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Synthesis, Characterization, Thermodynamic and Kinetic Properties of a New Series of Dinuclear Pt^{II} Complexes

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The dinuclear Pt^{II} complexes bis{[(1*R*,2*R*)-(–)-1,2-diaminocyclohexane]chloroplatinum(II)}(μ-1,8-octanediamine), bis{[(1*R*,2*R*)-(–)-1,2-diaminocyclohexane]chloroplatinum(II)}(μ-1,10-decanediamine) and bis{[(1*R*,2*R*)-(–)-1,2-diaminocyclohexane]chloroplatin(II)}[μ-1,4-bis(3-pyridyl)buta-1,3-diyne] were synthesized. Acid-base titrations and concentration and temperature dependent measurements of the reactions with chloride and thiourea were performed to study the influence of the nature of the bridging ligand on the thermodynamic and kinetic properties of the complexes. The reactions with chloride and thiourea were followed under pseudo-first-order conditions by stopped-flow and UV/Vis spectrophotometry. The results indicate that the bridging ligand has an influence on the reactivity and stability of the complexes towards nucleophiles as well as on possible electronic interactions between the two Pt^{II} centres. The experimental results are discussed in reference to structures obtained by DFT (BP86/LACVP*) calculations.

Introduction

Since the successful application of cisplatin in cancer treatment, around 30000 new platinum complexes have been synthesized with the intention to enlarge or at least to retain the spectrum of activity of cisplatin and to reduce the dose-limiting toxicities. The circumstance that a resistance against cisplatin is developed during treatment with cisplatin is a limiting factor in its clinical use. Following the synthesis of several analogues of cisplatin, the antitumour chemistry involving platinum shifted more to the development of non-classical platinum complexes. We recently reported on some dinuclear platinum complexes synthesized in our group,[1] which consist of two Pt^{II} centres bridged by a long aliphatic chain and are in addition coordinated by a chelating ligand system consisting of pyridine donors. In the present study we synthesized complexes that combine the advantages of oxaliplatin and highly charged multinuclear platinum complexes (see Figure 1).

Oxaliplatin, a third-generation platinum antitumour compound, shows activity in tumour types that are resistant to cisplatin.[2] In oxaliplatin a 1,2-diaminocyclohexane (DACH) ligand substitutes the primary ammine groups of cisplatin. The improved activity of oxaliplatin is amongst others ascribed to the DACH ligand. Pt-DACH adducts seem to induce cell death more efficiently than cisplatin.[3] Furthermore, the DACH ligand forms a five-membered ring with Pt^{II}, which is more stable towards hydrolysis and substitution compared to the ammines in cisplatin. Highly charged multinuclear platinum complexes are the representatives of a new class of DNA damaging agents. The high charge results in an improved water solubility and electrostatic interactions with the polyanionic DNA.[4] Furthermore, the long-range interstrand crosslinks mainly formed by dinuclear platinum complexes are considered to be more difficult to repair.[5]

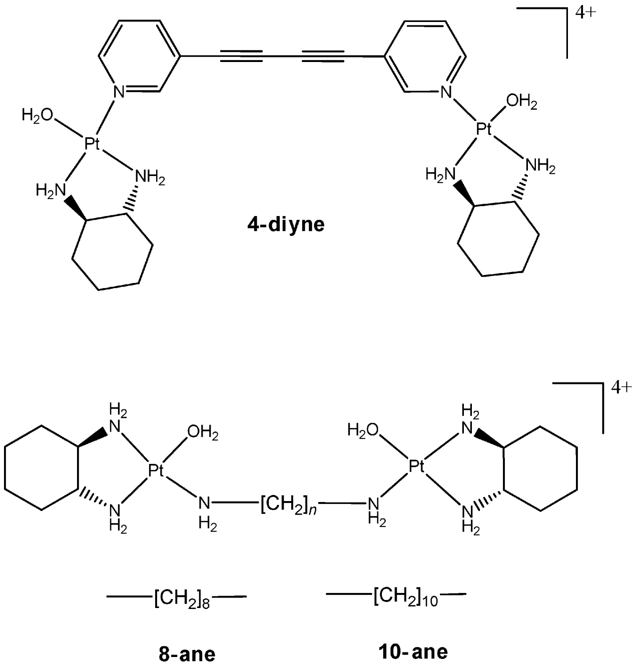

Figure 1. Schematic structures and abbreviations used for the investigated complexes.

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We are particularly interested to study the influence of the nature of the bridging ligand on the thermodynamic and kinetic properties of each of the two platinum centres. 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 when the overall charge on the complex changes during the reaction. Therefore, we selected chloride as an entering nucleophile, which is also present in blood and cells. Thiourea (TU) is a strong sulfur donor nucleophile with a high solubility and can act as a good model compound for thiolate and thioether present in the cell. Thiourea has also for a long time been used as protecting agent to minimize nephrotoxicity following cisplatin treatment.[6]

Results and Discussion

Synthesis of the Complexes

Some interesting studies have been published that reported dinuclear Pt^{II} complexes that are bridged by an sp carbon chain.[7] These complexes consist of a carbon chain that is directly coordinated to the platinum centre and are synthesized via an oxidative coupling reaction. The **4**-diyne complex that is part of the current study also contains a short sp carbon chain and the corresponding ligand 1,4-bis(3-pyridyl)buta-1,3-diyne was synthesized through an oxidative coupling reaction (see Figure 2). The resulting ligand is treated with an intermediate complex that was obtained by chloride displacement in the presence of a silver salt to generate the final complex (see Figure 3). The complexes **8**-ane and **10**-ane were synthesized in a similar way.

