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Journal of Coordination Chemistry

ISSN: 0095-8972 (Print) 1029-0389 (Online) Journal homepage: www.tandfonline.com/journals/gcoo20

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To cite this article: Gerald Enos, Allen Mambanda & Deogratius Jaganyi (2013) Substitution of aqua ligands from alkyldiamine-bridged dinuclear Pt(II) complexes using azole nucleophiles, Journal of Coordination Chemistry, 66:24, 4280-4291, DOI: 10.1080/00958972.2013.867026

To link to this article: https://doi.org/10.1080/00958972.2013.867026

Journal of Coordination Chemistry, 2013
Vol. 66, No. 24, 4280–4291, http://dx.doi.org/10.1080/00958972.2013.867026

Substitution of aqua ligands from alkyldiamine-bridged dinuclear Pt(II) complexes using azole nucleophiles

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(*Received 17 June 2013; accepted 5 November 2013*)

The rate of substitution of aqua ligands in dinuclear Pt(II) complexes, which are bridged by alkyldiamine linkers of variable chain lengths, and their mononuclear Pt(II) analogues were studied under pseudo-first order conditions as a function of concentration and temperature using azoles. The results indicate that substitution of aqua ligands of the dinuclear Pt(II) complexes occurs simultaneously and increases as the alkyl chain length of the diamine bridge increases. Steric hindrance due to the C_{2h} conformational symmetry, whose influence decreases as the length of alkylamine linker increases, appears to be the dominant factor controlling the reactivity of the dinuclear Pt(II) complexes. **Prop**, a homologue which has a 1,3-propanediamine bridge and a C_{2v} conformation, shows an unusual high reactivity. Weak sigma donicity due to the α,ω-alkyldiamine bridge is evident when the reactivity of dinuclear species is compared to their mononuclear analogues. Mononuclear Pt(II) complexes are more reactive than the dinuclear Pt(II) complexes with their reactivity increasing with increasing chain length of the alkylamine tail. The nucleophilicity of the azoles decreases in the order **Pz** > **Tz** > **mPz**. This is in accord with the basicity of the coordinating nitrogen donor in the case of **Pz** and **Tz**, while a steric hindrance to the approach of 1-methylpyrazole due to the ortho *N*-methyl substituent on the ring is evident for **mPz**. The substitution of aqua ligands by azoles remains associatively-activated.

Keywords: Aqua substitution; Dinuclear Pt(II) complexes; Azoles; α,ω-Alkyldiamine bridges

Introduction

The coordination chemistry of cisplatin has extended the search for more potent metallo-based drugs to other metal ions [1a]. The realization that a simple square-planar Pt(II) complex could treat cancers sprang unprecedented interest in exploring the coordination and redox properties of not only the Pt(II) metal ion but also its isoelectronic metal analogues such as Pd(II) and Au(III) [1b,c]. The development has also been extended to Ru(III)/(II) metal ions [1d–g]. For example, exploration of the redox chemistry of the central metal ion afforded third generation Pt(IV) ions [1a] and Ru(III) [1e,f] prodrugs with promising anticancer activity. Another promising route has been the development of multinuclear Pt(II) complexes. Extending the coordination and binding capabilities to more than one metal center saw a 100-fold improvement [1h,k] in the cytotoxicity of cisplatin. This

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group of multinuclear Pt(II) complexes make use of favorable electrostatic and hydrogen bonding interactions within their linking units in addition to covalent binding at the terminal platinum atoms. The mechanism of action of cisplatin and its related generations is now accepted to be the coordination of DNA nucleobases on the Pt(II) metal ion, mainly via the N7 atoms of the guanine [1a,b]. This triggers apoptosis mainly in hypoxic cells leading to their death.

Cancer is a daunting condition characterized by hyperactive growth of the cells caused by abnormalities which may develop in genetic materials leading to the formation of malignant tumor cells called neoplasms. Malignant tumors can invade neighboring tissues and spread to other parts of the body through metastasis via the blood and lymphatic systems [2–7].

Cancer ranks amongst the leading killer diseases in the world [8]. It can be treated by surgery [9], radiotherapy [10] and chemotherapy [11] with the latter method offering best prospects for cure [10, 11]. The most successful chemotherapeutic regimens in the clinic have been cisplatin and its analogues, carboplatin and oxaliplatin [12–25]. These three Pt (II) complexes share a common mechanism of action on the target sites, now widely believed to be the DNA nucleobases [26, 27]. They all form mainly 1,2-GG-intrastrand crosslinks which causes a conformational twist in the helical structures of DNA leading to cell death [27]. Cisplatin is highly effective in the treatment of testicular and ovarian cancers and is also widely employed for treating bladder, cervical, head, neck and small-cells lung cancers [28]. However, cisplatin treatment is shrouded by severe side-effects including nephrotoxicity, neurotoxicity, ototoxicity, nausea and development of resistance.

