Molecular Recognition of an Adenine Derivative by Organoplatinum(II) Complexes with Hydrogen-Bonding Functionality

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Dedicated to Prof. R. J. Puddephatt, FRS, on the occasion of his 75th birthday and in recognition of his many outstanding contributions to organometallic chemistry.

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Abstract

The first examples of adenine binding by isomeric organoplatinum(II) complexes bearing H-bonding nicotinic and isonicotinic acid ligands are reported. Notably, a subtle switching of the H-bonding functionality from the 3- to 4-position of the pyridyl ring leads to a significant change in both the strength of association and the site of adenine binding.

Keywords

Platinum; nucleobase; molecular recognition; carboxylic acid; H-bonding.

1. Introduction

There is great interest in the study of synthetic receptors for the selective binding of nucleobases [1, 2], particularly derivatives of adenine, owing to their many important functional roles in biological systems, e.g. intracellular energy transfer, signal transduction and nucleic acid synthesis. The interest of these systems is aimed at better understanding the intermolecular interactions that are involved in these diverse molecular bio-recognition processes, and to provide tools to aid in the design of efficient tailor-made probes and drugs that could be potentially applied in number of theranostic applications [3, 4]. Hydrogen bonding interactions are a major driving force in the formation of numerous supramolecular structures involving nucleobases with a variety of structural geometries [5]. Indeed, natural and artificial host-guest complexes as well as many nucleic acid structural elements are a direct result of specific, highly-directional intermolecular hydrogen bonding interactions [5, 6]. Various modes of hydrogen-bonding recognition have been shown to occur between nucleobases and simple carboxylic acids. For example, it has been demonstrated that many aromatic carboxylic acids preferentially bind Hoogsteen (HG) sites whereas aliphatic carboxylic acids bind preferentially at the Watson-Crick (WC) site [7, 8]. In addition to hydrogen-bonding, π-stacking is usually found to augment the interaction involving aromatic hosts and nucleobase guests, and both macrocyclic and non-macrocyclic molecular receptors containing hydrogen-bonding and/or π-stacking binding domains have been reported [9-22], all of which have the capacity to target nucleobases such as adenine and its derivatives. Theoretical studies have also complemented this work [14, 15].

Macrocyclic nucleobase receptors can discriminate their guest molecule by attributes such as size, electronic properties, nature of the hydrogen-bonding groups and the π-stacking surface area [9, 10, 16, 23]. In contrast, non-macrocyclic "molecular tweezers" possess two binding

sites with convergent functionality which are linked together by a spacer unit [9, 11-13, 17, 19-22]. Molecular tweezers usually possess one or more hydrogen-bonding functionalities such as carboxylic acids or amides and, in some cases, converging aromatic surfaces that have the capacity to undergo π-stacking interactions. Organometallic complexes in which direct coordination of adenine to the metal centre is augmented by H-bonding and π-stacking interactions are also known [24, 25], but to the best of our knowledge there exist no examples in these systems whereby metal coordination does not play a key role in the recognition motif.

We have previously reported the preparation, pK_a data and X-ray structures of mononuclear σ-phenylplatinum(II) complexes bearing carboxylic acid functionalities [26, 27]. Herein we report an example of the recognition of 9-*sec*-pentyladenine (9-PA) by two isomeric σ-phenylplatinum(II) complexes of the type *trans*-[Pt(σ-C_6H_5)($PMePh_2$)$_2$L]OTf (L = isonicotinic **1** or nicotinic acid **2**) bearing a single carboxylic acid functionality. We have found that the binding modes and association constants (K_{assoc}) for the binding of 9-PA by the complexes differ quite considerably in $CDCl_3$ solution.

