Hydrogen isotope exchange in Pt^{II}–thiazole complexes †

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Hydrogen–deuterium exchange of the carbon-bound protons of thiazole coordinated to Pt^{II} in complexes **1**, **2** and **3**, has been measured in aqueous buffer solutions, at 60 °C, by ^1H NMR spectroscopy. Analysis of the rate data indicates that Pt^{II} enhances exchange of C(2)–H by a factor of *ca.* 10^6, with respect to the neutral substrate, but is *ca.* 10^3–10^4 times less effective compared to H^+ or Et^+. Exchange of C(5)–H is enhanced *ca.* 6×10^3 by Pt^{II} relative to the neutral heterocycle; an effect much less than that for C(2)–H exchange. We also report the first quantitative measurement of C(4)–H exchange in a thiazole moiety, as observed in **1** under moderate conditions (pD 8.69 and 60 °C, $k_2 = 2.54\ dm^3\ mol^{-1}\ s^{-1}$). The C(5)–H exchange process in complex **1** is moderately faster than C(4)–H exchange, a result opposite to that expected on the basis of an inductive/field effect by Pt^{II}. This is ascribed to the enhanced stabilization of the carbanionic intermediate at C(5) by the adjacent sulfur atom which is absent in the carbanion at C(4). This factor overrides the inductive/field effect of Pt^{II}, and accounts for the order of reactivity observed in this study, C(2)–H ≫ C(5)–H > C(4)–H.

The involvement of metal ions in the biological processes of life has long been a subject of interest. The modes of action of these metal ions are often complex but are believed, at least in part, to involve bonding to the heteroatoms (N, O, S) of the heterocyclic residues of biological molecules, *i.e.*, proteins, enzymes, nucleic acids, *etc.* The wide occurrence of heterocyclic moieties such as imidazoles, thiazoles, histidines, purines, *etc.*, in biological systems renders model studies of metal ion–biomolecule interactions important.

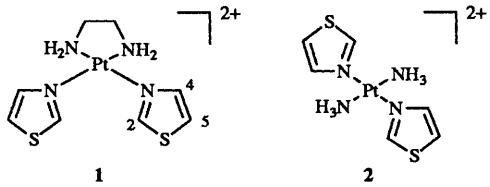
A useful handle for mechanistic studies is provided by the acidity of C(2)–H in imidazoles, thiazoles, histidines, *etc.*, and of C(8)–H in purines, nucleosides/nucleotides, nucleic acids, *etc.*, enabling studies of isotopic H/D/T exchange under conditions of catalysis by H^+ and M^{n+}.[1-6] Literature reports consistently show that metal ions are *ca.* 10^3–10^4 times less effective as catalysts compared to the proton in isotopic hydron (H/D/T) exchange in thiazoles,[1e,7] imidazoles,[5,7] histidines[4] and purines.[1a,3a,b] However, metal ions enhance reactivity, by a factor of *ca.* 10^4–10^6 compared to the neutral uncomplexed heterocycles;[1a,b,3a,b,4,7] the so-called 'metal activation factor, maf'.[1a] In most of such studies, salts of the metal ions (M^{n+} = Ag^+, Cu^{2+}, Ni^{2+}, $MeHg^+$, Zn^{2+}, *etc.*) are added in increasing amounts to aqueous solutions of the heterocycle.[1a,c,4,7] Since these metal ions form predominantly *labile* complexes in solution,[8] analysis of the kinetic data for isotopic exchange in these substrates is often complicated by the involvement of multiple stoichiometric equilibra.[7]

To avoid this complication, metal ions known to form predominantly *substitution-inert* complexes in solution, *e.g.*, Co^{III}, Cr^{III} and Pt^{II}, have been employed.[5,6k] Here, the metal ion–heterocycle complexes were isolated and characterized prior to the exchange measurements.[5,6k] In one such study, we recently reported the first observation of a metal ion-coordinated imidazole complex, *cis*-$[Cr(en)_2(MeIm)Cl]Cl_2$, where catalysis by Cr^{III} was found to be more effective than by H^+.[6k]

In the present work, hydrogen–deuterium (H/D) exchange in thiazole coordinated to Pt^{II}, a d^8 metal ion of the third transition series, has been studied. This class of metal ion is characterized by significant π-type metal-to-ligand back-bonding properties[9] and large atomic sizes. Pt^{II}, with a relatively small +2 charge and ionic radius (0.72 Å),[8b] is classified as a group 'b' metal ion, where the electrostatic (σ-withdrawing) effect on complexed ligands is weak.[10] The complexes of Pt^{II} are predominantly substitution-inert in solution. A number of Pt^{II}–ammine complexes have antitumour properties,[11] accounting for the large number of investigations into its coordination complexes with a host of biological molecules.[12]

The present study, as well as our previous findings for the Cr^{III} system, serve as models towards a better understanding of the effects of metal ions complexed to biologically important heterocycles by traversing the spectrum of metal ions that are either predominantly σ-withdrawing (electrostatic), *e.g.*, Cr^{III}, or act *via* a combination of σ + π (covalent) interactions, *e.g.*, Co^{III} and Pt^{II}. Towards this end, we have synthesized a series of Pt^{II}-complexed thiazoles **1**, **2** and **3**, and report here their isotopic C–H exchange measurements. To our knowledge, isotopic exchange studies of Pt^{II}-complexed thiazoles have not been previously reported.