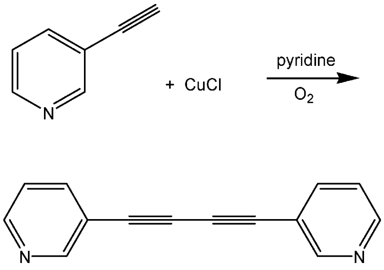

Figure 2. Method of synthesis of 1,4-bis(3-pyridyl)buta-1,3-diyne.

pK_a Determinations for the Diaqua Complexes

The investigated complexes are characterized by two Pt^{II} centres who are linked by different bridging ligands. Where the **10**-ane and **8**-ane complexes (Figure 4) consist of a diaminoalkane bridge of different chain lengths (10 and 8 CH_2 units, respectively), the platinum atoms of the **4**-diyne complex (Figure 5) are linked over a conjugated system. The diaminoalkane chain is flexible, but the carbon chain is rigid, more lipophilic and allows because of the conjugated π-electron system an electronic interaction between the platinum centres. All the complexes have in common that each of the Pt^{II} centres is in addition coordinated by a (1*R*,2*R*)-(–)-1,2-diaminocyclohexane chelate and a water ligand. We know from earlier studies on slightly different

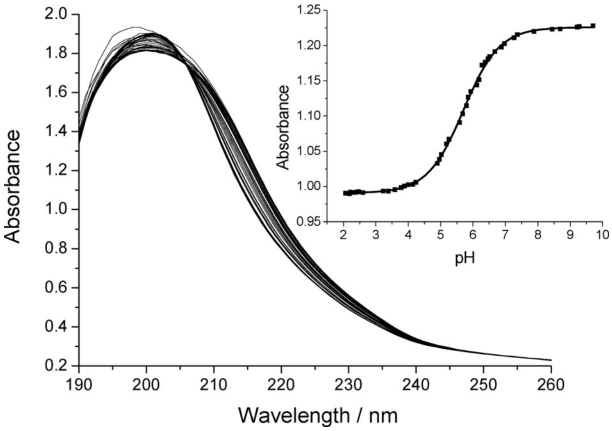

Figure 4. UV/Vis spectra of the **8**-ane diaqua complex recorded as a function of pH in the range 2 to 10; $I = 0.01$ M ($NaSO_3CF_3$), $T = 25.0$ °C. Inset: Plot of absorbance vs. pH at 216 nm.

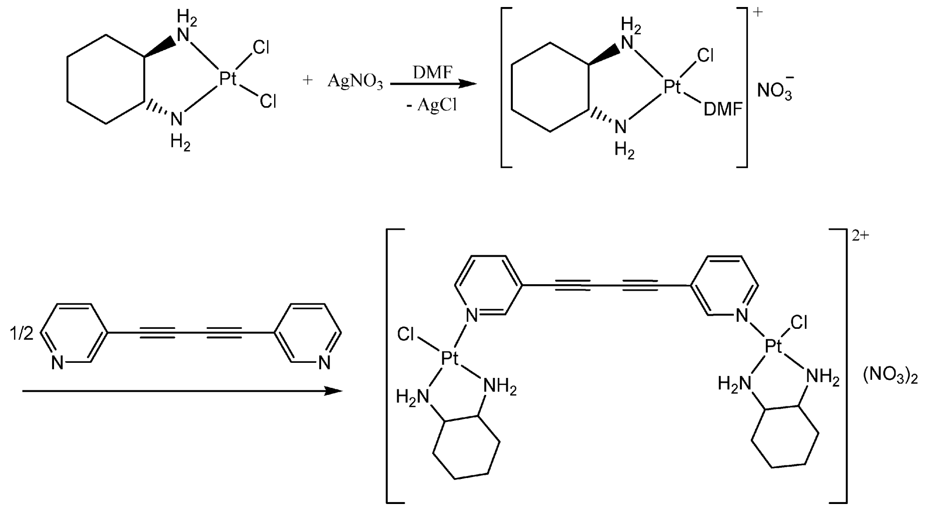

Figure 3. Method of synthesis of the **4**-diyne dichloro complex.

dinuclear platinum complexes that the water ligands coordinated to each of the platinum centres can exhibit different pK_a values depending on the distance between the two Pt^{II} centres.[1] The two platinum centres in these complexes are thermodynamically and kinetically independent of each other and therefore exhibit the same pK_a values for their water ligands when they are linked through a diaminoalkane bridge with 10 CH_2 units. The results from the pK_a titrations with the complexes investigated during this study show that the two complexes with the saturated carbon bridge (**8**-ane and **10**-ane) do not differ significantly in terms of their pK_a values (see Table 1). Their water ligands show similar pK_a values and the platinum atoms in both complexes are so far apart from each other that any possible electronic communication between them can be ruled out.