2. Results and Discussion

The synthesis of complexes **1** and **2** has been previously reported by our group [26]. In the ^{1}H NMR spectrum of free 9-PA in $CDCl_3$ solution, the two resonances observed at δ 8.37 and δ 7.80 are assigned to H-2 and H-8, respectively. In the presence of **1**, for example, the former signal was found move slightly upfield (ΔδH-2 = 0.02 [28]) whilst the latter shifted significantly downfield (ΔδH-8 = 0.10) consistent with a strong association between the nearby N-7 atom and the platinum(II) complex [7, 8]. Furthermore, the exocyclic NH_2 signal was shifted downfield by 0.58 ppm indicating that, as observed with N-7, it is directly involved in the binding to the receptor molecule. The significant shifts associated with both the H-8 and

NH_2 signals in the presence of 9-PA are consistent with **1** binding to the H-8 (HG) site of the nucleobase. A Job titration of 9- PA and **1** was conducted at 298 K by maintaining the total molar concentration of both solutes constant in $CDCl_3$ solution [29]. Due to the water sensitivity of NH_2 signal, the chemical shift of H-8 was recorded and then plotted against the mole fraction (Figure 1). The maximum appears at a mole fraction of 0.5 which is consistent with the platinum(II) complex binding to 9-*sec*-pentyladenine in a 1:1 stoichiometry; no other binding modes or aggregation stoichiometries were observed at concentrations up to 30 mM whereby complete saturation was observed. By means of a Scatchard analysis (Figure 2) [30], the value of K_{assoc} for **1**.9-PA was calculated to be 25 ± 4 M^{-1} (at 12 mM).

For the isomeric complex **2**, the carboxylic acid functionality is located at the 4- rather than 3-position. The stoichiometry of binding remains 1:1 (Figure 3). However, a dramatic switch is observed in the binding mode where the WC site of 9-PA is favoured. From the Scatchard plot (Figure 4), the value of K_{assoc} is calculated to be approximately two orders of magnitude higher (2200 ± 330 M^{-1}) than the isomeric **1** at 4.4 mM; the lower solubility of complex **2** relative to its isomer **1** in $CDCl_3$ solution precluded an assessment of K_{assoc} at 12 mM. In the ^{1}H NMR spectrum of complex **2** in $CDCl_3$ solution, the considerable upfield shift of the H-2 proton is consistent with binding through the WC site. Preliminary molecular modelling experiments using DFT (B3LYP hybrid functional using the 6-311G** basis set) show that there are no steric issues which would account for the significant differences in K_{assoc} for the two complexes and thus electronic factors are more likely to dominate. Maitra and co-workers have reported that aromatic carboxylic acids favour Hoogsteen binding, while aliphatic carboxylic acids prefer WC binding [7]. This appears to hold true for **1** but not for **2**. The pK_a values of **1** and **2** (3.51 ± 0.08 and 4.85 ± 0.10, respectively, in 1:1 H_2O/EtOH solution at 295 K [26]) are significantly different and may in part account for the observed differences in K_{assoc}. Indeed,

in a low-polarity solvent such as $CDCl_3$, protonation of the most basic sites in adenine, e.g. N-7, by **1** would result in a strong ion-pair association with the triflate ion and molecular recognition of the guest molecule may be greatly inhibited leading to a significant lower K_{assoc} value. This trend appears to agree with literature whereby an increase in K is associated with a higher pK_a of the carboxylic acid [7]. Alternatively, the triflate ion may strongly bind to the carboxylic acid functionality of the organoplatinum(II) complex prior to binding to the adenine derivative, as previously seen in the solid state for *trans*-[Pt(σ-C_6H_5)(PEt_3)$_2$L]OTf (L = isonicotinic acid) by means of X-ray diffraction [26], however, the high K_{assoc} value observed for the less Brønsted acidic **2** is inconsistent with this proposal. Finally, self-association of complex **1** to form strong, H-bonded dimers has been reported previously [26] and this competing equilibrium might account for the significantly lower K_{assoc} of **1**.9-PA compared to that of **2**.9-PA but the site selectivity is not as readily explained.

$^{19}F\{^1H\}$ NMR experiments were conducted for both complexes **1** and **2** with and without the presence of 9-PA. The chemical shift differences observed between the free complex and the 9-PA adduct were not significant (< 0.05 ppm) however, any conclusions in this case should be made with care as hydrogen-bonding interactions may not lead to any significant differences owing to the distal nature of the CF_3 group relative to the recognition site. Furthermore, the use of other counter-ions (e.g. *para*-tolylsulfonate) instead of triflate did not lead to any observable differences in K_{assoc} for the two adducts.