Studies of C(2)–H exchange in the thiazolium ring are pertinent to the mode of action of thiamine, **4**, since it is known that base-induced abstraction of the C(2) proton of the thiazolium moiety of thiamine is intimately involved in its catalytic functions.[13,14]



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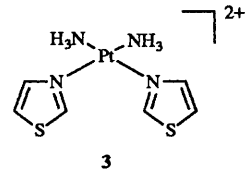

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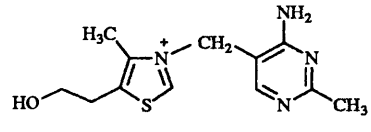

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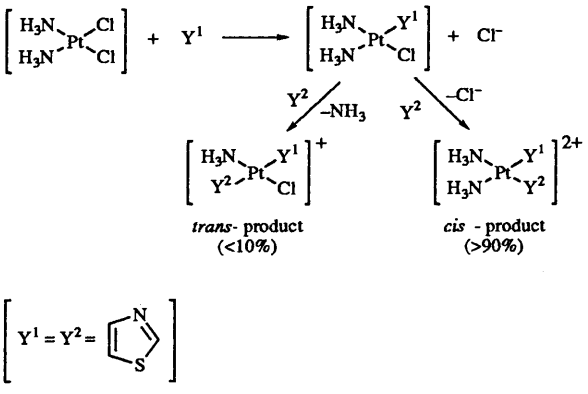
† Metal ion–biomolecule interactions. Part 17.

Results

(*a*) Synthesis of complexes

The synthetic route described previously for *trans*-$[Pt(NH_3)_2(MeIm)_2]Cl_2$,[15] was first used for the Pt^{II}–thiazole complexes, **1–3**. In this method, an aqueous suspension of the appropriate dichlorodiammine platinum(II) complex is reacted with a stoichiometric amount of thiazole, at 60 °C, for *ca.* 1 h. This procedure was successful for **1**, as expected, since stereochemical demands by the chelating diamine ligand (ethane-1,2-diamine, en) would lead to formation of a single isomeric product. As noted above, this procedure was used in the synthesis of *trans*-diamminebis(1-methylimidazole)platinum(II) complex by reacting *trans*-$[Pt(NH_3)_2Cl_2]$ with 2 mol equiv. of 1-methylimidazole.[15] In the present work an analogous reaction with thiazole gave **2**, also as expected. However, in the preparation of **3** reaction of *cis*-$[Pt(NH_3)_2Cl_2]$ with a stoichiometric amount of thiazole gave a mixture of *cis*-$[Pt(NH_3)_2(Th)_2]^{2+}$ (>90%) and *trans*-$[Pt(NH_3)(Th)_2Cl]^+$ (<10%) products. Assignment of *cis* and *trans* structures in this reaction was based on chemical shift positions of the ring protons while the relative amounts were determined from integration of the proton signals in the ^1H NMR spectra of the isolated product. The minor peaks in the ^1H NMR spectra of this product are shifted 0.2–0.4 ppm downfield with respect to free thiazole,[16] indicating that these are not impurities from the unchanged thiazole ligand.

The observation of a mixture of products (*cis* and a *trans* by-product) in the synthesis of **3** above can be rationalized by consideration of the mechanism of ligand substitution in square-planar Pt^{II} complexes shown in Scheme 1 which



Scheme 1 Mechanism of ligand substitution in the reaction of *cis*-$[Pt(NH_3)_2Cl_2]$ with 2 mol equiv. of thiazole (Y^1, Y^2)

illustrates pathways for ligand substitution in the reaction of *cis*-$[Pt(NH_3)_2Cl_2]$ with 2 mol equiv. of thiazole (Y^1, Y^2). In the first step of the reaction, a *cis*-bound Cl is replaced by the first thiazole ligand (Y^1) and the heterocycle (Y^1) is now *trans* to one of the *cis*-NH_3 ligands.[17,18] Subsequently, ligand (Y^2) substitution of the second *cis* Cl to form *cis*-$[Pt(NH_3)_2(Th)_2]^{2+}$, as well as a *trans-labilized* NH_3 group (by Y^1) to form *trans*-$[Pt(NH_3)(Th)_2Cl]^+$, can both occur under these conditions.[18] The Cl^- ion is a much better leaving group than NH_3, which is in accord with formation of the *cis* isomer as the major product (>90%) and the *trans* isomer as a minor by-product (<10%).