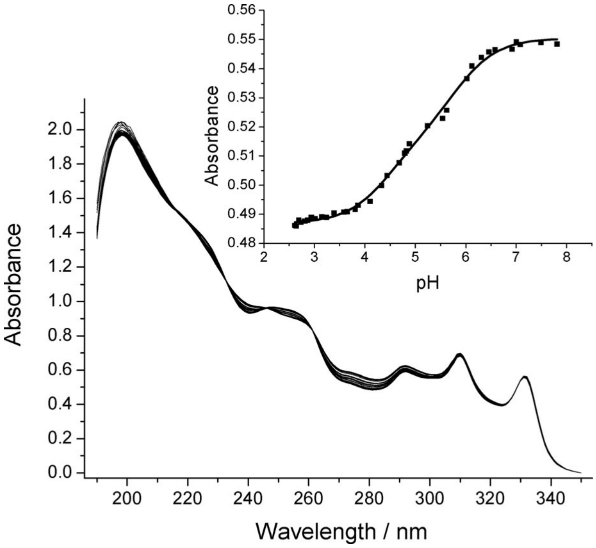

Figure 5. UV/Vis spectra of the **4**-diyne diaqua complex recorded as a function of pH in the range 2 to 10; I = 0.01 M ($NaSO_3CF_3$), T = 25.0 °C. Inset: Plot of absorbance vs. pH at 281 nm.

Table 1. Summary of pK_a values for the deprotonation steps of the aqua complexes at 25 °C.

	8-ane	**10**-ane	**4**-diyne	Pt(dach)[8]
pK_{a1}	5.71	5.60	5.15	6.01
pK_{a2}	–	–	7.33	7.69

In the case of the **4**-diyne complex with the unsaturated and conjugated carbon bridge, we obtained two pK_a values. The reason for this could be that the distance between the two platinum atoms at this complex (13.42 Å) is smaller than in the case of the other complexes (15.31 and 17.62 Å, respectively). A short distance between the platinum atoms of dinuclear complexes results in the addition of the single charges of the platinum centres. Because of this higher positive charge, each platinum centre becomes more electrophilic and thus more acidic, which leads to lower pK_a values. After deprotonation of the first water ligand the overall charge of the complex decreases to +3, and also the electrophilicity and acidity of the second platinum centre, such that it is possible to determine a second pK_a value for this complex. Furthermore, the conjugated π-electron system of the bridging ligand supports electronic communication between the platinum centres and contributes to the existence of two pK_a values in the case of the **4**-diyne complex.

If we compare the results of the pK_a titrations of our complexes with the pK_a value of the mononuclear equivalent [Pt(diaminocyclohexane)$(H_2O)_2$]$^{2+}$, Pt(dach),[8] we see that the coordination of the bridging ligand in the *cis* position to the water ligand causes a decrease of the pK_a value for all the complexes (see Table 1). *Trans* ligands can for instance influence the bond length between the platinum centre and the leaving group, but also the energy of the ground and transition states. The influence of the cis ligand is mainly based on the change of the electron density of the metal centre. Therefore, the decrease in the pK_a value in the case of the **4**-diyne complex compared to Pt(dach) is comprehensible because the electron withdrawing property of the 1,4-bis(n-pyridyl)buta-1,3-diyne bridge decreases the electron density of the platinum centre making it more electrophilic and acidic. Furthermore, both the short distance between the platinum centres and the conjugated carbon bridge enable electronic communication and lead to the addition of the single charges of the Pt^{II} centres. A higher overall charge on the platinum atom is also a reason for the lower pK_a values. As the butadiyne ligand is mainly characterized by a π-acceptor ability, the diaminoalkane chains of the **8**-ane and **10**-ane complexes are σ-donor ligands. This means that the electron density on the Pt^{II} centres is higher for the coordination of this diaminoalkane ligand. This causes a decrease in the electrophilicity and acidity of the platinum atom, from which we would expect higher pK_a values for the **8**-ane and **10**-ane complexes than for the Pt(dach) complex. The fact that we still found lower pK_a values could be due to the fact that **8**-ane and **10**-ane are dinuclear platinum complexes. We know from other dinuclear platinum complexes investigated in our group that the platinum atoms in dinuclear complexes are more acidic than the platinum atoms of the corresponding mononuclear complex.[1] For instance the complex [Pt_2{N,N,N',N'-tetrakis(2-pyridylmethyl)-1,10-decanediamine}-$(H_2O)_2$]$^{4+}$, which consists of two thermodynamically and kinetically independent Pt^{II} centres because of the large distance between them, has a lower pK_a value (4.37) than the corresponding mononuclear complex [Pt{bis(2-pyridylmethyl)-amine}H_2O]$^{2+}$ (pK_a = 5.5).[9] Finally, the lower pK_a value for the **8**-ane and **10**-ane complexes than for the Pt(dach) complex could be also a result of a stabilization of the hydroxo ligand by intramolecular hydrogen bond formation with the amino group of the diaminoalkane chain as it was reported for similar systems.[10]

To gain deeper insight into the structural details of the unspoiled Pt centres, we performed DFT (BP86/LACVP*) calculations on mononuclear model aqua and hydroxo complexes (model-OH_2 and model-OH). As already observed before,[8] hydroxo complexes can be stabilized by intramolecular hydrogen bonds, which is not possible in the case of model-OH_2, as depicted in Figure 6. We attribute this different behaviour to the clearly shortened Pt–OH bond (by 0.14 Å compared to Pt–OH_2), and the *cis*- and *trans*-influence of the OH ligand. The hydroxo complex has a 0.09 Å longer Pt–N_{dach} bond *trans* to the hydroxo ligand, compared to the Pt–N_{dach} bond *trans* to the aqua ligand and in parallel the *cis* bonds are elongated by 0.02/0.03 Å. Thereby, the distance between the non-chelating neighbouring groups becomes shorter and hydrogen bond stabilization becomes possible.