3. Conclusion

Complexes **1** and **2** are the first examples of organometallic H-bonding receptors which do not require metal coordination for nucleobase recognition. Despite the subtle switching of the carboxylic acid functionality from the 3- to 4-position of the substituted pyridyl ligand in the

two isomers, remarkable differences were observed in the binding of an adenine derivative not only in terms of the strength of association but also the site of binding. We are currently exploring other organoplatinum(II) derivatives possessing H-bonding functionality for the selective recognition of nucleobases, including amide derivatives and dinuclear "tweezer" species, and the results of this work will be reported in due course.

4. Experimental Section

All NMR spectra were recorded at room temperature on a Varian Gemini 2000 NMR spectrometer with an Oxford 300 MHz magnet. ^{1}H NMR chemical shifts were reported in ppm relative to tetramethylsilane (TMS).

Complexes **1** and **2** were prepared as previously described [26].

4.1 Preparation of NMR samples for Job plots and Scatchard analyses

Job's method was carried out by mixing aliquots of two equimolar stock solutions of the two species to be observed in dry $CDCl_3$, i.e. **1** or **2** and 9-PA. This was done to keep the total concentration of the two components constant, while the ratio of the two components varies in the NMR solution [29]. Stock solutions of the desired concentrations of complex **1** or **2** and 9-sec-pentyladenine were made in volumetric flasks in dry $CDCl_3$. In NMR tubes, aliquots of each solution were added such that the stoichiometry of each component varied, but the total volume of solution remained at 500 μL. The ^{1}H NMR spectrum was obtained for each sample, and the chemical shift of the H-2, H-8 or NH_2 signals were determined. This value was then plotted against the mole fraction of the platinum(II) complex using Microsoft Excel 2016. A Scatchard analysis was also performed in order to determine K_{assoc} [30].

4.2 Determination of pK_a values

The pK_a determinations for **1** and **2** were carried out by making up a stock solution of the complex **1** or **2** in 50% ethanol/H_2O solution. The solution was then titrated with KOH in 50% ethanol/H_2O solution. The pH was measured using a glass electrode with 0.1 M silver-silver chloride electrode at 298 K. The electrode was first calibrated with a buffer solution (pH 4.0) [31].

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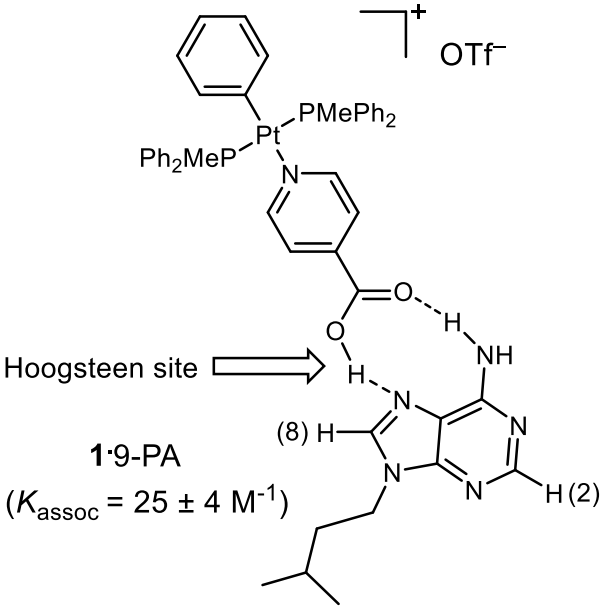
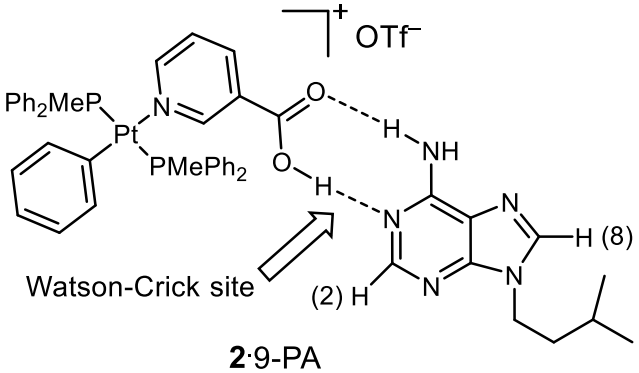
Conflicts of Interest

There are no conflicts of interest to declare.



