Influence of the bridging ligand on the substitution behaviour of dinuclear Pt(II) complexes. An experimental and theoretical approach†

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A series of dinuclear Pt(II) complexes of the type [Pt_2(*N*,*N*,*N*′,*N*′-tetrakis(2-pyridylmethyl)-diamine(H_2O)$_2$]$^{4+}$ were synthesized. Acid–base titrations, and concentration and temperature dependent stopped-flow measurements of the reaction with chloride were performed to study the thermodynamic and kinetic behaviour of the dinuclear bridged complexes. The results indicate that there is a clear interaction between the two Pt(II) centres, which becomes weaker as the aliphatic chain increases in length. From a certain chain length onwards, the Pt(II) centres become independent of each other and exhibit identical thermodynamic and kinetic properties. The experimental results are discussed in reference to structures obtained by DFT (BP86/LACVP*) calculations.

Introduction

Since Rosenberg and co-workers[1] discovered the anti-tumour activity of *cis*-diamminedichloroplatinum(II) (cisplatin), it has been established as the leading compound for the treatment of different types of cancer.[2] Notwithstanding the success story of cisplatin, there are a number of problems that need to be considered during the treatment of cancer with cisplatin. For instance, there are numerous side effects such as nephrotoxicity, neurotoxicity and emetogenesis that need to be taken into account, the anti-tumour activity is limited to certain types of cancer, and some tumours develop a resistance against cisplatin during the therapy.[3] As a result of these negative properties, research in recent years has focused more on non-classical platinum complexes such as multinuclear species and their anti-tumour activity, even if there is still much effort put into improving the properties of mononuclear complexes.[4–7] These dinuclear complexes consist of either two or three platinum centres that are linked through a flexible bridge such as an aliphatic chain,[8] or a rigid bridge that consists for instance of azole molecules.[9] The reason for the increasing interest in multinuclear complexes is their ability to form DNA adducts that differ significantly from those formed by cisplatin and related complexes,[10] which results in a completely different anti-tumour behaviour.

Clinical tests have already been performed on multinuclear platinum complexes synthesized by Farrell *et al.*[11] The platinum centres of these complexes are bridged by an aliphatic chain and coordinated by primary amines. They are therefore in agreement with the structure–activity relationship that requires at least one NH moiety within the ligand.[12,13] However, it has recently been shown that these complexes react with sulfur containing nucleophiles, which leads to the release of the bridging ligand and loss of cytotoxicity.[14] On the basis of these observations, we expect that our complexes in which the platinum centres are coordinated by a tridentate ligand should show a higher stability against the *trans* influence of strong donor ligands. Furthermore, the selected chelate in this study coordinates *via* tertiary amines and forms a planar and aromatic moiety with the pyridine rings. Even if these features violate the structure–activity relationship, there are several cytostatic active substances known where the platinum centre is coordinated by tertiary amines.[12,15–18] Furthermore, we expect that the selected, sterically non-demanding picolylamine unit enables an unhindered interaction of the complex with DNA, which should lead to significant cytostatic activity (see Fig. 1). This work is a continuation of an earlier study from our group on

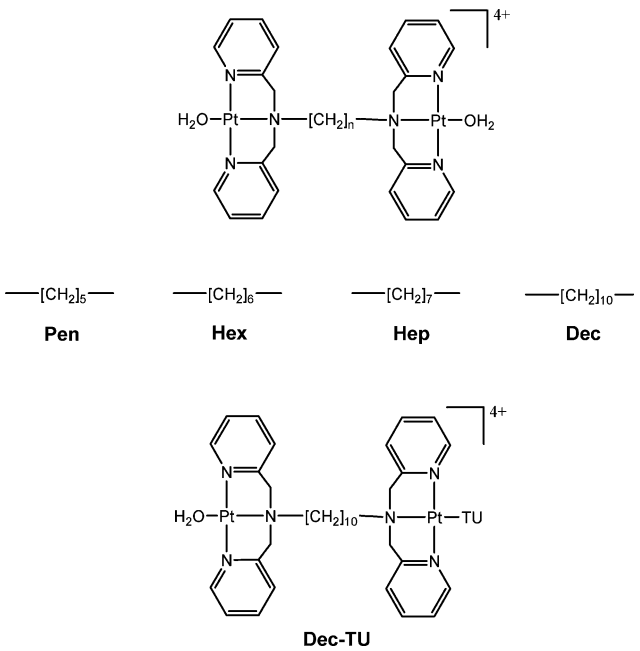

Fig. 1 Schematic structures and abbreviations used for the investigated complexes.

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propane and butane bridged platinum complexes,[19] and is intended to resolve the thermodynamic and kinetic properties of the complexes as a function of the chain length of the bridging ligand. We are particularly interested to know which chain length is required for the two platinum centres to behave thermodynamically and kinetically independent from each other. For this reason we performed pK_a titrations and nucleophilic substitution reactions with the synthesized complexes. It is easier to distinguish between two platinum centres with different reactivity toward nucleophiles if the overall charge of the complex changes during the reaction. Therefore, we selected chloride as the entering nucleophile. The experimental work is supported by quantum chemical calculations that allow distance correlations to be made.