Carboplatin and oxaliplatin were developed to address the toxicity and the resistance problems of cisplatin. Carboplatin can be administered at higher dozes than cisplatin owing to its reduced toxicity due to its slow substitution kinetics of the bidentate dicarboxylate leaving group. Oxaliplatin has shown reduced resistance in cisplatin-sensitive cells possibly due to the slight structural differences on the DNA-Pt crosslink backbone conferred by the sterically demanding 1,2-diaminocyclohexane, the non-leaving group. These two drugs have not only complemented cisplatin-treatment but alleviated some of the long-term problems associated with cisplatin chemotherapy. However, all three drugs are only effective in a narrow spectral window of tumors due to their similar mechanism of action [29, 30].

Reedijk [31] has underscored that platinum-based drugs which are more effective than the ones currently in the clinic will come from tailored synthetic designs based on an intimate understanding of the mechanism and reactivity of the metal complexes including a clear consideration of their *in vivo* reactivity with bionucleophiles which forms the basis of the toxicity and development of resistance [32, 33].

In line with this thinking and as a way of consolidating this understanding, the substitution reactivity of symmetrical dinuclear Pt(II) complexes using azole nucleophiles, modelling reactions which may occur between the Pt(II) metal centers and homo-proteins, some of which are known to contain azoles as coordinating ligands, was undertaken. We choose azoles as incoming nucleophiles because they are good representatives of the nitrogen-containing biomolecules such as proteins which can possibly react with platinum drugs. Some of the reactions are thought to cause toxicity [26]. Moreover, the azoles are moderate nucleophiles unlikely to cause substitutional attack leading to the decoordination of two of the tetra-pyridyl chelating units of the alkyldiamine bridging ligand as reported in a similar study for strong thiourea nucleophiles [34, 35]. The important difference between the previous study [34, 35] and this work is that the thiourea nucleophiles represented bio-mimicking model nucleophiles simulating possible detoxifying and other bio-transformations of Pt(II) drugs which may lead to the development of drug resistance.

For this study, a series of dinuclear Pt(II) complexes bridged by α,ω-alkyldiamines of variable chain lengths together with their mononuclear analogues bearing alkyl pendants were synthesized. The structures of the dinuclear Pt(II) complexes (shown in figure 1 as their aqua derivatives) offer attractive possibilities of forming DNA cross-links which are remarkably different from those formed by cisplatin and its analogues. It is known that the flexible and long range adducts offer improved circumvention to the development of cisplatin resistance [14].

A comparison of the reactivity of the dinuclear and their mononuclear analogues will provide important information relating to the factors that control the reactivity of the dinuclear Pt(II) complexes.

Experimental

Synthesis of complexes and preparation of kinetic solutions

The tridentate and hexadentate nitrogen donor ligands were prepared according to a published method of Sato *et al*. [36]. Coordination of the nitrogen tridentates and hexadentates to a Pt(II) precursor was done according to a published method of Hofmann *et al*. [37]. The

