²), S                                              |
| 0.037, 0.091, 0.99                                     |
| No. of reflections                                     |
| 2802                                                   |
| No. of parameters                                      |
| 175                                                    |
| No. of restraints                                      |
| 0                                                      |
| H-atom treatment                                       |
| H atoms treated by a mixture of independent and constrained refinement |
| ρₑᵣₑᵣ, ρₑᵣₑᵣ (e Å⁻³)                                  |
| 3.08, −0.72                                            |
3. Results and discussion

3.1. Structure of K[PtCl₃(caffeine)]

Crystal data and experimental details of the structure determination are listed in table 1. The perspective view of the asymmetric unit of the crystal structure of K[PtCl₃(caffeine)] is shown in figure 3 and the crystal packing is depicted in figure 4.

Figure 3. ORTEP [30] drawing showing molecular structure of K[PtCl₃(caffeine)] with the non-H atom numbering scheme with thermal ellipsoids at 30% probability level.

Figure 4. MERCURY [40] drawing of the crystal packing of K[PtCl₃(caffeine)] showing infinite one-dimensional chains parallel to the c-axis. View direction is close to the b-axis.

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From a structural point of view, one must emphasize two features of the K\[PtCl₃(caffeine)\] complex, the coordination of the Pt₁ atom and the crystal packing. The Pt₁ atom has the usual square-planar coordination, formed here by one N and three Cl⁻ ions (figure 3). The main geometrical features of the PtNCl₃ group are reported in table 2. This group is slightly distorted, but is nevertheless almost perfectly planar since the maximum displacement from the weighted least-squares plane (N9/Cl3/Cl2/Cl1) is 0.027(6) Å for N9 and the angle between the plane through Cl2–Pt1–Cl1 and N9–Pt1–Cl3 atoms is 0.75(2)°. Displacement from the basal (N9/Cl3/Cl2/Cl1) plane for Pt1 is 0.0059(4) Å. Finally, as is always observed for Pt(II) complexes of purines, the imidazole plane is rotated by 80.4° away from the coordination plane. All other bonding parameters (table 2) fall in the range found in the literature [41].

We compared the bond lengths and angles of K[PtCl₃(caffeine)] with those reported for [PtCl₃(caffeine)]⁻ [19] and K[PtCl₃(theobromine)] [42] (table 2). At the level of the statistical significance of the data we have compared, there are no differences in the bond distances and angles for any of these compounds. However, there are some noticeable perturbations. In K[PtCl₃(theobromine)] [42], the internal ring angle at N1 (129.7(6)°) is larger than in the other structures. This could be attributable to the absence of a methyl substituent at this position. This difference (the absence of a methyl substituent at N1) contributes to other perturbations in bond distances and angles in K[PtCl₃(theobromine)] [42], but these effects are small and are at the margins of statistical significance. It was reported [42] that the shortest Pt–Cl bond is that \textit{trans} to the Pt–N bond which is not the case in K[PtCl₃(caffeine)].

The closest contacts of K₁ are 3.119(3) Å for both Cl₂ (x, y, z + 1) and Cl₂ (−x + 1, y, −z + 1/2) and the slightly larger value of 3.271(3) Å for Cl₁ (x, y, z + 1) and Cl₁ (−x + 1, y, −z + 1/2). These weak interactions are responsible for formation of 1-D polymeric chains parallel to the c-axis in the crystal structure of K[PtCl₃(caffeine)] (figure 4). We have not found classical hydrogen bonds in intra- or intermolecular space.

### 3.2. ¹H NMR measurements

In this paper, we studied the interactions of K[PtCl₃(caffeine)] with 5’-GMP and Ino at molar ratio 1 : 1 by ¹H NMR in D₂O.

The ¹H NMR spectrum of K[PtCl₃(caffeine)] (figure S1) showed a singlet at 8.44 ppm (H8) that describes the coordination of caffeine through N9 for platinum(II). Coordination of caffeine to the metal through N9 was reported earlier [14].

Addition of one equivalent of 5’-GMP to a solution of K[PtCl₃(caffeine)] (10 mmol L⁻¹) induces new signals in the ¹H NMR spectrum (figure S2). The singlet that is attributed to H8 of coordinated caffeine in K[PtCl₃(caffeine)] also occurs at δ = 8.44 ppm. At the same time, there is a signal at 7.93 ppm, from H8 of free caffeine [13].