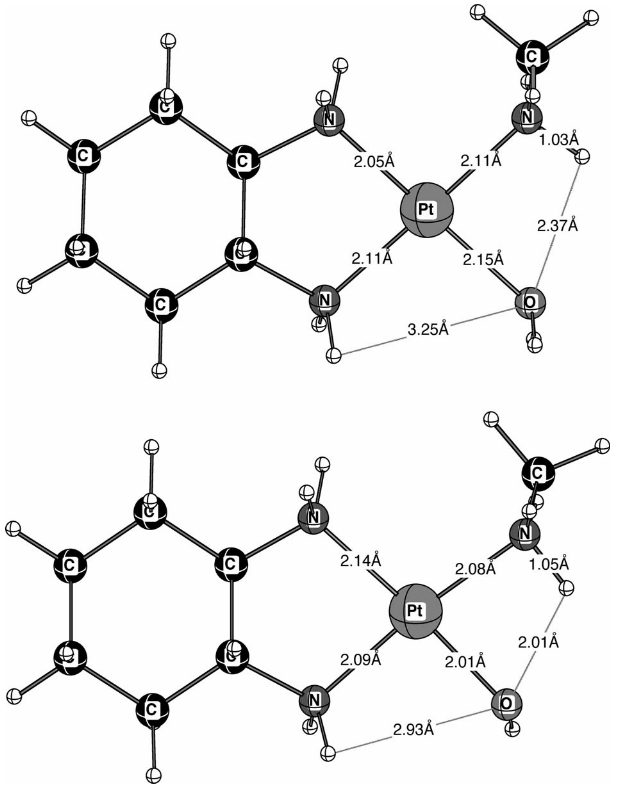

Figure 6. Calculated structure (BP86/LCVP*) of model-OH_2 and model-OH.

In addition, we tested the model compounds for binding an extra water molecule via hydrogen bonding, since all reactions were done in aqueous media (see Figure 7). Both model complexes can bind an extra water molecule in a six-membered ring system. Model-OH is more effective in binding the solvent molecule via two hydrogen bonds of 1.67 ($NH{\cdots}O_{water}$) and 1.70 Å ($O_{water}H{\cdots}O_{hydroxid}$). In contrast, model-$OH_2$ chelates the OH_2 via a short 1.63 Å and a somewhat longer hydrogen bond (2.02 Å). Whereas in model-OH_2 the hydrogen bond bound water is only a hydrogen-bond acceptor for two hydrogen bonds, in model-OH the bound solvent water acts as a hydrogen-bond acceptor and as a hydrogen-bond donor. This enables the possibility for a proton transfer from the water molecule to the complexed OH ion. A similar mechanism was already discussed in related Pt complexes for Pt-bound water ligands.[8]

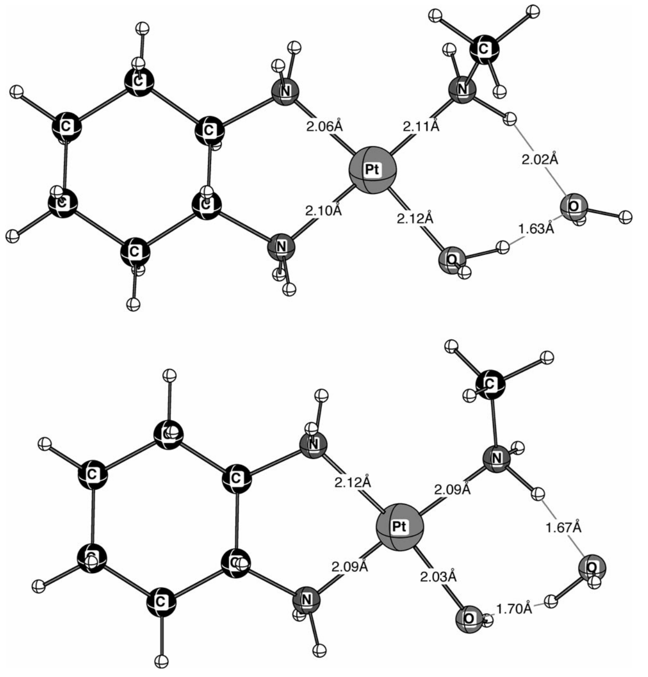

Figure 7. Calculated structure (BP86/LCVP*) of model-OH_2 and model-OH.