Experimental

Preparation of the ligands *N*,*N*,*N*′,*N*′-tetrakis(2-pyridylmethyl)-1,5-pentanediamine (1), *N*,*N*,*N*′,*N*′-tetrakis(2-pyridylmethyl)-1,6-hexanediamine (2), *N*,*N*,*N*′,*N*′-tetrakis(2-pyridylmethyl)-1,7-heptanediamine (3) and *N*,*N*,*N*′,*N*′-tetrakis(2-pyridylmethyl)-1,10-decanediamine (4)[20]

To a solution of 12 mmol 2-(chloromethyl)pyridinium in H_2O (0.5 mL), 3 mL 20% NaOH were added with stirring under nitrogen. To the resulting red solution, 3 mmol of the corresponding diamine, 3 mL 20% NaOH, and 0.021 mL of a 25% hexadecyltrimethylammoniumchloride solution were added. The mixture was stirred vigorously for 24 h at room temperature. It was then extracted with CH_2Cl_2 (3 × 10 mL), the extract washed with 10 mL H_2O and dried over Na_2SO_4. After evaporation of the solvent, the ligands **1**, **2** and **4** were obtained as brown solids and **3** as a brown oil. **1**, **3** and **4** were purified by column chromatography (Al_2O_3, CH_2Cl_2–EtOAc = 1 : 1, first fraction) and ligand **2** was recrystallized from acetone, giving white solids in all cases.

1. Yield: 690 mg (1.48 mmol, 49%). Anal. Calc. for $C_{29}H_{34}N_6$: C, 74.65; H, 7.34; N, 18.01. Found: C, 74.43; H, 8.56; N, 18.01%. ^{1}H NMR (DMSO, 300.0 K): δ 8.46 (d, $^3J_{HH}$ = 4.9 Hz, 4H), δ 7.73 (t, $^3J_{HH}$ = 6.5 Hz, 4H), δ 7.47 (d, $^3J_{HH}$ = 6.8 Hz, 4H), δ 7.23 (t, $^3J_{HH}$ = 4.9 Hz, 4H), δ 3.67 (s, 8H), δ 2.38 (t, 4H), δ 1.35 (m, 4H), δ 1.18 (m, 2H).

2. Yield: 865 mg (1.8 mmol, 60%). Anal. Calc. for $C_{30}H_{36}N_6$: C, 74.97; H, 7.55; N, 17.48. Found: C, 74.88; H, 8.39; N, 17.11%. ^{1}H NMR (DMSO, 300.0 K): δ 8.45 (d, $^3J_{HH}$ = 5.3 Hz, 4H), δ 7.73 (t, $^3J_{HH}$ = 7.1 Hz, 4H), δ 7.48 (d, $^3J_{HH}$ = 7.8 Hz, 4H), δ 7.21 (t, $^3J_{HH}$ = 4.9 Hz, 4H), δ 3.69 (s, 8H), δ 2.36 (t, 4H), δ 1.39 (m, 4H), δ 1.09 (m, 4H).

3. Yield: 384 mg (0.78 mmol, 26%). Anal. Calc. for $C_{31}H_{38}N_6$: C, 75.27; H, 7.74; N, 16.99. Found: C, 73.33; H, 8.55; N, 15.53%. ^{1}H NMR (DMSO, 300 K): δ 8.45 (d, $^3J_{HH}$ = 5.3 Hz, 4H), δ 7.73 (t, $^3J_{HH}$ = 6.5 Hz, 4H), δ 7.49 (d, $^3J_{HH}$ = 7.4 Hz, 4H), δ 7.22 (t, $^3J_{HH}$ = 5.0 Hz, 4H), δ 3.70 (s, 8H), δ 2.39 (t, 4H), δ 1.39 (m, 4H), δ 1.08 (m, 6H).

4. Yield: 820 mg (1.53 mmol, 51%). Anal. Calc. for $C_{34}H_{44}N_6$: C, 76.08; H, 8.26; N, 15.66. Found: C, 76.34; H, 8.91; N, 15.41%.^{1}H NMR (DMSO, 300 K): δ 8.52 (d, $^3J_{HH}$ = 4.5 Hz, 4H), δ 7.80 (t, $^3J_{HH}$ = 6.6 Hz, 4H), δ 7.57 (d, $^3J_{HH}$ = 6.0 Hz, 4H), δ 7.28 (t, $^3J_{HH}$ = 4.5 Hz, 4H), δ 3.78 (s, 8H), δ 2.46 (t, 4H), δ 1.46 (m, 4H), δ 1.24 (m, 12H).

Synthesis of the complexes[19]