Hence a revised procedure originally employed in the synthesis of a series of *cis*-diammine(chloro)(nucleobase)-platinum(II) complexes by Lippert and co-workers,[19] was adopted for the synthesis of **3**. In this procedure the two *cis*-bound Cl ligands were replaced by aquo ligands (H_2O) and the diaquo complex, *cis*-$[Pt(NH_3)_2(H_2O)_2]^{2+}$, was reacted with a stoichiometric amount of the heterocycle *in situ*. Since H_2O is

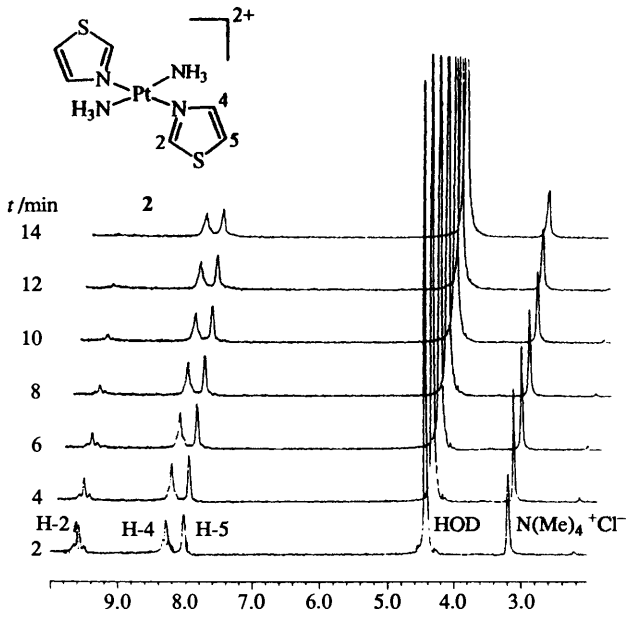


Fig. 1 ^1H NMR (200 MHz) spectra of **2** (pD 8.31; 60 °C) showing exchange of C(2)–H with increasing time

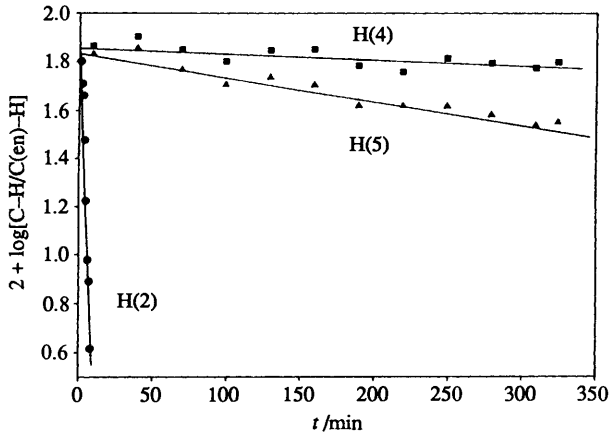


Fig. 2 Typical first-order plots for C–H exchange in **1** (pD 8.69; 60 °C) illustrating the reactivity order C(2)–H ≫ C(5)–H > C(4)–H

a better leaving group than the Cl^- ion in ligand substitution reactions of square planar Pt^{II} complexes,[17,18] replacement of the two *cis*-bound aquo ligands by thiazole under mild conditions (RT, 17 h) occurs much faster than the isomerization pathway, as evidenced by the single isomeric product isolated by this method.

(*b*) Isotopic C–H exchange studies

Rates of H/D exchange in the Pt^{II}–thiazole complexes **1–3** were measured in aqueous phosphate buffers, at 60 °C, by ^1H NMR spectroscopy. This technique allows one conveniently to assign chemical shifts of the coordinated thiazole ring protons, *i.e.*, H-2, H-4 and H-5, due to the strongly diagnostic ^{195}Pt–^1H coupling[20] between the metal ion (Pt^{2+}) and the ring protons, as well as monitor possible decomposition and/or ring-cleavage; both processes leading to loss of Pt–H coupling. In Fig. 1 are shown typical ^1H NMR traces of the kinetic exchange of C(2)–H with increasing time. The plots of log [C–H exchange/C–H non-exchanging] *versus* time were linear over three half-lives for C(2)–H, or one half-life for the much slower C(4)–H/C(5)–H exchange processes, as shown in Fig. 2. The pseudo-first-order rate constants of exchange (k_{obs}/s^{-1}) obtained from the slopes of