It is well known that 5’-GMP can be coordinated to metal ions through N1 and N7, depending on the pH of the solution [43]. The coordination to the metal center here occurs via N7 (figure S2), because...
at pH 5.0, the N1 is protonated (pKₐ (N1) = 9.3, pKₐ (N7) = 2.48) [44]. Coordination through N7 can be followed based on the chemical shifts for H8 and H8' of 5'-GMP. H8 from free 5'-GMP appears as a singlet at 8.2 ppm, while the signal of H8 of coordinated 5'-GMP is at 8.3 ppm. Signals from H8' of free and coordinated 5'-GMP occur at 5.85 ppm and 6.08 ppm, respectively. This clearly indicates coordination of 5'-GMP to the metal center and at the same time the cleavage of the platinum-N9 (caffeine) bond with the release of caffeine from the coordination sphere of the complex.

**Figure 6.** Calculated (B3LYP/LANL2DZ) structures of the investigated platinum complexes.
Table 2. Selected geometrical parameters for K\([PtCl_3(caffeine)]\) in comparison with the same geometrical parameters of PtCl\(_3\)(caffeine)\(^{-}\) [19] and K\([PtCl_3(theobromine)]\) [42].

|                  | K\([PtCl_3(caffeine)]\) | [PtCl\(_3\)(caffeine)]\(^{-}\) [19] | K\([PtCl_3(theobromine)]\) [42] |
|------------------|--------------------------|--------------------------------------|----------------------------------|
| **Coordination sphere** |                          |                                      |                                  |
| Atoms            | Bond lengths (Å)         | Bond angles (°)                      |                                  |
| Pt1–N9           | 2.014(6)                 | 2.021(5)                            | 2.016(6)                         |
| Pt1–Cl3          | 2.290(2)                 | 2.301(2)                            | 2.303(2)                         |
| Pt1–Cl2          | 2.292(2)                 | 2.294(2)                            | 2.289(2)                         |
| Pt1–Cl1          | 2.293(2)                 | 2.308(2)                            | 2.299(2)                         |
| Atoms            |                          |                                     |                                  |
| N9–Pt1–Cl3       | 87.58(18)                | 89.1(1)                             | 89.7(2)                          |
| N9–Pt1–Cl2       | 177.89(17)               | 179.1(1)                            | 177.7(2)                         |
| Cl3–Pt1–Cl2      | 90.39(7)                 | 90.85(6)                            | 89.4(6)                          |
| N9–Pt1–Cl1       | 90.32(18)                | 89.1(1)                             | 89.7(2)                          |
| Cl3–Pt1–Cl1      | 177.83(8)                | 176.24(5)                           | 178.2(1)                         |
| Cl2–Pt1–Cl1      | 91.72(8)                 | 90.88(5)                            | 91.2(1)                          |
| **Caffeine**     |                          |                                      |                                  |
| Atoms            | Bond lengths (Å)         | Bond angles (°)                      |                                  |
| N1–C1            | 1.480(10)                | 1.467(7)                            |                                  |
| N1–C2            | 1.410(9)                 | 1.395(7)                            | 1.365(10)                        |
| N1–C6            | 1.377(8)                 | 1.403(7)                            | 1.391(10)                        |
| C2–N3            | 1.371(10)                | 1.392(7)                            | 1.386(9)                         |
| C2–O2            | 1.202(9)                 | 1.210(7)                            | 1.220(9)                         |
| N3–C4            | 1.376(8)                 | 1.371(6)                            | 1.396(10)                        |
| N3–C3            | 1.474(9)                 | 1.451(8)                            | 1.451(11)                        |
| C4–C5            | 1.354(10)                | 1.364(7)                            | 1.352(11)                        |
| C4–N9            | 1.371(9)                 | 1.379(7)                            | 1.351(9)                         |
| C5–N7            | 1.386(9)                 | 1.381(6)                            | 1.376(9)                         |