[Pt_2(*N*,*N*,*N*′,*N*′-tetrakis(2-pyridylmethyl)-1,5-pentanediamine)Cl_2]-(ClO_4)$_2$ (**5**), [Pt_2(*N*,*N*,*N*′,*N*′-tetrakis(2-pyridylmethyl)-1,5-hexanediamnine)Cl_2](ClO_4)$_2$ (**6**), [Pt_2(*N*,*N*,*N*′,*N*′-tetrakis(2-pyridylmethyl)-1,7-heptanediamine)Cl_2](ClO_4)$_2$ (**7**), and [Pt_2(*N*,*N*,*N*′,*N*′-tetrakis(2-pyridylmethyl)-1,10-decanediamine)Cl_2](ClO_4)$_2$ (**8**), were all synthesized following the same procedure: To a solution of 200 mg (0.48 mmol) K_2PtCl_4 in 50 mL 0.01 M HCl, a solution of 0.24 mmol of the corresponding bridging ligand in 50 mL 0.01 M HCl was added. The mixture was refluxed for 24 h, filtered if necessary, and the product was precipitated by addition of 1.5 mL of saturated $NaClO_4$ solution. The resulting powder was filtered off, washed with H_2O, EtOH and Et_2O, and dried under vacuum. The resulting product was recrystallized from water if necessary. [Pt_2(*N*,*N*,*N*′,*N*′-tetrakis(2-pyridylmethyl)-1,10-decanediamine)(Cl)(TU)](ClO_4)$_3$ (**9**) was synthesized by adding 3.18 mg (0.04 mmol) of thiourea (TU) to a solution of 50 mg (0,04 mmol) of **8** in 0.01 M CF_3SO_3H and refluxing the solution overnight. The product was precipitated by addition of 1.5 mL of a saturated $NaClO_4$ solution. The resulting powder was filtered off, washed with H_2O, EtOH and Et_2O, and dried under vacuum.

5. Yield: 168 mg (1.49 mmol, 62%). Anal. Calc. for $C_{29}H_{34}Cl_4N_6O_8Pt_2$: C, 30.92; H, 3.04; N, 7.46. Found: C, 30.33; H, 3.22; N, 7.26%. ^{1}H NMR (DMSO, 300 K): δ 8.73 (d, $^3J_{HH}$ = 6.7 Hz, 4H), δ 8.26 (t, $^3J_{HH}$ = 7.4 Hz, 4H), δ 7.69 (m, 8H), δ 5.23 (d, $^3J_{HH}$ = 15.2 Hz, 4H), δ 4.69 (d, $^3J_{HH}$ = 16.8 Hz, 4H), δ 2.27 (m, 4H), δ 1.28 (m, 4H), δ 1.09 (m, 2H).

6. Yield: 172 mg (1.51 mmol, 63%). Anal. Calc. for $C_{30}H_{36}Cl_4N_6O_8Pt_2$: C, 31.59; H, 3.18; N, 7.37. Found: C, 30.97; H, 2.88; N, 7.02%. ^{1}H NMR (DMSO, 300 K): δ 8.76 (d, $^3J_{HH}$ = 5.6 Hz, 4H), δ 8.27 (t, $^3J_{HH}$ = 6.2 Hz, 4H), δ 7.67 (m, 8H), δ 5.27 (d, $^3J_{HH}$ = 15.4 Hz, 4H), δ 4.69 (d, $^3J_{HH}$ = 16.8 Hz, 4H), δ 2.27 (m, 4H), δ 1.30 (m, 4H), δ 0.97 (m, 4H).

7. Yield: 194 mg (1.68 mmol, 70%). Anal. Calc. for $C_{31}H_{38}Cl_4N_6O_8Pt_2$: C, 32.25; H, 3.32; N, 7.28. Found: C, 30.49; H, 3.01; N, 6.60%. ^{1}H NMR (DMSO, 300 K): δ 8.76 (d, $^3J_{HH}$ = 6.5 Hz, 4H), δ 8.26 (t, $^3J_{HH}$ = 7.1 Hz, 4H), δ 7.67 (m, 8H), δ 5.27 (d, $^3J_{HH}$ = 14.5 Hz, 4H), δ 4.73 (d, $^3J_{HH}$ = 15.5 Hz, 4H), δ 2.89 (m, 4H), δ 1.37 (m, 4H), δ 1.06 (m, 6H).

8. Yield: 178 mg (1.49 mmol, 62%). Anal. Calc. for $C_{34}H_{44}Cl_4N_6O_8Pt_2$: C, 34.12; H, 3.71; N, 7.02. Found: C, 33.62; H, 3.99; N, 6.96%. ^{1}H NMR (DMSO, 300 K): δ 8.77 (d, $^3J_{HH}$ = 6.0 Hz, 4H), δ 8.27 (t, $^3J_{HH}$ = 5.1 Hz, 4H), δ 7.71 (m, 8H), δ 5.30 (d, $^3J_{HH}$ = 16.5 Hz, 4H), δ 4.76 (d, $^3J_{HH}$ = 15.0 Hz, 4H), δ 2.95 (m, 4H), δ 1.42 (m, 4H), δ 1.08 (m, 4H), δ 0.97 (m, 8H).

9. Yield: 40 mg (0.03 mmol, 72%). Anal. Calc. for $C_{35}H_{48}Cl_4N_8O_{12}Pt_2S$: C, 31.45; H, 3.62; N, 8.38; S, 2.40. Found: C, 30.98; H, 3.57; N, 7.80; S, 2.27%. ^{1}H NMR (DMSO, 300 K): δ 8.78 (t, $^3J_{HH}$ = 12 Hz, 4H), δ 8.27 (q, $^3J_{HH}$ = 33 Hz, 4H), δ 7.71 (m, 8H), δ 5.26 (t, $^3J_{HH}$ = 39 Hz, 4H), δ 4.78 (t, $^3J_{HH}$ = 39 Hz, 4H), δ 2.99 (m, 4H), δ 1.39 (m, 4H), δ 1.06 (m, 4H), δ 0.96 (m, 8H).