Table 1 Summary of k_{obs} values for C(2)–H exchange in complexes **1–3**, at 60 °C[a]

1			2			3		
pD[b]	$[OD^-]/10^{-6}$ mol dm^{-3}[c]	$k_{obs}/10^{-3}$ s^{-1}	pD[b]	$[OD^-]/10^{-6}$ mol dm^{-3}[c]	$k_{obs}/10^{-3}$ s^{-1}	pD[b]	$[OD^-]/10^{-6}$ mol dm^{-3}[c]	$k_{obs}/10^{-3}$ s^{-1}
6.67	0.074	0.019	6.04	0.017	0.088	6.41	0.04	0.040
8.10	2.00	1.62	6.93	0.135	0.152	6.93	0.135	0.108
8.31	3.24	2.66	8.10	2.00	2.08	8.10	2.00	1.37
8.46	4.57	4.12	8.31	3.24	3.20	8.31	3.24	2.55
8.69	7.76	7.04	8.46	4.57	4.59	8.69	7.76	6.60
			8.59	6.16	6.13	8.79	9.77	8.63

[a] Estimated error in k_{obs} is *ca.* ± 10%. [b] Room temperature measurements (pD = measured pH + 0.4).[40] [c] Calculated using pK_w (D_2O) at 60 °C = 13.8 (extrapolated value).[41]

Table 2 Rate constants for C(4)–H/C(5)–H exchange in complexes **1–3**, at 60 °C

		$k_{obs}/10^{-5}$ s^{-1}	
Complex	pD[a]	C(4)–H	C(5)–H
1	8.69	1.97	3.75
2	8.59	—	2.58
3	8.79	—	1.58

[a] Room temperature measurements (pD = measured pH + 0.4).[40]

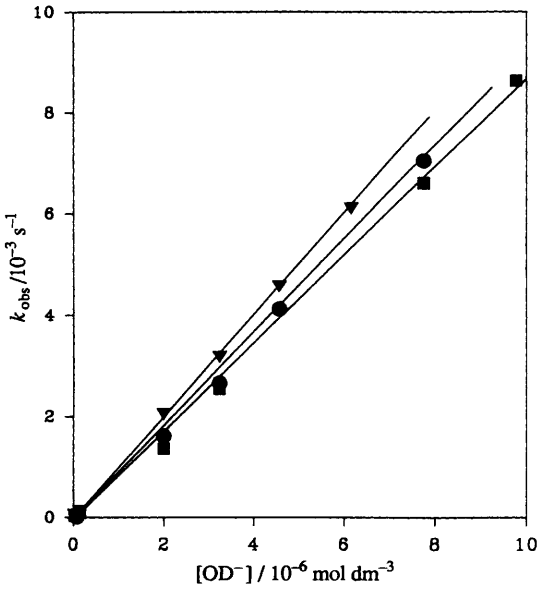


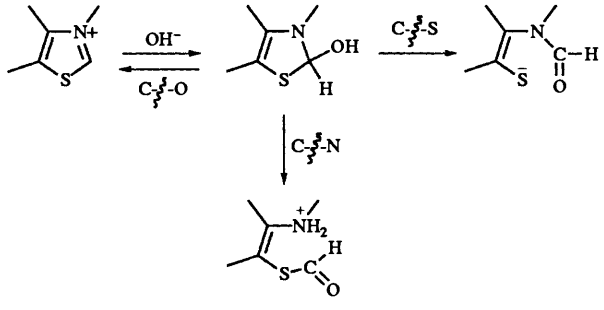
Fig. 3 Plots of k_{obs} *vs.* $[OD^-]$ for C(2)–H exchange in complexes **1–3** (60 °C): (**1**), ●; (**2**), ▼; (**3**), ■. The second-order rate constants (k/dm^3 mol^{-1} s^{-1}) shown in Table 3 were obtained from the slopes of these plots.

these plots (see the Experimental section) are given in Tables 1 and 2 for C(2)–H exchange and C(4)–H/C(5)–H exchange, respectively. In Fig. 3 are shown the plots of k_{obs} *vs.* $[OD^-]$ for C(2)–H exchange from which second-order rate constants (k_m/dm^3 mol^{-1} s^{-1}) for complexes **1–3**, at 60 °C, are obtained (Table 3). In the case of the slower C(4)–H and C(5)–H exchange processes, measurements could not be made in the higher pD region due to decomposition or ring-opening in these complexes. Hence the second-order rate constants (k_m) for these processes were calculated from the ratio of the k_{obs} value at the pD of measurement and the corresponding $[OD^-]$ [eqn. (2)].