Kinetic Measurements

Substitution reactions with chloride and thiourea were performed at pH 2 where the complexes exist in their diaqua form, and the protonation of thiourea can be ruled out as reported recently.[11] At least a 40-fold excess of nucleophile over the complex concentration was selected in order to guarantee pseudo-first-order conditions for the substitution process. The determined pseudo-first-order rate constants, $k_{obs(1,2)}$, were plotted against the nucleophile concentration, and the resulting linear dependence on the nucleophile concentration without a meaningful intercept indicates that the reverse reaction with water is too slow to contribute significantly to the values of $k_{obs(1,2)}$ (see Figures 8, 9, 10, and 11 exemplary for **8**-ane and **4**-diyn**e**, and Figures S2 and S3 for **10**-ane in the Supporting Information).

The results of the substitution reaction with chloride have for all studied complexes in common that we were able to detect only one substitution process. Both platinum centres in the bridged complex do not differ in their kinetic behaviour towards chloride (see Table 2). The Pt^{II} centres are so far apart from each other that any possible electronic communication is not strong enough to detect platinum centres with different kinetic properties. The **8**-ane and **10**-ane complexes that only differ by the length of the bridge between the platinum centres show very similar values for rate constants for the substitution of water by chloride. This means that the average distance of 15.31 Å between the platinum centres in the case of the **8**-ane complex is long enough to provide a dinuclear complex with two platinum centres kinetically indistinguishable from each other. The stronger electronic communication between the platinum

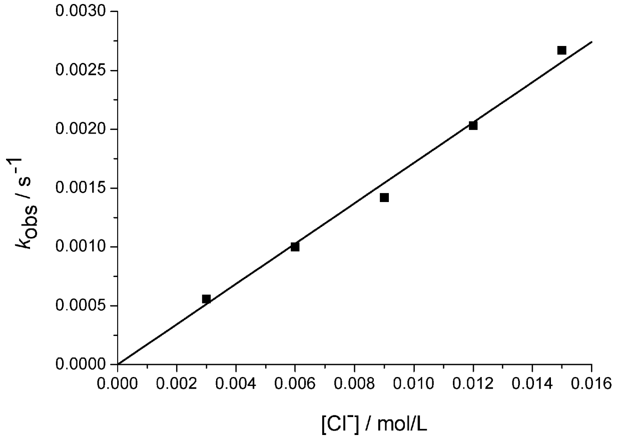

Figure 8. Plot of k_{obs} vs. chloride concentration for the reaction with the **8**-ane complex. I = 0.2 M (CF_3SO_3Na), T = 25.0 °C, pH = 2.0.

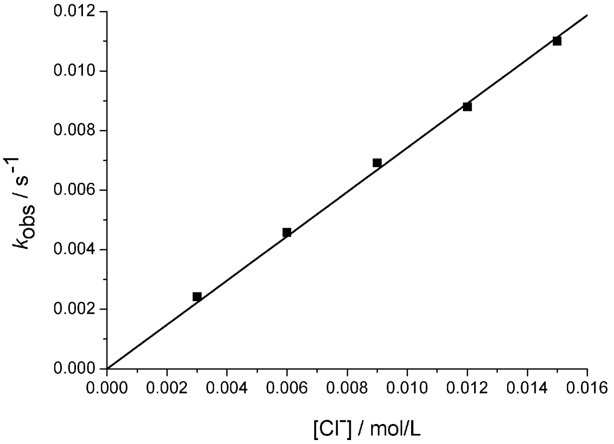

Figure 9. Plot of k_{obs} vs. chloride concentration for the reaction with the **4**-diyne complex. I = 0.2 M (CF_3SO_3Na), T = 25.0 °C, pH = 2.0.

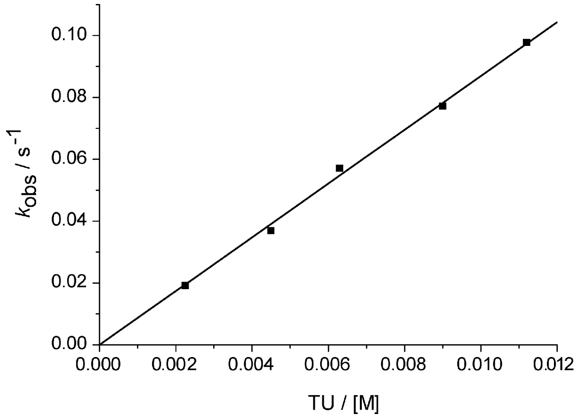

Figure 10. Plot of k_{obs} vs. thiourea concentration for the reaction with the **8**-ane complex. I = 0.2 M (CF_3SO_3Na), T = 25.0 °C, pH = 2.0.

centres in the case of the **4**-diyne complex as a result of the shorter distance and the conjugated character of the bridge, made it possible to detect two pK_a values for this complex.

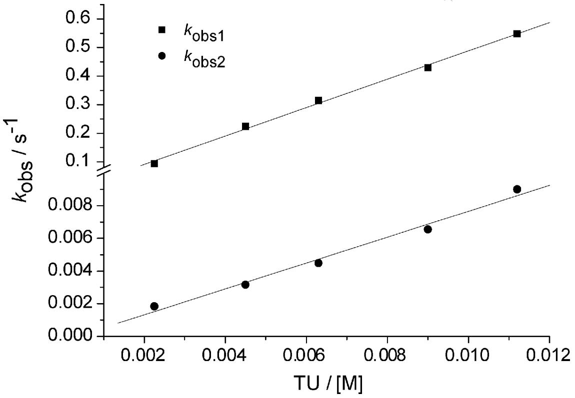

Figure 11. Plots of k_{obs1} and k_{obs2} vs. thiourea concentration for the reaction with the **4**-diyne complex. I = 0.2 M (CF_3SO_3Na), T = 25.0 °C, pH = 2.0.