Preparation of complex solutions

The desired solutions of the aqua complexes of **Pen**, **Hex**, **Hep**, **Dec** and **Dec-TU** (see Fig. 1) were prepared by dissolving a known amount of the chloro complexes **5**–**9** in 0.001 M trifluoromethanesulfonic (triflic) acid and adding a stoichiometric excess (with respect to chloride) of silver triflate (150–200%). The mixture was then stirred in the dark overnight at 40–50 °C. The precipitated silver chloride was filtered off, and the pH of the resulting solution was adjusted to 10–11 by addition of 0.1 M NaOH, which resulted in the precipitation of brown Ag_2O. The precipitate was then removed with a Millipore filter and the remaining solution was acidified to pH = 2.0 with triflic acid. The resulting solution was diluted with 0.01 M triflic acid to give the desired complex concentration of 0.1 mM. For all investigations, the pH of the solution was kept at 2.0 and the ionic strength was adjusted to 0.01 M.

Instrumentation and measurement

NMR spectroscopy (Bruker Avance DPX 300) and a Carlo Erba Elemental Analyser 1106 were used for characterization and chemical analysis of the synthesized compounds. A Varian Cary 1G spectrophotometer equipped with a thermostated cell holder was used to record UV-Vis spectra for the determination of the pK_a values of the diaqua complexes. Kinetic measurements were performed on an Applied Photophysics SX 18MV stopped-flow instrument. Data acquisition was done with a J & M TIDAS 200–620 nm rapid scan detector and a J & M TIDAS V 3.0 light source connected with light guides to the stopped-flow instrument.

Quantum chemical calculations

All structures were pre-optimized at the RHF/LANL2MB[21–25] level of theory. The characterization as minima was done by computation of vibrational frequencies at the same level. We performed density functional structure optimizations with no other constrains than symmetry using BP86/LCVP* as implemented in Jaguar 6.5.[26–34]

Results and discussion

DFT calculations

In this study one of the most important structural parameters is the distance between the Pt(II) coordination sites. We performed RBP86/LACVP* calculations to obtain structures that are not affected by solvent or neighbouring groups. Depending on the number of $(CH_2)_n$ groups in the bridge, we obtained C_{2h} symmetry when n is an even number and C_{2v} symmetry when n is an odd number (see Fig. 2). The best descriptor for the distance between both Pt coordination sites is the distance covered by the N–$(CH_2)_n$–N bridge, since this value shows in contrast to the Pt–Pt distance no dependence on the symmetry. An analysis of the calculated

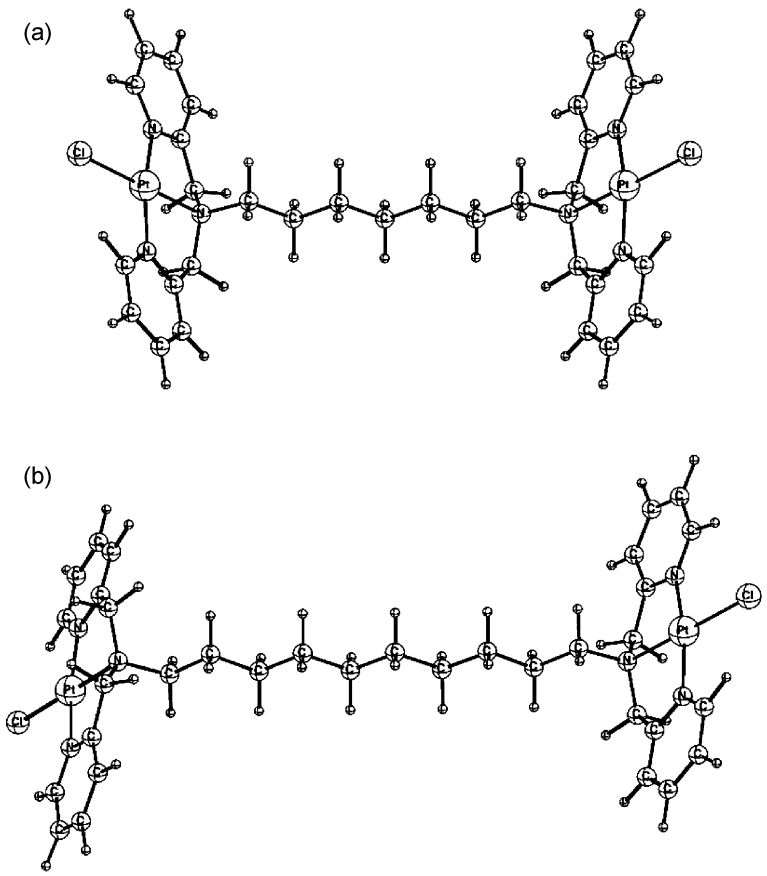

Fig. 2 (a) Calculated structure (C_{2v}) BP86/LCVP* of **Hep**. (b) Calculated structure (C_{2h}) BP86/LCVP* of **Dec**.

distances shows that every additional CH_2 group adds 1.3 Å to the distance covered by the N–$(CH_2)_n$–N bridge (see Fig. 3a). In addition, a good correlation with the pK_a values and substitution rate constants is observed (see Fig. 3b and 3c).

The –$(CH_2)_n$– chain can adopt different conformers, of which the *gauche* conformations will result in shorter Pt–Pt distances. To obtain a significantly shorter Pt–Pt distance, a couple of *gauche* conformations are necessary, which however result in structures of significantly higher energy than the C_{2v} or C_{2h} structures. We, therefore, consider the C_{2v} and C_{2h} structures as appropriate for the further discussions.