Discussion

In this work we have measured isotopic exchange in the thiazole moiety of the Pt^{II} complexes **1**, **2** and **3**. It was found possible to evaluate this exchange at all ring positions, *i.e.*, C(2), C(4) and C(5). In comparing our results with those reported for related systems, it is noteworthy that in past studies of thiazolium or thiamine derivatives[21] complications have arisen from competitive ring cleavage, which has limited obtention of results for C(5)–H exchange, and prevented altogether evaluation of C(4)–H exchange. For example in neutral thiazole, C(4)–H exchange was not observed,[21a] while in an alkylated thiazole, exchange of C(5)–H was competitive with ring-cleavage; the ring cleavage at C(4) was very much faster than C(4)–H exchange.[21b] Thus, while C(2)–H exchange in thiazole and its derivatives is commonly observed under basic conditions,[1e,7,13,21–25] complications arising from hydrolytic ring cleavage predominates over exchange at other positions of the ring, especially at C(4).[21a,b]

The mechanism of ring cleavage is shown in Scheme 2[25,26,28–35] and involves formation of a tetrahedral *pseudobase*



Scheme 2 Base-induced ring-opening in thiazolium moieties

intermediate.[25–35] This can undergo ring opening (C–S or C–N bond scission) or revert back to the starting substrate under acidic conditions.[33] This process continues to attract much interest and studies have shown that the ring-opened product passes through biological membranes more easily than thiamine.[34]

The generalized mechanism for isotopic exchange of C(2)–H in heterocycles such as imidazole and thiazole and their derivatives is shown in Scheme 3. The first step involves rate-determining proton abstraction, which can occur either on the protonated species [path (*a*)], neutral species [path (*b*)], or on the metal ion-coordinated species [path (*c*)]. Since our study involves direct measurement of isotopic exchange on the isolated substitution-inert Pt^{II}–thiazole complexes, the ensuing discussion simplifies to consideration of the boxed-in portion of Scheme 3.

Table 3 Comparison of second-order rate constants (k/dm^3 mol^{-1} s^{-1}), at 60 °C, for C–H exchange in thiazole (Th) and its derivatives

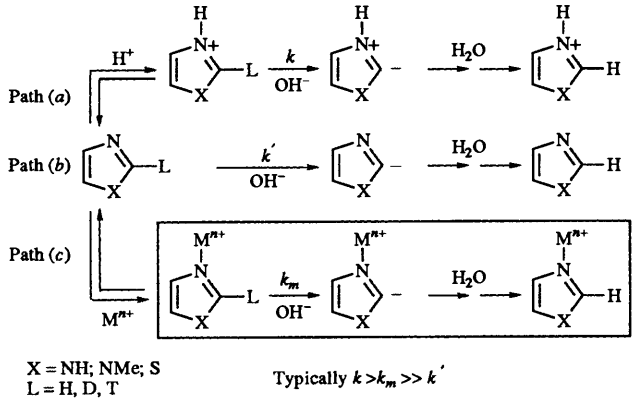
Ring position	Th	H^+–Th	Et^+–Th I^-	1	2	3
C(2)–H	9.3×10^{-4}	4.2×10^{6} [a]	1.9×10^{7} [b]	0.92×10^{3}	0.99×10^{3}	0.91×10^{3}
C(4)–H	—[c]	—	—[d]	2.54[f]	—	—
C(5)–H	7.0×10^{-4}	—	—[e]	4.83[f]	4.22[f]	3.69[f]
Ref.	21(*c*)	21(*c*)	21(*a*)	This work	This work	This work

[a] Calculated from data at pD 2.80 and T = 60.7 °C [ref. 21(*c*)]. [b] Study done at 31 °C [ref. 21(*a*)], extrapolated to 60 °C using E_a = 20.2 kcal mol^{-1} for C(2)–H exchange in thiazole [ref. 21(*c*)]. [c] C(4)–H exchange was not observed. [d] Ring cleavage is very much faster than this exchange [ref. 21(*b*), (*c*)]. [e] Exchange is competitive with ring cleavage. [f] Calculated from the ratio k_{obs}/[OD$^-$] [eqn. (2)].

Table 4 Relative rates of C–H exchange for protonated, *N*-alkylated and Pt^{II}–complexed thiazoles, with respect to neutral thiazole

Substrate	Relative rates[a] C(2)–H	C(5)–H	Ref.
Thiazole (Th)	1	1	21(*c*)
H^+–Th	4.5×10^{9}	—	21(*c*)
Et^+–Th (I^-)	2.0×10^{10}	—	21(*a*)
1	1.0×10^{6}	6.9×10^{3}	This work
2	1.1×10^{6}	6.0×10^{3}	This work
3	1.0×10^{6}	5.3×10^{3}	This work

[a] Rate constants for C(2)–H and C(5)–H exchange for these substrates are given in Table 3.