| C5–C6            | 1.426(10)                | 1.422(7)                            | 1.425(10)                        |
| C6–O6            | 1.216(8)                 | 1.227(7)                            | 1.216(10)                        |
| N7–C8            | 1.322(9)                 | 1.335(7)                            | 1.327(10)                        |
| N7–C7            | 1.475(8)                 | 1.453(7)                            | 1.462(10)                        |
| C8–N9            | 1.332(8)                 | 1.349(7)                            | 1.355(10)                        |
| Atoms            |                          |                                     |                                  |
| C6–N1–C2         | 126.4(6)                 | 126.9(4)                            | 129.7(6)                         |
| C2–N1–C1         | 115.7(6)                 | 115.8(4)                            |                                  |
| C6–N1–C1         | 117.8(6)                 | 117.4(4)                            |                                  |
| O2–C2–N1         | 120.4(7)                 | 121.2(5)                            | 121.8(7)                         |
| N3–C2–N1         | 117.4(6)                 | 117.6(5)                            | 116.3(6)                         |
| C2–N3–C4         | 119.1(6)                 | 118.6(5)                            | 119.0(6)                         |
| C4–N3–C3         | 122.8(7)                 | 124.7(5)                            | 121.6(6)                         |
| C5–C4–N9         | 110.5(6)                 | 109.7(4)                            | 111.0(7)                         |
| N9–C4–N3         | 127.9(7)                 | 128.3(5)                            | 128.3(7)                         |
| C4–C5–N7         | 105.3(6)                 | 106.6(4)                            | 106.0(6)                         |
| C4–C5–C6         | 123.3(7)                 | 123.8(5)                            | 124.6(7)                         |
| N7–C5–C6         | 131.3(6)                 | 129.5(5)                            | 129.3(7)                         |
| N1–C6–C5         | 112.0(6)                 | 111.1(5)                            | 109.6(7)                         |
| C8–N7–C5         | 107.5(6)                 | 107.0(4)                            | 106.9(6)                         |
| N7–C8–N9         | 112.0(6)                 | 110.0(5)                            | 111.7(7)                         |
| C8–N9–C4         | 104.8(6)                 | 104.7(4)                            | 104.3(6)                         |
| O2–C2–N3         | 122.1(7)                 | 121.2(5)                            | 121.9(7)                         |
| O6–C6–N1         | 122.1(7)                 | 126.6(5)                            | 121.7(7)                         |
| C8–N7–C7         | 125.8(6)                 | 125.3(4)                            | 125.9(7)                         |
| C2–N3–C3         | 117.7(6)                 | 116.7(5)                            | 119.5(6)                         |
| C4–N3–C3         | 122.8(7)                 | 124.7(5)                            | 121.6(6)                         |
| O6–C6–C5         | 125.9(7)                 | 126.6(5)                            | 128.6(7)                         |
| **K[PtCl\(_3\)(caffeine)] complex** |                          |                                      |                                  |
| Atoms            | Bond lengths (Å)         | Bond angles (°)                      |                                  |
| K1–O2            | 2.709(6)                 | O2–K1–O2                            | 140.8(3)                         |
| K1–O2\(^i\)      | 2.709(6)                 | O2–K1–Cl2\(^i\)                    | 76.24(15)                        |
|                  |                          | O2–K1–Cl2\(^ii\)                   | 74.54(15)                        |
|                  |                          | O2–K1–Cl1\(^i\)                    | 92.21(14)                        |
|                  |                          | O2–K1–Cl1\(^ii\)                   | 96.47(14)                        |