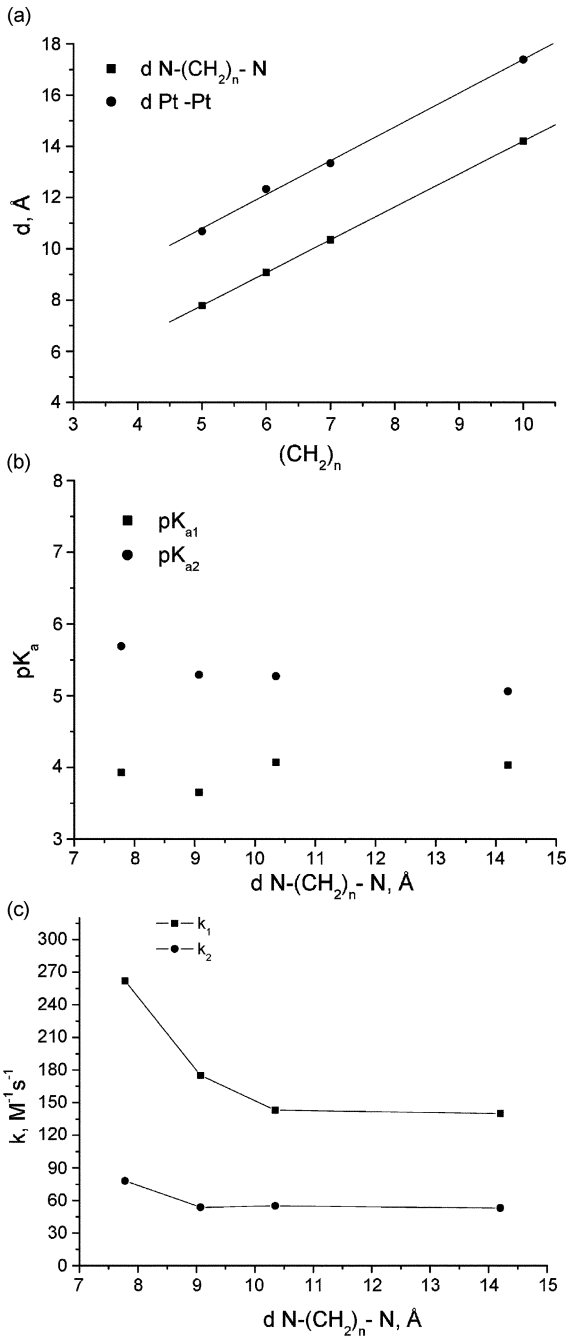

Fig. 3 (a) Correlation between the number of CH_2 groups and the calculated N–$(CH_2)_n$–N and Pt–Pt distances. (b) Correlation between the calculated N–$(CH_2)_n$–N distances and the measured pK_{a1} and pK_{a2} values. (c) Correlation between the calculated N–$(CH_2)_n$–N distance and the measured k_{obs1} and k_{obs2} values.

pK_a determinations for the diaqua complexes

The pK_a values of the diaqua complexes were determined by performing a spectrophotometric pH titration with NaOH in the pH range 2–9. To increase the pH from 2 to 3, solid NaOH was used, whereas for the further increase in pH, NaOH solutions of different concentrations were used. After each addition of NaOH, 1 mL samples were taken from the complex solution to measure the pH. The samples were discarded because of probable contamination and subsequent substitution reactions with chloride anions coming from the pH electrode. The pH dependence of the diaqua complex was monitored by UV-Vis spectroscopy. A typical example of the spectral changes observed during the pH titration is shown in Fig. 4a. The spectral data were analysed with Specfit Global Analysis software. The data give an excellent fit for a system with two dissociation steps (see Fig. 4b) with equilibrium constants K_{a1} and K_{a2}, for which the

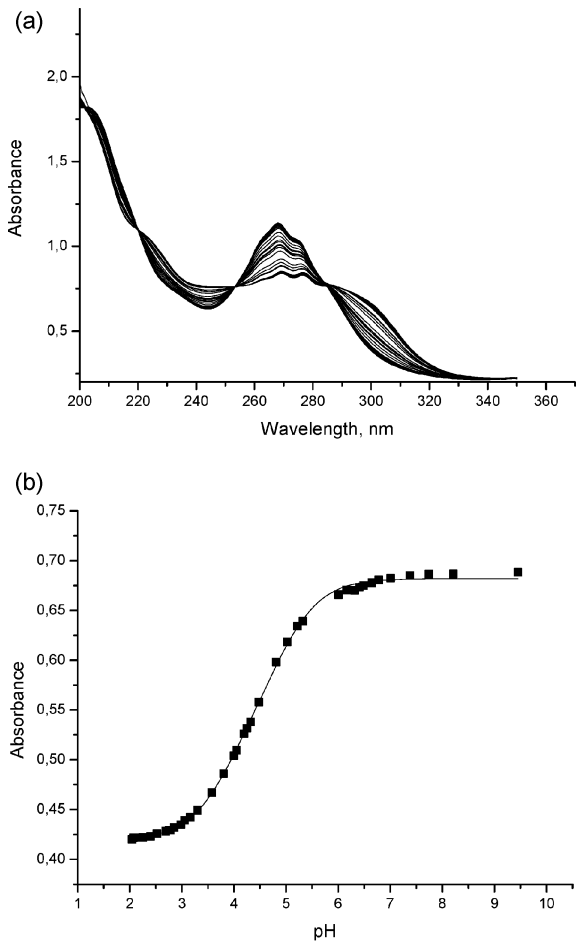

Fig. 4 (a) UV-vis spectra of the decane bridged diaqua complex recorded as a function of pH in the range 2 to 10; I = 0.01 M ($NaSO_3CF_3$), T = 25.0 °C. (b) Plot of absorbance *versus* pH at 298 nm for the decane bridged diaqua complex.