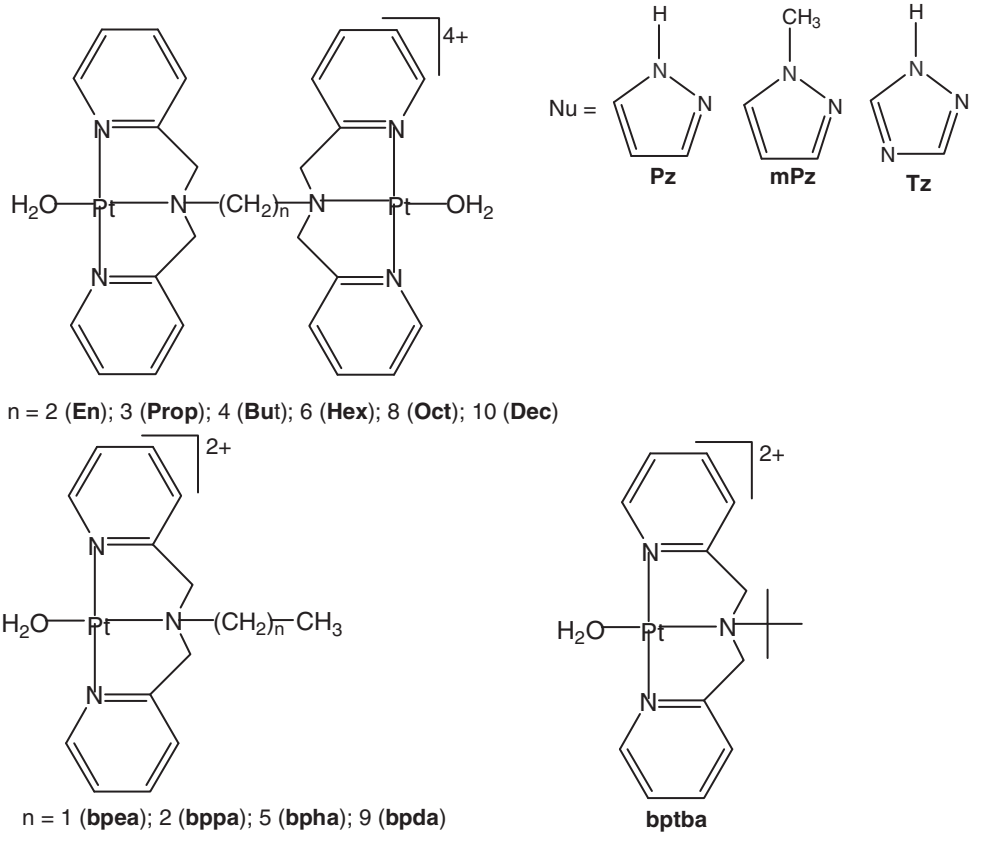


Figure 1. Structures of dinuclear and mononuclear Pt(II) complexes. Included in the figure are the structures of the azoles.

identity and purity of the compounds were confirmed by ^{1}H NMR, ^{13}C NMR, FTIR, ESI^{+}-TOF MS and elementary analysis.

The chloro derivatives were converted to their aqua forms by reacting with a silver salt following the method of Bugarčić *et al.* [38] and were diluted to the desired concentrations using a solution which comprised 0.09 M $NaClO_4$ dissolved in 0.01 M $HClO_4$. The structures of the aqua complexes are shown in figure 1. Nucleophile solutions of pyrazole (**Pz**), 1,2,4-triazole (**Tz**) and 1-methylpyrazole (**mPz**) were prepared freshly before each kinetic analysis by dissolving an appropriate amount of the nucleophiles in a 0.1 M ionic strength solution comprising 0.09 M $NaClO_4$ in 0.01 M $HClO_4$.

Physical measurements and instrumentation

Ligands and their Pt(II) complexes were characterized by NMR (Bruker Avance DRX 500), mass spectrometry (ES^{+}-TOF), FTIR and micro analysis (Flash 2000 Organic elemental analyser) and their data agree with previously reported values [34, 35]. UV/Visible spectra were recorded on a Varian Cary 100 spectrophotometer equipped with a thermostated cell compartment.

Kinetics

In order to determine the wavelengths at which kinetic analyses could be done, each Pt(II) complex was reacted with each azole nucleophile and a wavelength at which maximum absorbance change was observed was selected for monitoring the substitution reactions. All the substitution reactions were studied as a function of the concentration of azole nucleophiles and temperature under pseudo first-order conditions. The concentration of the azoles was always in 20-fold excess over the dinuclear Pt(II) complexes and 10-fold for the mononuclear Pt(II) complexes, respectively. The reaction mixture was maintained at a pH of 2 using a 0.01 M $HClO_4$ solution, whose ionic strength had been adjusted to 0.1 M with $NaClO_4$. This ensured that only the aqua forms of the complexes existed in solution [38, 40]. This is based on the fact that the pK_a values of these complexes range from 3.31 to 6.30 as reported in the literature [34, 35]. Representative spectra, showing the absorbance changes for the substitution of the aqua ligands for the reaction between **But** (0.2 mM) and **mPz** (16 mM), are shown in figure 2.

As seen from the inset in figure 2, when the spectral data due to the absorbance changes taken at 248 nm is fitted to an exponential decay function [41], a perfect fit showing only a single step for the substitution process is observed. This was true for all the reactions for all the other complexes. To check if there was a second and subsequent step, each complex was reacted with the most concentrated solution of each nucleophile at room temperature for at least 48 h with only one reaction step being observed. A representative kinetic trace, fitting only to a single exponential decay equation, is shown in figure SI 1 (see online supplemental material at http://dx.doi.org/10.1080/00958972.2013.867026) for the substitution of the aqua ligands in **Dec** (0.2 mM) by **Pz** (20 mM). It is therefore reasonable to conclude that the attack of the azoles on the symmetrical chelates of the Pt(II) dinuclear complexes occurs simultaneously and the dechelation reported in the literature [35] does not occur possibly due to the azoles being weaker nucleophiles in comparison to the thioureas.