But even if the overall charge of the complex is changed during substitution by chloride, we were not able to distinguish between the kinetics of the two platinum centers. The slightly faster substitution reaction of **4**-diyne compared to **8**-ane and **10**-ane is a result of the decrease in the electron density of the platinum centre caused by the π-acceptor ability of the pyridine ligand. We can also state that the σ-donor properties of the diaminoalkane bridge in the case of **8**-ane and **10**-ane increase the electron density of the platinum centre and slow down the nucleophilic substitution reaction.

Table 2. Summary of the second-order rate constants for the displacement of coordinated water by chloride and thiourea at 25 °C and pH = 2.[a]

Nucleophile:	thiourea	chloride	thiourea	chloride
	k_1 [M^{-1} s^{-1}]		k_2 [M^{-1} s^{-1}]	
8-ane	8.7 ± 0.10	0.17 ± 0.004	–	–
10-ane	8.9 ± 0.15	0.19 ± 0.003	–	–
4-diyne	48.6 ± 0.6	0.74 ± 0.008	0.79 ± 0.05	–
Pt(dach)[8]	21 ± 1	–	11.5 ± 0.5	–

[a] Ionic strength = 0.2 M (NaOTf).

The substitution reaction with thiourea is considerably faster than the reaction with chloride. This is due to the fact that thiourea is a much stronger nucleophile than chloride. The **4**-diyne complex shows two reaction steps with thiourea. The first one is the simultaneous substitution of both water ligands by thiourea. The second reaction is assigned to the release of the bridge following the coordination of a further thiourea ligand to the platinum centre. It is indeed possible for thiourea to displace also the diaminocyclohexane ligand, but this reaction is much slower as known from the literature.[8] We could demonstrate by proton NMR measurements that the 1,4-bis(3-pyridyl)buta-1,3-diyne bridge is not a strong ligand, since dmso started to displace the bridge after dissolution of the complex in [D$_6$]DMSO (see Figure 12). The **8**-ane and **10**-ane complexes showed during the observed time window only one substitution process. The diaminoalkane bridge proves to be a stronger ligand than 1,4-bis(3-pyridyl)buta-1,3-diyne. There is once again no significant difference in the reactivity of the **8**-ane and **10**-ane complexes. If we compare the reactivity of the complexes with the mononuclear complex Pt(dach), it is seen that **4**-diyne shows a faster substitution reaction than Pt(dach) caused by the more electrophilic character of the platinum centres due to the reasons given for the pK_a titrations. Because of the lower pK_a values of the **8**-ane and **10**-ane complexes than Pt(dach), one would also expect faster substitution reactions with thiourea. However, the σ-donor properties of the diaminoalkane bridge seem to influence the reactivity of the complexes significantly. The increase in electron density causes slower nucleophilic substitution reactions than in the case of Pt(dach).

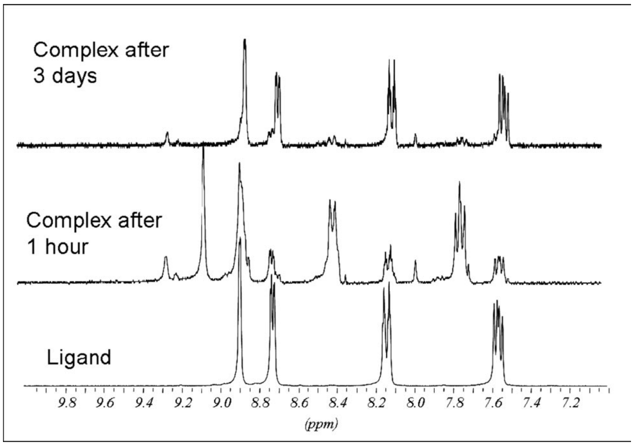

Figure 12. Proton NMR spectra of the complex **4**-diyne in [D$_6$]-DMSO.

Temperature Dependence

The activation parameters $\Delta H^{\#}$ and $\Delta S^{\#}$ were determined at a pH of 2 by measuring the rate constants for each of the substitution reactions of the complexes with thiourea and chloride as a function of temperature. The parameters were calculated using the Eyring equation (see Figures S4 to S9, Supporting Information) and are summarized in Table 3. In general, substitution reactions of square planar Pt^{II} complexes proceed according to an associative mechanism and are characterized by negative intrinsic $\Delta S^{\#}$ values as a result of bond formation in the transition state. The results for the activation entropies for all the investigated complexes confirm the associative character for the substitution process. We observed that the substitution reaction with the charged nucleophile chloride gives smaller values for the activation entropy than for the neutral nucleophile thiourea. In the case of the **10**-ane complex, we even obtained a value close to zero. Since the substitution reaction with chloride is accompanied by charge neutralization, this 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.