overall process can be presented by reaction (1).

$$\begin{aligned} &H_2O\text{-Pt-N-}(CH_2)_n\text{-N-Pt-}OH_2^{4+} + H_2O \overset{K_{a1}}{\rightleftharpoons} \\ &\qquad H_2O\text{-Pt-N-}(CH_2)_n\text{-N-Pt-}OH^{3+} + H_3O^+ \\ &H_2O\text{-Pt-N-}(CH_2)_n\text{-N-Pt-}OH^{3+} + H_2O \overset{K_{a2}}{\rightleftharpoons} \\ &\qquad HO\text{-Pt-N-}(CH_2)_n\text{-N-Pt-}OH^{2+} + H_3O^+ \end{aligned} \quad (1)$$

The pK_{a1} values (summarized in Table 1) for the two dissociation steps move closer together as the length of the bridging ligand increases along the series of complexes (see correlation in Fig. 3b). This nicely corroborates earlier work performed in our group in that the pK_a value for the first deprotonation step of the dinuclear complex is always lower than that of the mononuclear complex, and the difference between these values becomes smaller as the distance between the platinum centres of the dinuclear complexes becomes longer.[19] A short distance between the platinum centres of dinuclear complexes results in the addition of the single charges on the platinum centres. Because of this higher positive charge, each platinum centre becomes more electrophilic and thus more acidic, which leads to a lower pK_a value than that of the +2 charged platinum centre of the mononuclear complex. The effect of charge addition becomes weaker as the distance between the Pt(II) centres becomes longer.

For the same reason, the pK_{a2} values of the aquahydroxo complexes generated during the first deprotonation reaction are always higher than those of the diaqua complexes as a result of the overall charge of +3. The difference between the pK_a values of the aquahydroxo and diaqua complexes becomes smaller as the bridging chain becomes longer. On exceeding a specific chain length, it is not possible to distinguish between the two metal centres in terms of their electrophilicity and acidity anymore. This observation is already known for the multinuclear platinum complexes studied by Farrell and coworkers.[35] In the case of the decane bridged diaqua complex (**Dec**), analysis of the data in terms of a single dissociation step resulted in a pK_{a1} value that is slightly higher than the fit for a double dissociation step model. In order to differentiate whether the decane bridged complex shows one or two dissociation steps, we synthesized the decane bridged thiourea-aqua complex (**Dec-TU**) to determine the pK_a value for this complex, which now has only one acid dissociation step. Indeed, the pK_{a1} value of the **Dec-TU** complex has practically the same value as that found for the decane bridged diaqua complex using a double dissociation step model (see Table 1). Thus, it seems reasonable to assume that at least in the case of the decane bridged diaqua complex, the two platinum centres are so far apart from each other that we can exclude any interaction between them and can expect a similar acidity for both aqua ligands. Under such conditions K_{a1}/K_{a2} should converge to the statistical value of 4. This ratio for the decane bridged complex is close to 10 and indicates that the expected statistical factor has not yet been reached.

Kinetic measurements

The substitution reactions of the series of diaqua complexes in Fig. 1 with chloride as entering ligand were studied because of the biological role of chloride in blood and in cells. At least a 20-fold excess of chloride over the complex concentration was selected in our experiments in order to guarantee pseudo first order conditions for the consecutive substitution processes shown in reaction (2).

$$\begin{aligned} &H_2O\text{-Pt-N-}(CH_2)_n\text{-N-Pt-}OH_2^{4+} + Cl^- \xrightarrow{k_1} \\ &\qquad H_2O\text{-Pt-N-}(CH_2)_n\text{-N-Pt-}Cl^{3+} + H_2O \\ &H_2O\text{-Pt-N-}(CH_2)_n\text{-N-Pt-}Cl^{3+} + Cl^- \xrightarrow{k_2} \\ &\qquad Cl\text{-Pt-N-}(CH_2)_n\text{-N-Pt-}Cl^{2+} + H_2O \end{aligned} \quad (2)$$

The time dependent spectra observed for the reactions with chloride were analyzed with Specfit Global Analysis software. They indicated that the substitution reactions of complexes **Pen**, **Hex** and **Hep** are best described by a two exponential fit. The determined pseudo first order rate constants $k_{obs(1,2)}$ were plotted against chloride concentration. The resulting linear dependence on the chloride concentration with no intercept indicates that the reverse reaction with water is too slow to contribute significantly to the values of $k_{obs(1,2)}$. The first ligand substitution reaction is faster than the second one as shown by the plots of k_{obs} *versus* [Cl^-] for both reaction steps in Fig. 5a–e. This can be explained in terms of the decrease in the overall charge on the complex from +4 to +3 following the substitution of one water ligand by chloride. The platinum centre becomes less electrophilic because of the lower charge and the substitution of water by chloride becomes slower. The addition of a singly charged nucleophile becomes less efficient or even impossible during the stepwise lengthening of the aliphatic chain due to a decrease in the electrophilicity of the platinum centres. Thus the rate constants for the first substitution reaction of complexes with longer chains are smaller than the