Scheme 3 Mechanism of isotopic C(2)–L exchange (L = H, D, T) in heterocycles

The kinetic expression derived for this process is given by eqn. (1),[1,3] from which eqn. (2) follows where k_m is the second-order rate constant for exchange of the complexes **1**–**3**.

$$\text{Rate} = k_m[A_2PtTh_2]\,[OD^-] \quad (1)$$

$$k_{obs} = k_m[OD^-] \quad (2)$$

As required by eqn. (2), plots of k_{obs} *versus* [OD$^-$] are linear with zero intercept (Fig. 3), the slopes yielding the second-order rate constants, k_m (Table 3). In Table 3 are also included literature values of rate constants for exchange in neutral, protonated and *N*-alkylated thiazoles. For thiazolium substrates ring opening is competitive with or preferential to exchange, as noted previously, thus precluding measurement of C(4)–H or C(5)–H exchange rates. In the present work we were successful in measuring the rate of C(5)–H exchange for all the complexes, but C(4)–H exchange could only be determined for **1** in the pD region examined (Table 2). At higher pD values, decomposition or ring-opening occurred.

The comparative data in Table 4 reveal the reactivity order

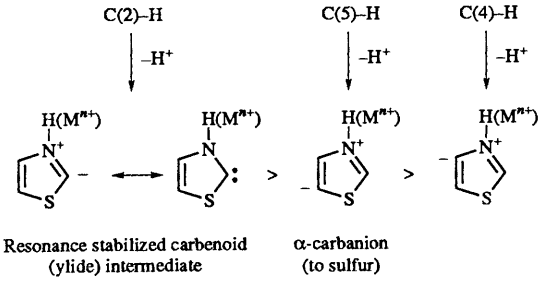


Fig. 4 Order of stabilization of carbanionic intermediate formed at C(2), C(4) and C(5) of thiazolium substrates on proton abstraction

for C(2)–H exchange as H^+–Th ~ Et^+–Th > Pt^{2+}–Th ≫ Th, with relative rates 10^9–10^{10}:10^6:1, respectively. The order of reactivity and the magnitude of the rate differences in this series follows most literature reports of C(2)–H exchange in heterocycles.[1a–c,3c–e,4,5,7] In contrast, C(5)–H exchange in thiazole is enhanced by a factor of *ca.* 6×10^3 for Pt^{II} relative to the neutral thiazole moiety; an effect much smaller than that for C(2)–H. It is noteworthy that in neutral thiazole the rate of C(2)–H exchange is closely similar to the rate of C(5)–H exchange, while C(4)–H exchange was not observed.[21b,c] In contrast, in the Pt^{II}–thiazole substrates, the rate of C(2)–H exchange is *ca.* 2×10^2 times greater than C(5)–H exchange. Finally, C(4)–H exchange in **1** was observed in this work, being the first quantitative measurement of this process in a thiazole moiety.

In general, C(2)–H exchange in heterocycles occurs much faster than C(5)–H and C(4)–H exchange.[1a,b,e,3c,d,4–7] Various factors have been invoked to explain the reactivity order:[1e,3b–d] (*a*) C(2) is adjacent to two electronegative atoms while both C(4) and C(5) are adjacent to only one, resulting in an intrinsically greater acidity of C(2)–H relative to C(4)–H and C(5)–H; (*b*) in the protonated substrate [path (*a*), Scheme 3], rate-limiting abstraction of C(2)–H results in a resonance-stabilized ylide intermediate (Fig. 4), this type of resonance is absent in the intermediate obtained on proton abstraction from C(4) and C(5);[1a,b,3–5,7] (*c*) σ-withdrawal by coordinated metal ions at N(3) (imidazoles, thiazoles, *etc.*) is much greater at C(2) than at C(5), *i.e.*, the through-bond inductive effect attenuates with distance.

It is interesting that in **1**, C(5)–H exchange occurs faster than C(4)–H exchange. If the inductive/field effect by Pt^{II} was solely responsible for the rate differences one would have expected the opposite to hold. Clearly, the dominant factor in this system must be that the intermediate formed on deprotonation at C(5) is an α-carbanion stabilized by the adjacent sulfur atom[21,36,37] (Fig. 4).