The pseudo first-order rate constants, k_{obs}, determined from fitting data to a single exponential decay function [41] (shown as inset in figure 2) were plotted against the

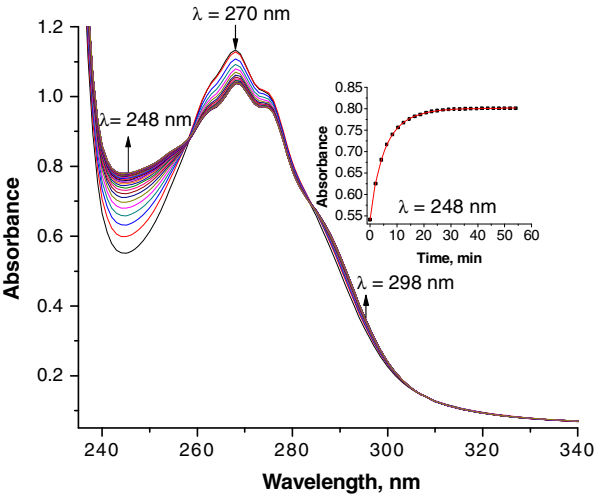


Figure 2. A representative plot showing the spectral changes that were recorded for simultaneous displacement of aqua ligands of **But** (0.2 mM) by **mPz** (16 mM), pH = 2.0, T = 298 K, I = 0.1 M {0.01 M $HClO_4$, adjusted with $NaClO_4$}. Inset is the kinetic trace at 248 nm.

concentration of the incoming azoles. Linear plots with no meaningful *y*-intercepts were obtained, indicating that the backward reactions or solvent pathway do not occur. Representative plots for the reactions for dinuclear and their corresponding mononuclear Pt(II) complexes with azoles are shown in figure 3a–d for **Dec**, **En**, **bpda** and **bpea**.

The slopes of each regression line afforded second-order rate constants, k_2 (M^{-1} s^{-1}), for the direct substitution of the coordinated water from the Pt(II) metal centers by the azole nucleophiles. The values of k_2 are summarized in tables 1a and 1b.

As already pointed out, the substitution of the aqua ligands in these Pt(II) complexes were studied as a function of temperature within the range 288 – 308 K. Representative Eyring plots are shown in figure 4a–d. The enthalpies of activation, $\Delta H^{\neq}$, for the substitution process were calculated from the slopes of the plots while the entropies of activation, $\Delta S^{\neq}$, were calculated from the extrapolated intercepts. The magnitude and sign of the activation parameters are useful indicators for mechanistic assignment and their values are collected in tables 1 and 2.

Discussion

As already stated, a reaction step fitting to a single exponential function is observed for the substitution reactions of all the mononuclear Pt(II) and dinuclear complexes with azoles. This observation supports a simultaneous substitution of the aqua ligands at the symmetrical Pt(II) centers of the dinuclear complexes in all reactions.

Scheme 1 depicts the proposed pathway illustrating the simultaneous substitution of the aqua ligands via a dual and symmetrical bipyramidal transition state.

A look at the data in table 1 shows a monotonic increase in the rate of the simultaneous substitution of the aqua ligands as the alkyl chain length of the diamine bridge increases