Table 1 Summary of pK_a values for the first and second deprotonation steps of the aqua complexes, second order rate constants and activation parameters for the displacement of coordinated water by chloride, and the calculated (BP86/LACVP*) N–$(CH_2)_n$–N and Pt–Pt distances

	Pen	Hex	Hep	Dec	Dec	Dec-TU
pK_{a1}	3.93 ± 0.03	3.65 ± 0.06	4.07 ± 0.02	4.03 ± 0.04	4.37 ± 0.01	4.11 ± 0.05
pK_{a2}	5.69 ± 0.03	5.29 ± 0.05	5.27 ± 0.06	5.06 ± 0.06	—	—
k_1 at 25 °C/M^{-1} s^{-1}	262 ± 13	175 ± 5	143 ± 5	140 ± 2	59.7 ± 0.2	66 ± 2
k_2 at 25 °C/M^{-1} s^{-1}	78 ± 1	53.7 ± 0.6	55 ± 1	53 ± 0.2	—	—
$\Delta H_1^{\ddagger}$/kJ mol^{-1}	86 ± 7	89 ± 9	66 ± 7	78 ± 5	66 ± 2	59 ± 2
$\Delta H_2^{\ddagger}$/kJ mol^{-1}	87 ± 7	58 ± 3	62 ± 4	71 ± 2	—	—
$\Delta S_1^{\ddagger}$/J K^{-1} mol^{-1}	+87 ± 22	+96 ± 29	+16 ± 23	+58 ± 16	−37 ± 8	−60 ± 5
$\Delta S_2^{\ddagger}$/J K^{-1} mol^{-1}	+83 ± 24	−17 ± 10	−4 ± 15	+25 ± 7	—	—
d N–$(CH_2)_n$–N/Å	7.78	9.07	10.35	14.20	—	—
d Pt–Pt/Å	10.68	12.33	13.34	17.39	—	—

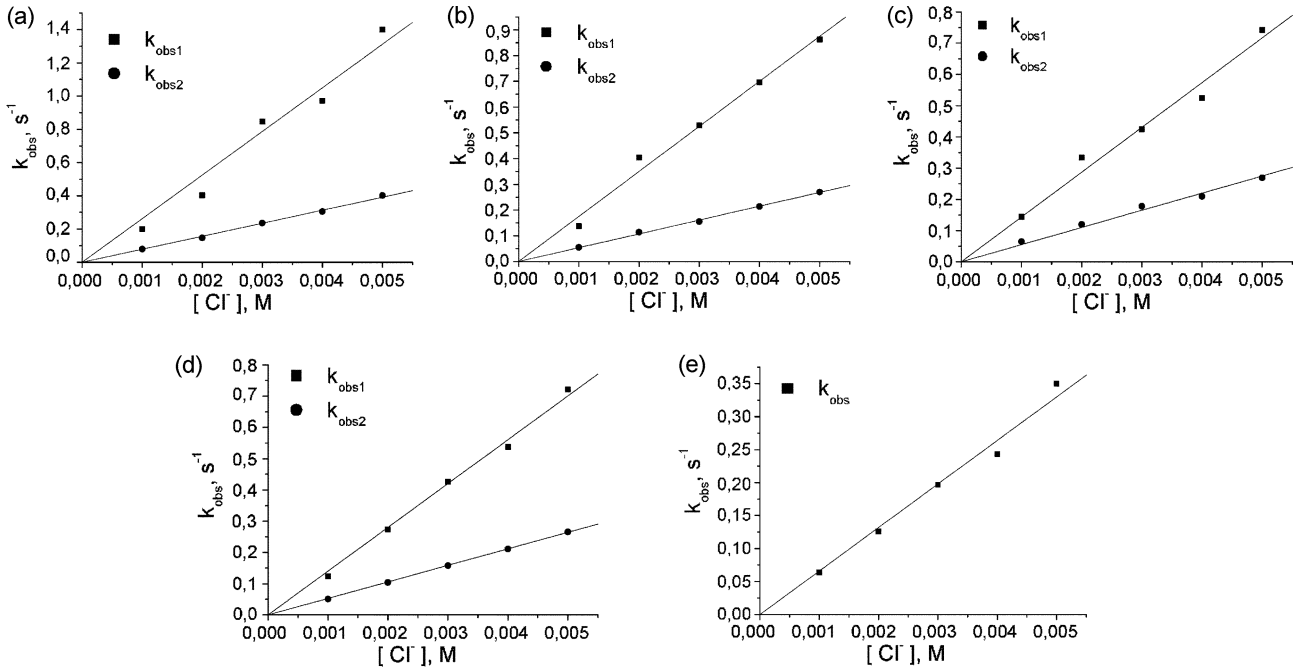

Fig. 5 (a) Plots of k_{obs1} and k_{obs2} *versus* chloride concentration for the reaction with the pentane bridged diaqua complex. $I = 0.01$ M (HSO_3CF_3), $T = 25.0$ °C, pH = 2.0. (b) Plots of k_{obs1} and k_{obs2} *versus* chloride concentration for the reaction of the hexane bridged diaqua complex. $I = 0.01$ M (HSO_3CF_3), $T = 25.0$ °C, pH = 2.0. (c) Plots of k_{obs1} and k_{obs2} *versus* chloride concentration for the reaction of the heptane bridged diaqua complex. $I = 0.01$ M (HSO_3CF_3), $T = 25.0$ °C, pH = 2.0. (d) Plots of k_{obs1} and k_{obs2} *versus* chloride concentration for the reaction of the decane bridged diaqua complex. $I = 0.01$ M (HSO_3CF_3), $T = 25.0$ °C, pH = 2.0. (e) Plot of k_{obs} *versus* chloride concentration for the reaction of the decane bridged thiourea-aqua complex. $I = 0.01$ M (HSO_3CF_3), $T = 25.0$ °C, pH = 2.0.