Finally, we would comment on possible reasons which have allowed the first successful measurement of C(4)–H exchange in the thiazole moiety of **1**. As shown by the data in Table 4, C(2)–H exchange in Et^+–Th is enhanced by 2×10^{10} relative to neutral thiazole, but in **1** this rate enhancement is only 1×10^6,

i.e., a significantly lower reactivity. Thiazole is a weak σ-donor but a fairly good π-receptor,[16] and it seems probable that the ability of Pt^{II} to participate in π-type metal-to-ligand back-donation would result in increased electron density in the thiazole rings, disfavouring attack by hydroxide ion. Hence formation of the tetrahedral pseudobase intermediate, the precursor in the ring-opening pathway (Scheme 2) is disfavoured in **1**, relative to the *N*-alkylated analogue, thus enabling C(4)–H exchange to become a competitively viable process.

Experimental

Materials

K_2PtCl_4 (99.9%) and *cis*-dichlorodiammineplatinum(II) (*c*-DPP or cisplatin) were purchased from Johnson Matthey. Na_2HPO_4 (99.9%), $NaH_2PO_4{\cdot}H_2O$ (99.9%), thiazole (99.9%), KI (99+%) and ethane-1,2-diamine (en, 99%) were obtained from Aldrich. NH_4OH was purchased from BDH and D_2O (99.9% atom D) was obtained from Matheson. The starting complexes [Pt(en)Cl_2] and *trans*-[$Pt(NH_3)_2Cl_2$] were synthesized according to literature procedures.[38]

Physical measurements

^1H NMR spectra of complexes **1**–**3** [in D_2O, referenced to TSP (sodium 3-trimethylsilylpentanoate)] were recorded on a Bruker ACF-200 spectrometer operating at 200.1 MHz frequency. IR spectra for samples in KBr disks were obtained on a Bomem-MB 200 FTIR spectrophotometer; melting points were determined on a Hoover Mel-Temp apparatus and are uncorrected while elemental analyses were performed by the Canadian Microanalytical Services, Delta, BC.

Isotopic C(2)/(4)/(5)–H exchange in the Pt^{II}–thiazole complexes **1**–**3** was measured for solutions in aqueous phosphate buffer (in D_2O), by ^1H NMR spectroscopy, using a kinetic program (REACT1H.AU) which automatically acquires kinetic data for hydrogen (^1H) exchange at some preset time intervals. All reactions were carried out at 60 ± 0.1 °C. Phosphate salts used in the preparation of the buffer solutions were initially exchanged with D_2O[21c] and buffers in the pH range of study were prepared according to the procedure of Perrin.[39] All pH values (in D_2O) are room temperature measurements on a Beckman Φ71 pH meter calibrated with standard aqueous buffers of pH 4, 7 and 10 (BDH). The corresponding pD values were obtained by adding 0.4 to the pH meter readings.[40]

Kinetic measurements

The exchange reaction was initiated by dissolving *ca.* 10 mg of complex in 0.5 cm^3 of the buffer solution in a vial (microcentrifuge, 1.5 cm^3), following which the mixture was rapidly transferred to a 5 mm NMR tube and placed in the spectrometer probe. A blank D_2O solution was used to lock and shim the magnet while kinetic parameters for data acquisition and processing were preset before introducing the kinetic sample into the probe. Rates of C–H ⟶ C–D exchange at various pD values were determined by following the decrease in area of the exchanging C–H peak relative to a non-exchanging C–H peak in the complex [in **1**, the aliphatic C(en)–H peak was used as an internal reference (these protons do not exchange under our conditions); while for **2** and **3**, $(CH_3)_4N^+Cl^-$ was used as an internal reference]. The measured pD of the kinetic samples before and after each run did not differ by more than 0.02 pH units. For C(2)–H ⟶ C(2)–D exchange (5 min $\leqslant t_{\frac{1}{2}} \leqslant$ 2 h), reactions were generally monitored over three half-lives, while the slower C(4)–H/C(5)–H exchange ($t_{\frac{1}{2}} \geqslant$ 5 h) was monitored for *ca.* one half-life. The first-order rates of exchange were obtained from the slopes of the linear plots of log [C–H(exchanging)/C–H(non-exchanging)] *versus* time (k_{obs} = −2.303 × slope). The estimated error in k_{obs} values from duplicate runs is *ca.* ± 10% for C(2)–H exchange, while errors in the slopes of the first-order plots are only *ca.* ± 5% in each kinetic run. The second-order rate constants (k_m/dm^3 mol^{-1} s^{-1}) for C(2)–H exchange in complexes **1**–**3**, at 60 °C, were determined from the slopes of the plots of k_{obs} *vs.* [OD^-]. For the slower C(4)–H and C(5)–H exchange processes, decomposition or ring-opening prevented measurements at higher pD region (pD > 9), and the second-order rate constants (k_m) were calculated from the ratio of the k_{obs} values at the pD of measurement with the corresponding [OD^-] values. The [OD^-] values were calculated from extrapolated literature pK_w (D_2O) at 60 °C (pK_w = 13.8).[41]