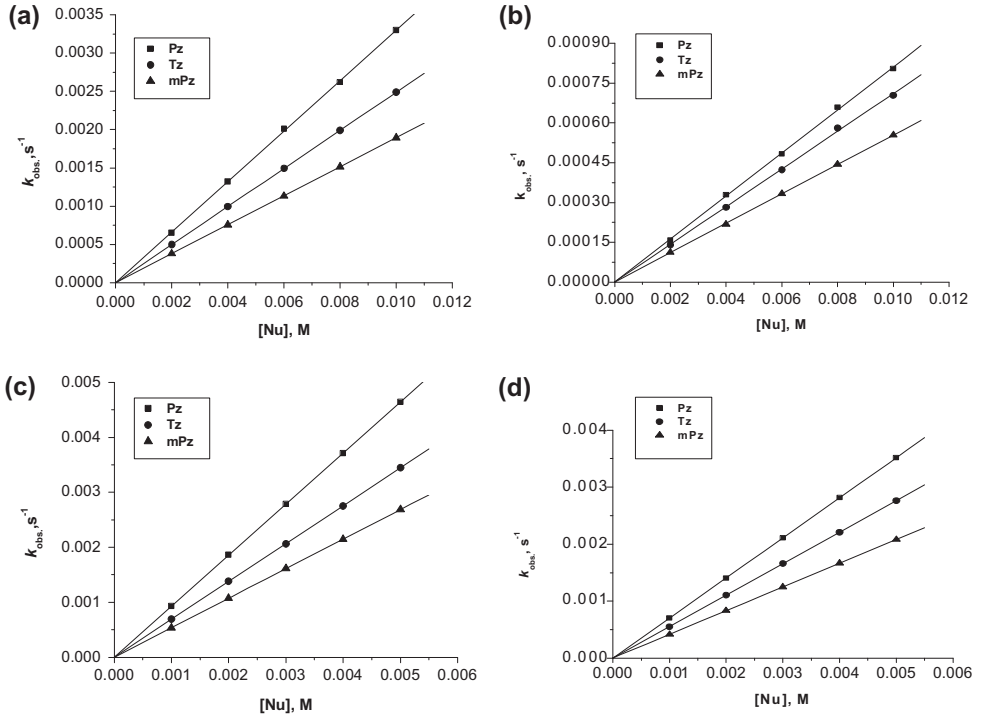


Figure 3. Concentration dependence of k_{obs}, s^{-1} for simultaneous substitution of the aqua ligands in **Dec** (a) and **En** (b) and substitution of the aqua ligands in **bpda** (c) and **bpea** (d) by azoles nucleophiles, pH = 2.0, T = 298 K, I = 0.1 M {0.01 M $HClO_4$ adjusted with 0.09 M $NaClO_4$}.

Table 1a. Summary of the second-order rate constants and activation parameters for the simultaneous displacement of aqua ligands of the dinuclear complexes by azoles.

Complex	Nucleophile	k_2, 10^{-3} M^{-1} s^{-1}	$\Delta H^{\neq}$, kJ mol^{-1}	$\Delta S^{\neq}$, J K^{-1} mol^{-1}
En	**Pz**	81 ± 1	51 ± 2	–96 ± 6
	Tz	64 ± 1	51 ± 1	–97 ± 4
	mPz	35 ± 1	58 ± 2	–116 ± 6
Prop	**Pz**	849 ± 7	47 ± 2	–88 ± 5
	Tz	764 ± 3	48 ± 1	–92 ± 3
	mPz	109 ± 1	50 ± 3	–96 ± 9
But	**Pz**	189 ± 6	45 ± 2	–107 ± 6
	Tz	71 ± 1	51 ± 2	–99 ± 7
	mPz	55 ± 1	58 ± 3	–107 ± 9
Hex	**Pz**	291 ± 6	47 ± 1	–65 ± 3
	Tz	229 ± 3	50 ± 1	–93 ± 4
	mPz	89 ± 1	54 ± 2	–85 ± 6
Oct	**Pz**	311 ± 2	58 ± 1	–60 ± 3
	Tz	283 ± 8	59 ± 1	–42 ± 3
	mPz	73 ± 6	68 ± 1	–77 ± 3
Dec	**Pz**	324 ± 1	48 ± 2	–60 ± 6
	Tz	250 ± 2	52 ± 1	–73 ± 3
	mPz	185 ± 3	57 ± 3	–70 ± 9

Table 1b. Summary of the second-order rate constants and activation parameters for the substitution of aqua ligands of mononuclear Pt(II) complexes by azoles.

Complex	Nucleophile	k_2, 10^{-3} M^{-1} s^{-1}	$\Delta H^{\neq}$, kJ mol^{-1}	$\Delta S^{\neq}$, J K^{-1} mol^{-1}
bpea	**Pz**	720 ± 1	49 ± 1	–83 ± 3
	Tz	550 ± 3	51 ± 2	–79 ± 6
	mPz	410 ± 2	58 ± 2	–88 ± 6
bppa	**Pz**	740 ± 7	47 ± 1	–89 ± 4
	Tz	570 ± 3	51 ± 2	–80 ± 6
	mPz	420 ± 6	55 ± 2	–86 ± 5
bpha	**Pz**	810 ± 3	47 ± 1	–88 ± 4
	Tz	600 ± 2	52 ± 2	–74 ± 5
	mPz	490 ± 1	53 ± 1	–105 ± 3
bpda	**Pz**	940 ± 1	50 ± 2	–79 ± 7
	Tz	670 ± 8	52 ± 2	–74 ± 5
	mPz	520 ± 8	57 ± 1	–94 ± 3
bptba	**Pz**	1260 ± 1	41± 3	–72 ± 9
	Tz	1130 ± 1	46 ± 2	–89 ± 6
	mPz	680 ± 1	58 ± 3	–82 ± 8