1·9-PA

(K_{assoc} = 25 ± 4 M^{-1})



2·9-PA

(K_{assoc} = 2200 ± 330 M^{-1})

Figure 1.

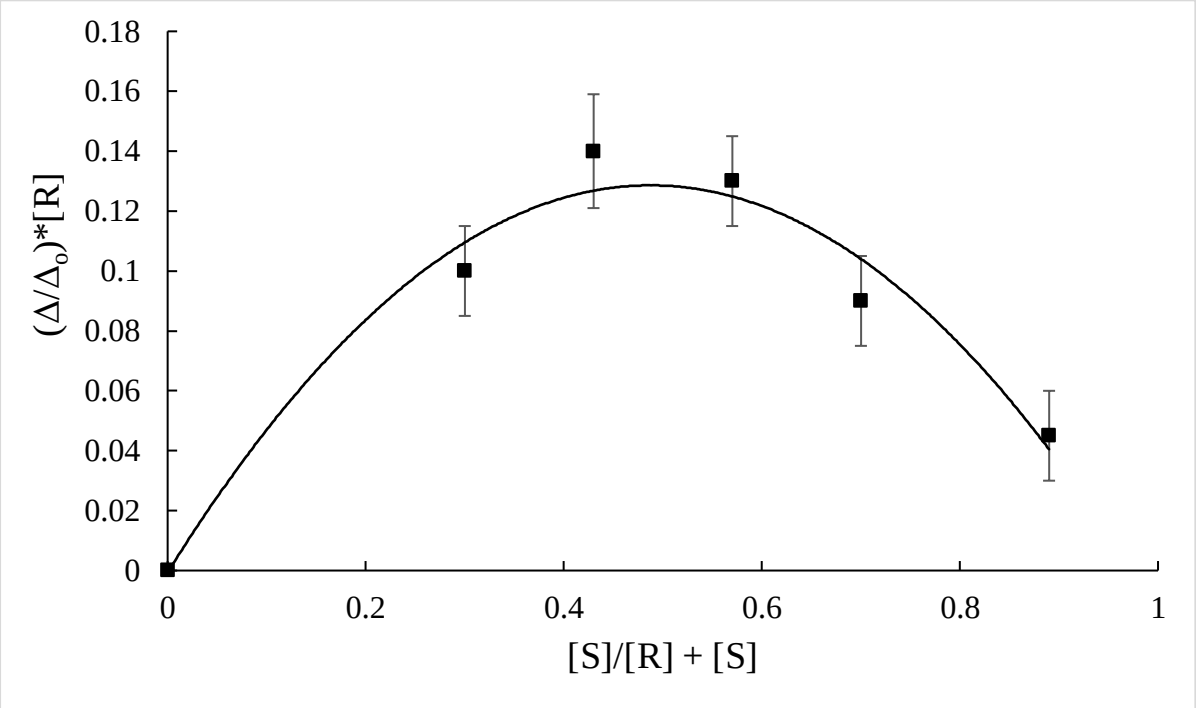


Figure 1. Job plot for **1** and 9-PA in $CDCl_3$ solution at 298 K (R = receptor (**1**), S = substrate (9-PA), $\Delta = \delta_R - \delta_{free}$ and $\Delta_o = \delta_R - \delta_{RS}$).

Figure 2.