Synthesis of complexes

[Pt(en)(Th)$_2$]Cl$_2$·2H$_2$O (1). This was prepared according to the method of Johnson *et al.*[15] Reaction of [Pt(en)Cl_2][38] (0.101 g, 0.31 mmol) in water (5 cm^3) with thiazole (55 μl, 0.62 mmol), at 60 °C, yielded a white fluffy solid. The crude product was purified by being redissolved in water (2 cm^3) and allowed to stand at room temperature for *ca.* 2 h before being filtered. Dropwise addition of acetone to the aqueous solution gave a white microcrystalline solid, yield 0.12 g (60%), mp 330–333 °C (darkens at *ca.* 150 °C). $\delta_H(D_2O)$ 9.25 (H-2, dd, $^3J_{Pt-H}$ = 27.3 Hz), 7.95 (H-4, dd, $^3J_{Pt-H}$ = 17.5 Hz), 7.77 (H-5, dd) and 2.70 (CH_2, s, $^3J_{Pt-H}$ = 43.3 Hz) (Found: C, 18.1; H, 3.05; N, 10.5. Calc. for $C_8H_{14}Cl_2N_4O_2PtS_2$: C, 18.05; H, 3.38; N, 10.53%).

***trans*-[Pt(NH$_3$)$_2$(Th)$_2$]Cl$_2$·2H$_2$O (2).** This complex was obtained by a similar procedure as for **1**.[15] Reaction of *trans*-[$Pt(NH_3)_2Cl_2$][38] (0.21 g, 0.70 mmol) with thiazole (120 μl, 1.4 mmol) gave a white microcrystalline solid, yield 0.20 g (70%). Complex darkens at *ca.* 245 °C without melting (up to 300 °C), $\delta_H(D_2O)$ 9.40 (H-2, dd, $^3J_{Pt-H}$ = 30 Hz), 8.14 (H-4, dd, $^3J_{Pt-H}$ = 18 Hz) and 7.86 (H-5, ddd) (Found: C, 13.55; H, 2.8; N, 11.3. Calc. for $C_6H_{16}Cl_2N_4O_2PtS_2$: C, 14.23; H, 3.16; N, 11.07%).

***cis*-[Pt(NH$_3$)$_2$(Th)$_2$][(NO$_3$)$_2$ (3).** Following the above procedure for the preparation of **1** and **2**, the reaction of *cis*-[$Pt(NH_3)_2Cl_2$] (0.208 g, 0.72 mmol) and thiazole (124 μl, 1.44 mmol) in water, 60 °C (30 min), yielded 0.157 g (48%) of a white flaky solid which on isolation and purification as above was found to consist of a mixture of *cis* (> 90%) and *trans* (< 10%) products as shown by ^1H NMR spectroscopy. Comparison of the proton chemical shifts for the minor product with that of free thiazole[16] indicates that this minor product does not represent impurities from unchanged thiazole ligand. $\delta_H(D_2O)$ (major product) 9.30 (H-2, d, $^3J_{Pt-H}$ = 28 Hz), 7.99 (H-4, dd, $^3J_{Pt-H}$ = 15.2 Hz) and 7.73 (H-5, dd); $\delta_H(D_2O)$ (minor product) 9.43 (H-2, dd), 8.12 (H-4, dd) and 7.86 (H-5, dd).

Preparation of **3** was finally achieved by modification of a procedure originally employed in the synthesis of a series of *cis*-diammine(chloro)(nucleobase)platinum(II) complexes by Lippert and co-workers.[19] To a suspension of *cis*-[$Pt(NH_3)_2Cl$] (0.153 g, 0.51 mmol) in water (5 cm^3) was added a solution of $AgNO_3$ (0.17 g, 0.99 mmol) in water (5 cm^3) and the mixture was stirred in the dark at room temperature for 4 h. The white precipitate of AgCl was filtered off and thiazole (86 μl, 1.02 mmol) added. After being stirred at room temperature for 17 h, the resulting solution gave a greyish-white precipitate which was filtered off and the filtrate evaporated to a small volume; addition of acetone (10 cm^3) yielded an off-white solid product which was isolated and purified by the method used for **1** and **2** above. Yield 0.155 g (69%), mp 179–181 °C (decomp.), $\delta(D_2O)$ 9.32 (H-2, br d, $^3J_{Pt-H}$ = 27.8 Hz), 8.01 (H-4, br d, $^3J_{Pt-H}$ = 18 Hz) and 7.77 (H-5, dd) (Found: C, 13.5; H, 2.25; N, 15.75. Calc. for $C_6H_{12}N_6O_6PtS_2$: C, 13.77; H, 2.29; N, 16.06%).

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