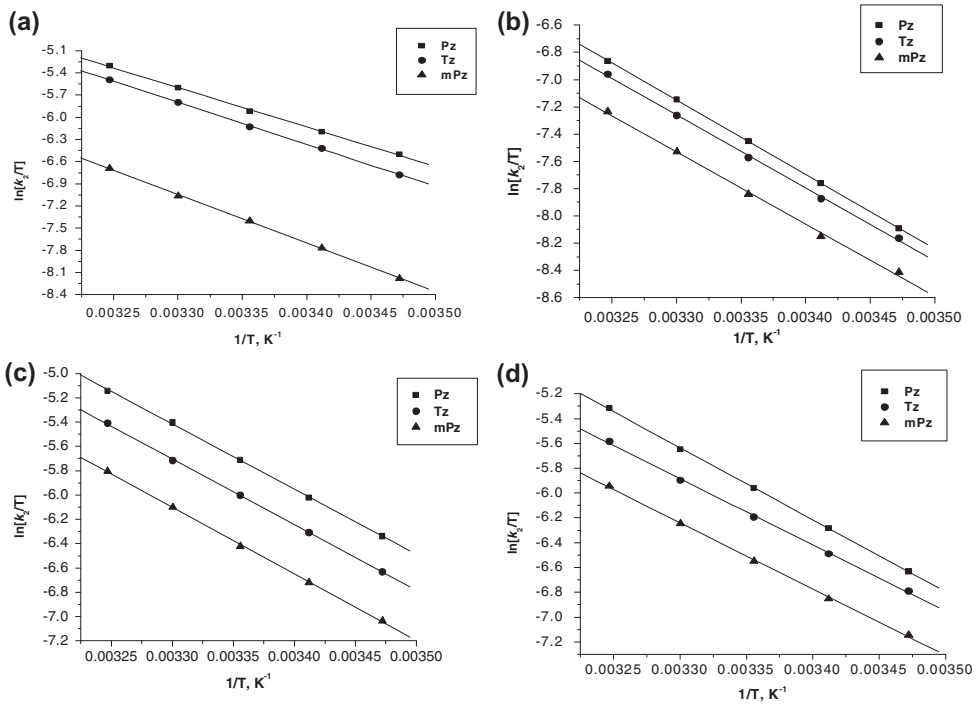


Figure 4. Eyring plots for simultaneous substitution of the aqua ligands in **Dec** (a) and **En** (b) and substitution of aqua ligands in **bpda** (c) and **bpea** (d), respectively, by azoles, pH = 2.0.

from **En** to **Hex**. A further increase in chain length beyond the hexyldiamine shows a small sequential increase. However, **Prop** (n = 3) is asynchronous to this. The complete trend of reactivity is **En** < **But** < **Hex** < **Oct** < **Dec** < **Prop**. For example, when **Pz** is the incoming nucleophile and the rate constant for **En** is taken as a base, the reactivity ratio comes to 1

Table 2. Comparison of second-order rate constants for aqua substitution from dinuclear and mononuclear Pt(II) complexes by **Pz**.

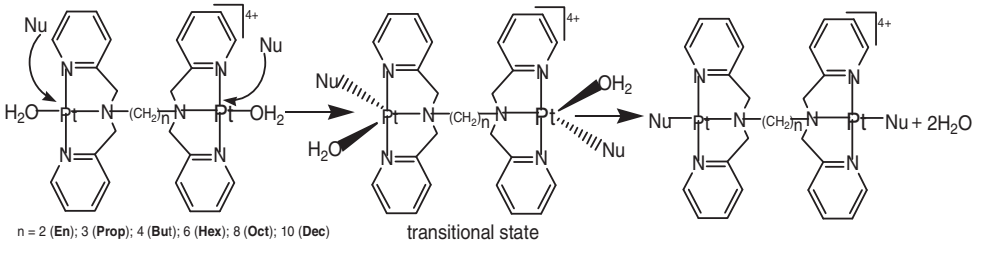
Dinuclear complex	k_2, 10^{-3} M^{-1} s^{-1}	Mononuclear complex	k_2, 10^{-3} M^{-1} s^{-1}	Reactivity factor (r_{srf})
En (n = 2)	81 ± 1	**bpea** (n = 2)	720 ± 1	9.0 ± 0.20
Prop (n = 3)	849 ± 7	**bppa** (n = 3)	740 ± 7	0.9 ± 0.01
Hex (n = 6)	291 ± 6	**bpha** (n = 6)	810 ± 8	2.8 ± 0.07
Dec (n= 10)	324 ± 0.5	**bpda** (n = 10)	940 ± 1	2.9 ± 0.01

n = number of CH_2 groups in a linker or tail of the Pt(II) complex.