values for complexes with shorter bridges (see correlation in Fig. 3c). Furthermore, the rate constants continuously decrease as a function of the distance of the two platinum coordination sites and the difference between the rate constants for the first and second substitution steps also becomes smaller on lengthening the aliphatic chain between the platinum centres (see Fig. 2c). Thus we expect, as in the case of the complexes studied by Farrell and co-workers,[10] that the two platinum centres will reach the same reactivity towards nucleophiles for a particular chain length. The two platinum centres can only be distinguished if there is a change in the charge of the complex during the reaction with the nucleophile. Therefore Jaganyi *et al.* were only able to obtain one rate constant for the reaction of their bridged platinum complexes with thiourea, where the charge of the complex is unchanged.[36]

It is not clear whether in the case of the decane bridged complex (**Dec**), the platinum centres act independently of each other and have the same reactivity or not, since the nucleophilic substitution reactions of this complex can be well described by both a double and a single exponential function (see data in Table 1). We again took the decane bridged aqua-thiourea complex (**Dec-TU**) to resolve this question. This complex shows only one substitution reaction for water by chloride since thiourea cannot be displaced by chloride. In this way we obtained data for a closely related system which we found to be best described by a single exponential function. From the data in Table 1 it follows that the rate constant for the decane bridged aqua-thiourea and diaqua complexes are in good agreement when the kinetic behaviour of the diaqua complex is described by a single exponential function.

The results in Table 1 also demonstrate that the ratio of the rate constants k_1/k_2 decreases along the series and reaches a value of 2.6 for the decane bridged complex. This is close to the limiting statistic factor of 2 expected for two equivalent platinum centres.

Temperature dependence

The activation parameters $\Delta H^{\#}$ and $\Delta S^{\#}$ were determined by measuring the rate constant of each of the substitution reactions of the complexes with 3 mM chloride as a function of temperature. The parameters were calculated using the Eyring equation (see Fig. S1–e, ESI†) and are summarized in Table 1. The values for the activation enthalpy become smaller on lengthening the bridging chain, which is compensated by a decrease in the activation entropy. In general substitution reactions of square planar Pt(II) complexes proceed according to an associative mechanism and should be characterized by negative intrinsic $\Delta S^{\#}$ values as a result of bond formation in the transition state. However, in the present case the substitution reactions outlined in (2) are accompanied by charge neutralization which will cause a decrease in electrostriction and release of electrostricted solvent molecules. This reorganization of the solvent will cause an increase in entropy and offset the negative intrinsic contribution as a result of bond formation. The overall activation entropies reported in Table 1 are in many cases close to zero within the experimental error limits as a result of this compensation effect. Nevertheless, there is no reason to believe that the substitution reactions do not follow an associative mechanism.

Conclusions

We studied the effect of increasing the aliphatic chain on the bridged complexes [{Pt(OH$_2$)(*N*,*N*,*N*′,*N*′-tetrakis(2-pyridylmethyl)}$_2$N–(CH$_2$)$_n$–N]$^{4+}$. We could observe an electrostatic interaction between the two platinum centres which becomes weaker on lengthening the aliphatic bridge. There is an addition of the separate charges on the platinum centres in complexes bridged through a short aliphatic chain. This increases the electrophilicity of the platinum centres, leads to lower pK_a values for the coordinated water ligands and a higher reactivity of the complex towards chloride. This interaction observed for the complexes with a shorter bridge cause each of the platinum centres to exhibit different thermodynamic and kinetic properties. The interaction reaches a minimum for the decane bridged complex where it becomes very difficult to distinguish between the kinetic behaviour of the two Pt(II) centres.

Analysis of the pH titration data by Specfit, in which the complete wavelength range spectra was used, gave a factor of 10 between the values for K_{a1} and K_{a2} for the decane bridged complex, although a value of 4 is expected for K_{a1}/K_{a2} based on the statistics for two Pt(II) centres completely independent of each other. However, single wavelength analyses gave good fits for K_{a1} and K_{a2} within a factor of 4. The reported factor of 10 may thus be subjected to large error limits and may strongly depend on the method of analysis employed.

Theoretical calculations assisted the analysis of the correlation between the thermodynamic and kinetic parameters as a function of the length of the bridging ligand. Further investigations will include a study of the reactivity of the complexes with biological relevant nucleophiles such as 5′GMP$^{2-/-}$ and L-methionine under physiological conditions. Because of the chosen chelate attached to the Pt(II) centre, we expect a higher stability than in the case of BBR3464 and BBR3610 for which the reaction with S-containing nucleophiles leads to degradation of both complexes.[14]

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