Table 3. Summary of the activation parameters for the displacement of coordinated water by chloride and thiourea at pH = 2.

Complex	Nu	$\Delta H_1^{\#}$ [kJ mol^{-1}]	$\Delta S_1^{\#}$ [J K^{-1} mol^{-1}]	$\Delta H_2^{\#}$ [kJ mol^{-1}]	$\Delta S_2^{\#}$ [J K^{-1} mol^{-1}]
8-ane	chloride	65 ± 3.8	–39 ± 13	–	–
10-ane	chloride	79 ± 4.8	8 ± 16	–	–
4-diyne	chloride	68 ± 3.1	–21 ± 10	–	–
8-ane	thiourea	57 ± 1.6	–149 ± 5	–	–
10-ane	thiourea	51 ± 0.9	–171 ± 3	–	–
4-diyne	thiourea	55 ± 1.5	–26 ± 5	59 ± 1.4	–164 ± 5

The second substitution step of the reaction with thiourea gives larger values for the activation entropy. Since the activation entropy presents the change in the order of the system on going to the transition state, a slower second substitution step means weaker molecular interactions and this will produce a looser molecular associate and a less negative activation entropy.

Conclusions

New square planar dinuclear Pt^{II} complexes that consist of two promising attributes were synthesized in this study. They were designed to be dinuclear so that they would be able to form long range interstrand crosslinks with DNA as possible antitumour compounds. The high positive charge arising from the dinuclear structure would furthermore lead to improved water solubility and electrostatic interactions of the complexes with DNA. We selected 1,2-diaminocyclohexane as the inert chelate because of the successful application of this ligand in the already established antitumour complex oxaliplatin. The investigated complexes simply differ in the length and type of the ligand that bridges the two Pt^{II} centres. The **4**-diyne complex consists of a bridge that is rather rigid and lipophilic. The platinum centres of the **8**-ane and **10**-ane complexes are linked through a flexible and saturated carbon chain. At first we were interested in the fundamental thermodynamic and kinetic properties of these complexes and the influence of the length and the nature of the bridge on the properties of the complexes. We, therefore, performed pK_a titrations, and concentration and temperature dependent nucleophilic substitution reactions with chloride and thiourea with the corresponding diaqua species of the synthesized complexes at pH 2.

One result of the study is that there is no significant difference in the thermodynamic and kinetic behaviour of the **8**-ane and **10**-ane complexes which only differ in the length of the bridge. The fact that the bridge of the **4**-diyne complex is rather short and electron withdrawing groups enhance the electrophilicity of the Pt^{II} centres, lead to a pK_a value lower than for the other complexes. The short distance and the conjugated π-electron nature of the bridge in the case of **4**-diyne enabled the detection of two pK_a values. The fact that lower pK_a values for **8**-ane and **10**-ane than for the mononuclear Pt(dach) complex were found contrary to the σ-donor character of the diaminoalkane bridge, can be ascribed to the stabilization of the hydroxo complex by hydrogen bonding that occurs between the hydroxo ligand and the NH$_2$ ligand in the *cis* position. For the interpretation of the results of the nucleophilic substitution reactions, the *cis* effect of the bridge has to be considered. The *trans* effect influences the reactivity of the complexes via ground state labilization (*trans* influence) and transition state stabilization (*trans* effect).[12] The effect of ligands *cis* to the leaving group is a result of increasing or decreasing electron density at the metal centre.[13] The diaminoalkane bridge in the case of the **8**-ane and **10**-ane complexes is a σ-donor and therefore enhances the electron density at the metal centre. This leads to a lower reactivity of these complexes towards nucleophiles. On the other hand, the π-acceptor ability of the bridge in the case of the **4**-diyne complex increases the reactivity of the complex. The results of the temperature dependence of the substitution reactions at pH 2 are in good agreement with an associative substitution mechanism for square planar Pt^{II} complexes based on the negative activation entropy values.

Experimental Section

Chemicals: 1,8-diaminooctane, 1,10-diaminodecane and 3-ethynylpyridine were obtained from Aldrich. All chemicals were used without further purification.

Preparation of the Ligand 1,4-Bis(3-pyridyl)buta-1,3-diyne:[14] Oxygen was bubbled into a solution of copper(I) chloride (1.56 mmol) in pyridine (8 mL) warmed to 40 °C, after which 3-ethynylpyridine (4.33 mmol) was added. The mixture was stirred for 3 h, after which it was cooled and concentrated by removal of pyridine by distillation. The crude mixture was washed with ammonium hydroxide until the blue colour disappeared, after which it was extracted with dichloromethane. The extract was dried (MgSO$_4$), filtered and evaporated to give a yellow solid, followed by chromatography on silica gel with hexane/ethyl acetate (1:2) as eluent, yielding the diyne derivative. Yield 329 mg (1.61 mmol, 37%). ^{1}H NMR (CDCl$_3$, 300 K): δ = 7.31 (dd, J 12, 2 H, CH), δ = 7.81 (dt, J = 12 Hz, 2 H, CH), δ = 8.61 (dd, J = 7.65 Hz, 2 H, CH), δ = 8.77 (s, 2 H) ppm. MS: m/z (%) = 204 (100) [M$^+$], 177 (29), 151 (50), 124 (35).