(**En**): 2 (**But**): 3.6 (**Hex**): 3.8 (**Oct**): 4 (**Dec**). A similar trend of reactivity is observed when **Tz** and **mPz** are the incoming nucleophiles. The reactivity follows the same trend as reported in the previous study [34]. An exception is that no dechelation of the pyridyl units of the hexadentate chelate ligands is observed with the azoles. This can be explained in two ways, the azoles are weaker nucleophiles compared to the thiourea used in the previous study [34] and the fact that the Pt-$N_{pyridyl}$ bond in the chelate of the complex are stronger than those which would be formed by the N-atom from azoles on dechelation. Assuming a near in-plane coordination of the aromatic rings on the Pt(II) center, the lone pair of electrons on the nitrogen of the pyridine should experience less lone pair/bonding pair repulsions from the ring electrons when compared to the azoles irrespective of their identity. The ring angle of 108° in 5-membered azoles projects the sp^2 hybrid orbital at an offset from the square plane, resulting in formation of weaker bonds. Thus, forming azole bonds through dechelation is disfavored on energy grounds.

The above trend of reactivity of the dinuclear Pt(II) complexes can be explained in terms of steric influences at the square-planar platinum center brought about by their C_{2h} conformations as reported in a previous study [34]. The steric influences at each Pt(II) chelate due to the C_{2h} symmetry become weaker as the chain length of the diamine linker increases, leading to a systematic increase in reactivity as the separation distance between the Pt(II) metal centers increase from **En** to **Dec**. The decrease in the steric influence conferred at the Pt(II) chelates as the chain length of the linker increases is reflected in the trend of the rate constants in table 1. For example, **En** (n = 2), which has the shortest linker, is about 4 times less reactive than **Dec** (n = 10) when **Pz** is the incoming nucleophile. Similar reactivity trends are observed for the other nucleophiles.

If the reactivity data for mononuclear Pt(II) complexes are considered, a similar trend to the one already outlined for the dinuclear Pt(II) complexes is observed. Again no dechelation of the pyridyl units was observed. However, the mononuclear Pt(II) complexes are



Scheme 1. Proposed reaction pathway, illustrating the simultaneous substitution of the aqua ligands by azoles in dinuclear Pt(II) complexes at pH = 2.

more reactive than their dinuclear Pt(II) analogues. These observations support the conclusion that reactivity of the dinuclear Pt(II) complexes is controlled by a dominating steric influence due to their C_{2h} conformations which does not exist in their mononuclear analogues, leaving only a weak sigma inductive effect to accelerate the reactions as the chain length of the alkylamine pendant increases in the latter set of complexes.

To further infer on the relationship between the reactivity data of the dinuclear Pt(II) complexes and their mononuclear analogues, we calculated a steric relief factor, r_{srf} where

$$r_{srf} = \frac{k_{2(\textbf{mononuclear}),}\mathrm{M}^{-1}\mathrm{s}^{-1}}{k_{2(\textbf{dinuclear}),}\mathrm{M}^{-1}\mathrm{s}^{-1}} \tag{1}$$

for each mononuclear complex. The values of r_{srf} are listed in table 2 when **Pz** is considered as the incoming nucleophile.

Excluding the **bppa**/**Prop**, the r_{srf} values decrease by a factor of 3 from the **bpea**/**En** to the **bpha**/**Hex** and remains constants to the **bpda**/**Dec** pairs of complexes. The decrease in r_{srf} with the increase in chain length of bridge/pendant clearly indicates that the steric effects are more predominant in the shorter bridge of **En** than in **Hex** which has a longer bridge and remains relatively constant as the chain length further increases to **Dec**. One can therefore conclude that the increase in reactivity from **Hex** to **Dec** is mostly due to increase in σ-inductive effect of the alkyl chain.

The higher reactivity of **Prop** clearly reflects the significant role of the conformational symmetry on the rate of simultaneous substitution in the dinuclear Pt(II) complexes. The data in table 1 show that **Prop** is more reactive than **Dec** which has the longest alkyldiamine linker. The C_{2v} conformational symmetry of **Prop** confers a bowl-like structure, which causes high reactivity due to the entrapment of the azole nucleophiles [34]. This kind of conformational effect on the reactivity has previously been reported [34, 35].

Apart from the steric influence, the reactivity of dinuclear complexes is also controlled by the sigma donicity from the alkyldiamine linker. This argument is supported by looking at the trend of reactivity of the mononuclear complexes. The rate of reactivity of the mononuclear complexes increases moderately with the chain length of alkylamine pendant from **bpea** to **bpda** due to a moderate increase in sigma donation towards the Pt(II) centers through the well-known *trans*-effect. This donation is stronger in the mononuclear complexes because the electron density of the alkylamine pendant is donated solely to a single Pt(II) metal center, while it is shared between the two Pt(II) metal ions in the dinuclear complexes. When the number of CH_2 groups increase in the diamine linker, so does the electron density within the linker. Thus, an increase in sigma donation of electron density via the tertiary nitrogen atoms of the diamine linker into the Pt-N bond occurs as the alkyldiamine chain length of the linker increases. This increased electron density strengthens the Pt-N bond while weakening the Pt-OH_2 bond *trans* to it. This *trans*-influence leads to an increase in substitution reactivity as the chain length of the alkylamine increases. Further evidence in support of the sigma donicity of the alkylamine towards the Pt(II) metal centers comes from the high reactivity of **bptba**, due to a much stronger electron donation from its tertiary butyl pendant. This argument is supported by theoretical data reported in the literature [35] which shows that **bptba** has the longest Pt-OH_2 bond length when compared to its analogues of the same chain length [35].