(Continued)
To gain deeper insight, we investigated the reaction of K\([\text{PtCl}_3(\text{caffeine})]\) (10 mmol L\(^{-1}\)) by adding one equivalent of Ino and the obtained spectrum is presented in figure S3. Two signals from H8 of caffeine can be seen, at 8.44 ppm from the metal coordinated caffeine and at 7.93 ppm from free caffeine. Coordination of Ino to platinum(II) ion occurs through its N7, which is confirmed by the downfield shift of H8 protons from 8.15 ppm to 8.3 ppm, for free and coordinated ligand, respectively. The coordination of Ino to the platinum center requires cleavage of the platinum-N9 (caffeine) bond.

The mechanism of the substitution reactions between the investigated complex K\([\text{PtCl}_3(\text{caffeine})]\) and the ligands 5′-GMP and Ino can be represented by scheme 1. The assignments of the selected resonance of the products are reported in table S1.

### 3.3. DFT calculations

To understand and rationalize the behavior in the substitution reactions, we performed quantum chemical calculations on \([\text{PtCl}_3(\text{caffeine})]\)^− and modeled Ino by 9-methylhypoxanthine and 5′-GMP by 9-methylguanine. The structures of 9-methylhypoxanthine and 9-methylguanine are shown in figure 5.

These model compounds are well established in bio-inorganic and complex chemistry [45]. To understand the preferred coordination to the PtCl3\(^−\)fragment, the following two model reactions were applied (scheme 2):

Without consideration of solvent effects, the coordination of caffeine to PtCl3\(^−\) seems to be favorable compared to coordination of 9-methylhypoxanthine and 9-methylguanine (see tables 3 and 4). This clearly can be understood as an artifact of missing solvent influences best described as gas phase, as the negative charge of PtCl3\(^−\) can be better stabilized by a larger ligand than by a smaller one. To overcome this artificial effect, we applied the CPCM solvent model as implemented in Gaussian 09. This crude approximation of water as a solvent gives extra stabilization to [PtCl3(9-methylhypoxanthine)]^− and [PtCl3(9-methylguanine)]^− and disfavors significantly [PtCl3(caffeine)]^−, independently of whether a smaller or bigger basis set is applied.

The stronger interaction between PtCl3\(^−\) and 9-methylhypoxanthine and 9-methylguanine compared to caffeine is also visible in the molecular structure, as the bond length between Pt and the coordinating N-atom in caffeine is elongated by 0.02 Å to 2.07 Å compared to 2.05 Å in [PtCl3(9-methylhypoxanthine)]^− and [PtCl3(9-methylguanine)]^− (see table 5 and figure 6).

While dealing with heterocycles, the question about influences of the aromaticity exists. A convenient tool for probing the aromaticity in all kinds of systems was developed 20 years ago by the team of Paul von Ragué Schleyer in Erlangen. Nucleus-independent chemical shift calculations, called NICS-calculations, have been developed to a widely used tool. Comparing uncoordinated and coordinated 9-methylhypoxanthine, 9-methylguanine and caffeine shows clearly no significant differences besides some polarization effects, as typical for coordinated heteroaromatics [46]. Additionally, the NICS-values of the investigated bio-related ligands show no significant differences between the aromaticity of the

\[
[\text{PtCl}_3(X)] + \text{Nu} \rightarrow [\text{PtCl}_3(\text{Nu})] + X
\]

\[
X = \text{caffeine}; \ \text{Nu} = 5′-\text{GMP}, \ \text{Ino}
\]

**Scheme 1.**
individual rings. In total, this is not surprising and easy to understand as aromaticity is a \( \pi \)-effect, while the coordination to the PtCl\(_3^-\)-fragment occurs via a perpendicular lone pair.

To learn about the electron density of a particular donor in a ligand, the gas phase proton affinity (PA) has proven to be a valuable and accessible number as a descriptor for basicity. The gas phase PA is calculated according to the well-established concept of equation (1) [47] (see table 6):

\[
\text{Base} + \text{H}^+ \longrightarrow \text{H} \cdot \text{Base}
\]  

(1)

Considering these calculated data, the coordinating N-atom in caffeine is much less proton affinitive and therefore basic, and does not coordinate as strongly to the transition metal ion as the 10–15 kcal mol\(^{-1}\) more proton affinitive 9-methylhypoxanthine or 9-methylguanine. As the five-membered rings in all three ligands are identical, the origin of the different bond strength has to be in the six-membered heterocycle, which in 9-methylhypoxanthine and 9-methylguanine are nearly identical, but is significantly different in caffeine. Caffeine’s six-membered ring contains two amide-like groups O=C–N(CH\(_3\)), including four electronegative atoms, the equivalent rings in 9-methylhypoxanthine and

\[
\text{[PtCl}_3\text{(X)}]^- + 9\text{-methylhypoxanthine} \longrightarrow \text{[PtCl}_3(9\text{-methylhypoxanthine})]^- + \text{X}
\]

\[
\text{[PtCl}_3\text{(X)}]^- + 9\text{-methylguanine} \longrightarrow \text{[PtCl}_3(9\text{-methylguanine})]^- + \text{X}
\]

\( \text{X} = \text{caffeine} \)

\[\text{Scheme 2.}\]

\[\text{Table 3. Calculated energies for exchange between caffeine and 9-methylhypoxanthine.}\]

| Method | \(\text{E}^{\text{B3LYP/LANLDZP} + \text{ZPE(B3LYP/LANLDZP)}}\) | \(\text{E}^{\text{B3LYP(CPCM/LANLDZP)//B3LYP/LANLDZP + PE(B3LYP/LANLDZP)}}\) | \(\text{E}^{\text{B3LYP(CPCM)/def2-TZVP//B3LYP/LANLDZP} + \text{ZPE(B3LYP/LANLDZP)}}\) |
|--------|----------------------------------|----------------------------------|----------------------------------|
|        | + 8.6 kcal mol\(^{-1}\)         | −2.0 kcal mol\(^{-1}\)          | −3.7 kcal mol\(^{-1}\)          |

\[\text{Table 4. Calculated energies for the exchange between caffeine and 9-methylguanine.}\]