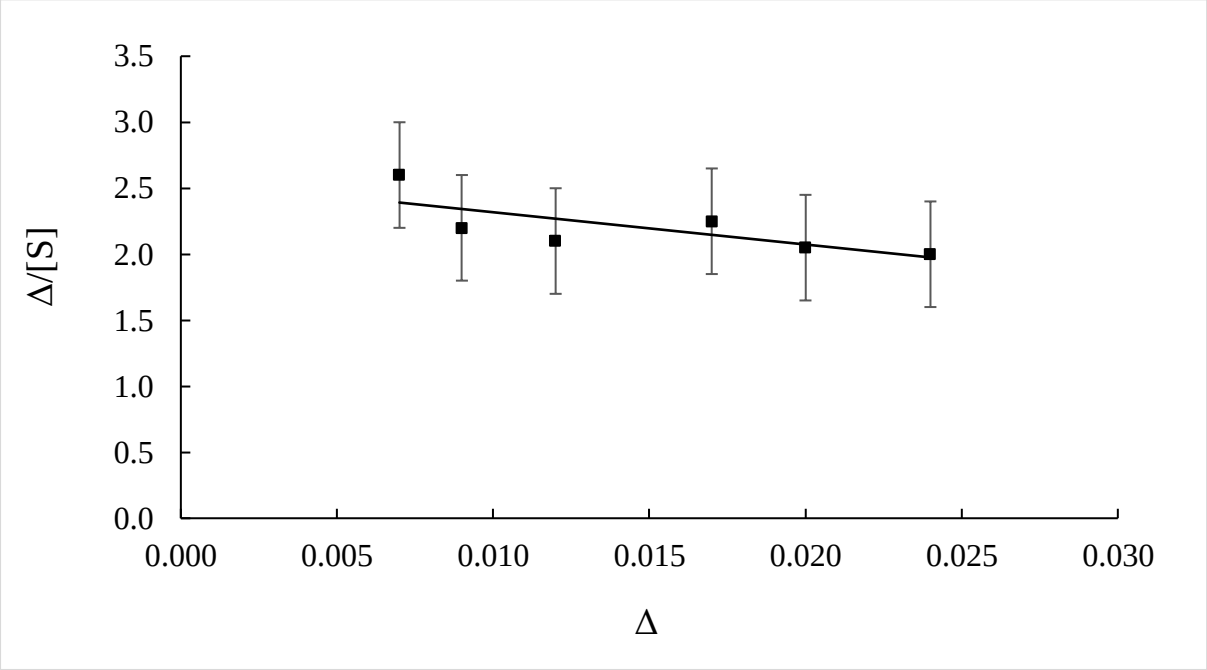


Figure 2. Scatchard plot for **1** and 9-PA in $CDCl_3$ solution at 298 K (R = receptor (**1**), S = *unbound* substrate (9-PA) = $[S_0] – (\Delta/\Delta_0)[R_0]$, where $S_0 = [S] + [RS]$, $R_0 = [R] + [RS]$, $\Delta = \delta_{obs} – \delta_{free}$ and $\Delta_o = \delta_{obs} – \delta_{RS}$).

Figure 3.