While the sigma induction effect is weaker than the steric effect in the dinuclear complexes, it is noteworthy to point out that these two factors supplement each other. The inductive effects are weaker when the chain length of the alkyldiamine bridge is short,

while the steric effects are stronger due to the C_{2h} conformational symmetry of the complexes. The supplementary effect is observed when the chain length is increased. From table 1, it is clear that the rate of substitution increases as the chain length of the alkyldiamine bridge increases with the rate constants for the mononuclear complexes being more linearly correlated with the increase in chain length of the bridge than it is for the dinuclear species, suggesting that the rate of substitution of the aqua ligands of the dinuclear species are affected by more than one factor.

The azoles substitute the aqua coordinated ligands in the order **Pz** > **Tz** > **mP**z. This trend correlates well with the basicity of the nucleophiles in the case of **Pz** (pK_a = 2.52) and **Tz** (pK_a = 2.19) [44–48] and steric effect in the case of **mPz**. A similar trend of reactivity for the azole nucleophiles was observed by Reddy *et al*. [48].

Despite the expected sigma inductive effect of the methyl group towards the azole ring, **mPz** reacted slower than **Tz** and **Pz**. This shows that the steric hindrance due to the ortho *N*-methyl group on the approach of pyrazole to the Pt(II) metal center was dominating over its sigma inductive effect, hence slowed down the reactivity of **mPz**.

To better our understanding on the nucleophilicity differences between **Pz** and **Tz**, we looked at the ionization energies of the lone pair of electrons on the nitrogen donor atoms. The ionization potential is a good gauge and pointer for the availability of electrons at the nitrogen donor atom. Comparing the ionization potential of **Tz** (10.0 eV) and that of **Pz** (9.5eV) [45], it is clear that **Tz** is a poorer electron donor than **Pz** towards the Pt(II) metal centers. This is in agreement with the relative magnitudes of the rate constants of **Pz** and **Tz** with all Pt(II) complexes.

The temperature dependence of the rate constants shows that the energy needed to activate the reaction through the transition state, $\Delta H^{\neq}$, ranges from about 30 to 60 kJ mol^{-1} while the entropy of activation, $\Delta S^{\neq}$, ranges from –100 to –40 J mol^{-1} K^{-1}. This mode of activation supports a strong contribution from bond-making in the transition state of the substitution process as shown in scheme 1. As expected, reactions involving the more reactive nucleophiles have smaller enthalpies of activation when compared to the activation enthalpies of the reactions involving the sterically hindered nucleophile (**mPz**). This further supports the associative mode of activation which is common for square-planar Pt(II) complexes.

Conclusions

This study has shown that the rate of substitution of aqua ligands by azoles in alkyldiamine-bridged Pt(II) complexes is controlled mainly by steric effects due to the C_{2h} conformational symmetry of the dinuclear Pt(II) complexes, which become weaker when the chain length of the alkyldiamine bridge is increased. However, **Prop** recorded an unusual reactivity due to the entrapment effect evolving from its bowl-shaped molecular structure. A weak sigma donicity due to the alkyldiamine is also a contributing factor to the reactivity of the dinuclear Pt(II) complexes. The reactivity of the mononuclear Pt(II) analogues is controlled by the σ-trans-effect of the alkylamine tail. The nucleophilicities of the azoles decrease in the order **Pz** > **Tz** > **mPz**. This is in accord with the basicity of the coordinating nitrogen donor (in case of **Pz** and **Tz**) and steric effect for **mPz**. In all cases, the substitution reactions are associative. We postulate that the C_{2h} conformational symmetries of dinuclear Pt(II) complexes may play a crucial role in the design of dinuclear complexes

that can avert unwanted side reactions due to steric influence of their bridges, but at the same time offering similar covalent binding capabilities with DNA nucleobases.

Acknowledgements

The authors gratefully acknowledge financial support and bursary for Mr. G. Enos from the University of KwaZulu-Natal and a study leave from the University of Dodoma (UDOM).

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