Synthesis of the Complexes[15]

Bis{[(1*R*,2*R*)-(–)-1,2-diaminocyclohexane]chloroplatinum(II)}(μ-1,8-octanediamine) (**8**-ane), bis{[(1*R*,2*R*)-(–)-1,2-diaminocyclohexane]chloroplatinum(II)}-(μ-1,10-decanediamine) (**10**-ane) and bis{[(1*R*,2*R*)-(–)-1,2-diaminocyclohexane]chloroplatinum(II)}[μ-1,4-bis(3-pyridyl)buta-1,3-diin] (**4**-diyne) were all synthesized following the same procedure: To a suspension of 0.4 mmol of [Pt{(1*R*,2*R*)-(–)-1,2-diaminocyclohexane}Cl$_2$] in 10 mL of dimethylformamide (DMF), a solution of 0.38 mmol of AgNO$_3$ in 1.2 mL of DMF was added drop wise over 2 h in the dark, and the resulting suspension was stirred for 5 h in the dark. The white precipitate of AgCl was then filtered off, and a solution of 0.18 mmol of the corresponding bridging ligand in 1 mL of DMF was added to the filtrate. The resulting solution was stirred overnight in the dark and then evaporated to dryness. The residue was dissolved in 3 mL of methanol. The product was precipitated with 35 mL of ether, stirred with ether for several hours to remove traces of DMF, filtered and dried in air.

8-ane: Yield 93 mg (0.10 mmol, 25%). $C_{20}H_{48}Cl_2N_8O_6Pt_2$ (957.71): calcd. C 25.08, H 5.05, N 11.70; found C 24.65, H 5.02, N 11.29. ^{1}H NMR (D$_2$O, 300 K): δ = 2.60 (m, 4 H, CHNR$_2$), 2.34 (m, 4 H, CH$_2$NR), 1.98 (m, 4 H, CH$_2$R$_2$), 1.54 (m, 8 H, CH$_2$R$_2$), 1.25 (s, 12 H, CH$_2$R$_2$), 1.08 (t, 4 H, CH$_2$R$_2$) ppm.

10-ane: Yield 165 mg (0.17 mmol, 43%). $C_{22}H_{52}Cl_2N_8O_6Pt_2$ (985.76): calcd. C 26.81, H 5.32, N 11.37; found C 26.10, H 5.16, N 10.81. ^{1}H NMR (D$_2$O, 300 K): δ = 2.60 (m, 4 H, CHNR$_2$), 2.34 (m, 4 H, CH$_2$NR), 1.97 (m, 4 H, CH$_2$R$_2$), 1.54 (m, 8 H, CH$_2$R$_2$), 1.24 (s, 16 H, CH$_2$R$_2$), 1.08 (t, 4 H, CH$_2$R$_2$) ppm.

4-diyne: Yield 77 mg (0.08 mmol, 20%). $C_{26}H_{36}Cl_2N_8O_6Pt_2$ (1017.68): calcd. C 30.69, H 3.57, N 11.01; found C 30.17, H 3.67, N 10.63. ^{1}H NMR (D$_2$O, 300 K): δ = 8.86 (s, 2 H, CH), δ = 8.68 (d, 2 H, CH), 8.10 (d, 2 H, CH), 7.52 (t, 2 H, CH), 2.47 (m, 4 H, CHNR$_2$), 2.01 (t, 4 H, CH$_2$R$_2$), 1.56 (d, 4 H, CH$_2$R$_2$), 1.30 (m, 4 H, CH$_2$R$_2$), 1.11 (m, 4 H, CH$_2$R$_2$) ppm.

Preparation of Complex Solutions: The desired solutions of the aqua complexes **8**-ane, **10**-ane and **4**-diyne (see Figure 1) were prepared by dissolving a known amount of the chloro complexes in 0.0010 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 0.10 M NaOH, which resulted in the precipitation of brown Ag$_2$O. 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 0.010 M triflic acid to give the desired complex concentration of 0.05 mM. For all investigations, the pH of the solution was kept at 2.0 and the ionic strength was adjusted to 0.2 M with sodium triflate.

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, respectively. Kinetic measurements on fast reactions were performed on an Applied Photophysics SX 18MV stopped-flow instrument coupled to an online data acquisition system. UV/Vis spectra were recorded on a Varian Cary 5G spectrophotometer equipped with a thermostatted cell holder for the study of slow reactions.

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 possible contamination and subsequent substitution reactions with chloride ions coming from the electrolyte in the pH electrode. The pH dependence of the diaqua complex was monitored by UV/Vis spectroscopy. Typical examples of the spectral changes observed during the pH titration are shown in Figures 4 and 5 for **8**-ane and **4**-diyne, respectively, and Figure S1 for **10**-ane (see Supporting Information). Plots of the absorbance vs. pH at specific wavelengths were used to determine the pK_a values of the coordinated water ligands. The data points were fitted using a non-linear least square procedure.

Quantum Chemical Calculations: All structures were pre-optimized at the RHF/LANL2MB[16–19] 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/LACVP* as implemented in Jaguar 6.5.[20–28]

Supporting Information (see also the footnote on the first page of this article): UV/Vis spectra and results of concentration and temperature dependent kinetic measurements are reported in Figures S1–S9.

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