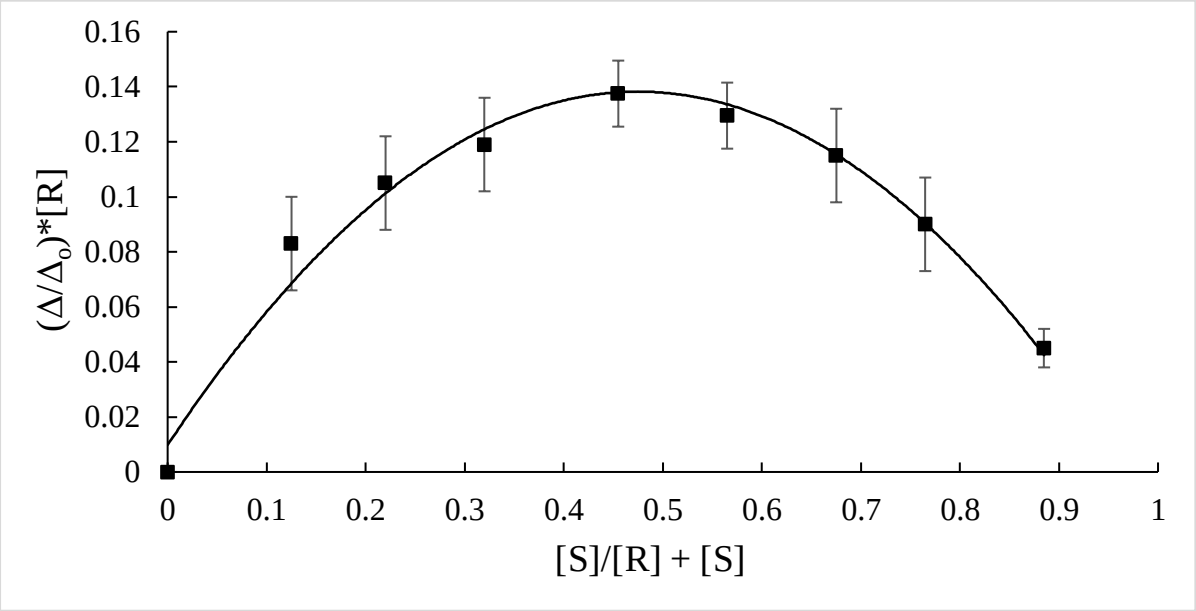


Figure 3. Job plot for **2** and 9-PA in $CDCl_3$ solution at 298 K (R = receptor (**2**), S = substrate (9-PA), $\Delta = \delta_R - \delta_{free}$ and $\Delta_o = \delta_R - \delta_{RS}$).

Figure 4.

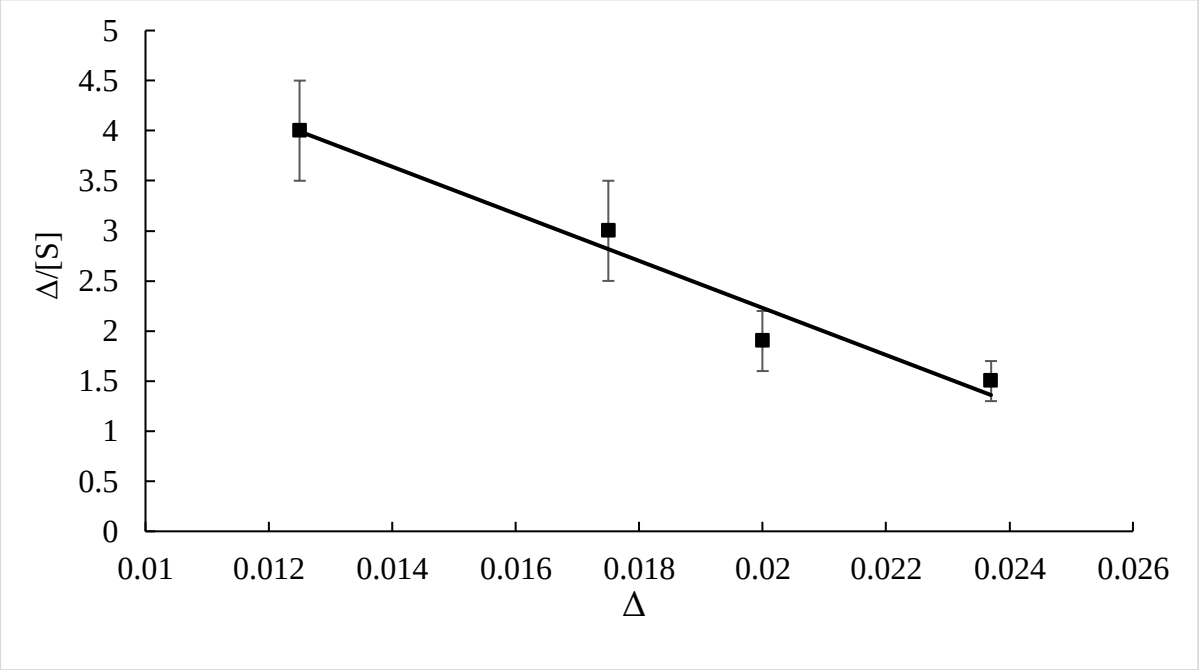


Figure 4. Scatchard plot for **2** and 9-PA in $CDCl_3$ solution at 298 K (R = receptor (**2**), S = *unbound* substrate (9-PA) = $[S_0] – (\Delta/\Delta_0)[R_0]$, where $S_0 = [S] + [RS]$, $R_0 = [R] + [RS]$, $\Delta = \delta_{obs} – \delta_{free}$ and $\Delta_o = \delta_{obs} – \delta_{RS}$).

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