| Method | \(\text{E}^{\text{B3LYP/LANLDZP} + \text{ZPE(B3LYP/LANLDZP)}}\) | \(\text{E}^{\text{B3LYP(CPCM/LANLDZP)//B3LYP/LANLDZP} + \text{ZPE(B3LYP/LANLDZP)}}\) | \(\text{E}^{\text{B3LYP(CPCM)/def2-TZVP//B3LYP/LANLDZP} + \text{ZPE(B3LYP/LANLDZP)}}\) |
|--------|----------------------------------|----------------------------------|----------------------------------|
|        | +10.1 kcal mol\(^{-1}\)         | −2.7 kcal mol\(^{-1}\)          | −1.3 kcal mol\(^{-1}\)          |

\[\text{Table 5. Calculated (B3LYP(CPCM)/def2-TZVP//B3LYP/LANLDZP) N–Pt bond distances.}\]

|                  | \(\text{N-Pt} [\text{Å}]\) | \(\text{NICS(0)}\) | \(\text{NICS(1)}\) | \(\text{NICS(0)}\) | \(\text{NICS(1)}\) |
|------------------|--------------------------|-----------------|-----------------|-----------------|-----------------|
| \(\text{Caffeine}\) | –                        | −11.2           | −9.0            | −2.9            | −2.8            |
| \(\text{[PtCl}_3\text{(caffeine)}^-\) | 2.07                      | −11.6           | −8.8            | −2.8            | −2.8            |
| \(\text{9-Methylhypoxanthine}\) | –                        | −11.8           | −9.7            | −4.0            | −5.1            |
| \(\text{[PtCl}_3(9\text{-methylhypoxanthine})^-\) | 2.05                      | −11.8           | −9.4            | −3.9            | −5.2            |
| \(\text{9-Methylguanine}\) | –                        | −11.1           | −9.2            | −2.9            | −3.4            |
| \(\text{[PtCl}_3(9\text{-methylguanine})^-\) | 2.05                      | −11.2           | −8.8            | −3.6            | −4.0            |

\[\text{Table 6. Calculated (B3LYP/6–311 + G**) gas phase PA [48].}\]

|                 | \(\text{Calculated gas phase proton affinity (kcal mol}^{-1}\) | \(\text{)}\) |
|-----------------|---------------------------------------------------------------|---------------|
| \(\text{Caffeine}\) | −216.7                                                        |               |
| \(\text{9-Methylhypoxanthine}\) | −224.7                                                        |               |
| \(\text{9-Methylguanine}\) | −232.1                                                        |               |
9-methylguanine have only one O=C-N(CH3) neighboring the coordinating five-membered ring nitrogen and an imine like C=N– in the six-membered ring. Therefore, the six-membered ring in caffeine will be more strongly electron withdrawing from the σ-system of the imidazole ring than in the case of the 9-methylhypoxanthine and 9-methylguanine model compounds.

4. Conclusion

In this paper, the X-ray crystal structure of the K[PtCl3(caffeine)] complex was determined. The square-planar Pt(II) ion is bound to N9 of the caffeine ligand, while the other three positions are occupied by Cl−. 1H NMR data also indicate monodentate coordination of caffeine to the metal center through N9. Comparing the structural features of K[PtCl3(caffeine)] with previously published [PtCl3(caffeine)]− and K[PtCl3(theobromine)], it can be seen that there are no differences in the bond distances and angles. The interactions of K[PtCl3(caffeine)] with an equimolar amount of Ino or 5′-GMP lead to formation of final reaction products [PtCl3(Nu)] (Nu = Ino or 5′-GMP). Cleavage of the platinum-N9 (caffeine) bond was confirmed, releasing caffeine from the coordination sphere of the complex. The higher stability of the bond between platinum(II) and Ino or 5′-GMP as compared to the stability of the platinum–caffeine bond is confirmed by DFT calculations using 9-methylhypoxanthine and 9-methylguanine as model.

The obtained results could contribute to a better understanding of the interactions of platinum complexes containing caffeine with biologically important nucleophiles, such as constituents of DNA, peptides, and proteins.

Supplementary material

Crystallographic data are deposited at the Cambridge Crystallographic Data Center as supplementary material number CCDC 1422222. Copies of this information may be obtained free of charge from the Director, CCDC, 12 Union Road, Cambridge, CB21FZ, UK (E-mail: deposit@ccdc.cam.ac.uk or www: http://www.ccdc.cam.ac.uk).

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Disclosure statement

No potential conflict of interest was reported by the authors.

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