

Studies on Pt–S bonds. Competition of chelating methylsulfanyl- or methylsulfinyl-acetate, -benzoate and -phenolate for $\text{Pt}^{\text{II}}(\text{H}_2\text{NCH}_2\text{CH}_2\text{NH}_2)$

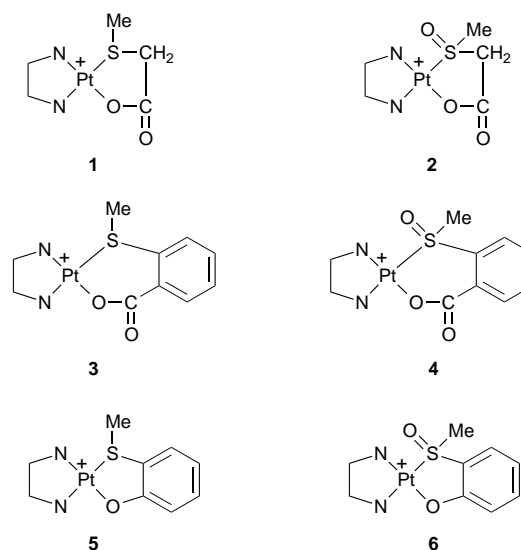
Alessandro Pasini* and Maurizio Moroni

Dipartimento di Chimica Inorganica, Metallorganica e Analitica, Università di Milano and CNR Centre, Via Venezian 21, 20133 Milano, Italy

The reactions of $[\text{Pt}(\text{en})(\text{L}-\text{S},\text{O})]^+$ (en = ethane-1,2-diamine) with L' , where both L and L' are the anionic chelating ligands methylsulfanylacetate, 2-(methylsulfanyl)benzoate, 2-(methylsulfanyl)phenolate and their methylsulfinyl analogues, have been studied by ^1H NMR spectroscopy in D_2O solutions at 40°C . Thioethers bind more strongly than sulfoxides to $\text{Pt}(\text{en})$ and within each series the order of affinity towards Pt is $^-\text{OC}_6\text{H}_4\text{SMe} > ^-\text{O}_2\text{CCH}_2\text{SMe} > ^-\text{O}_2\text{CC}_6\text{H}_4\text{SMe}$ and $^-\text{OC}_6\text{H}_4\text{S}(\text{O})\text{Me} > ^-\text{O}_2\text{CCH}_2\text{S}(\text{O})\text{Me} > ^-\text{O}_2\text{CC}_6\text{H}_4\text{S}(\text{O})\text{Me}$. The first step of the reactions is substitution of the Pt–O bond of L by the Pt–S bond of L' to give $[\text{Pt}(\text{en})(\text{L}-\text{S})(\text{L}'-\text{S})]$, with both ligands monodentate, S-co-ordinated, followed by closure of the chelate ring of L' , to give $[\text{Pt}(\text{en})(\text{L}'-\text{S},\text{O})]^+$, which occurs by displacement of the Pt–S bond of L by the oxygen atom of L' . The disubstituted species $[\text{Pt}(\text{en})(\text{O}_2\text{CCH}_2\text{SMe})_2]$, $[\text{Pt}(\text{en})(\text{O}_2\text{CC}_6\text{H}_4\text{SMe})_2]$ and $[\text{Pt}(\text{en})(\text{O}_2\text{CCH}_2\text{SMe})\{\text{OC}_6\text{H}_4\text{S}(\text{O})\text{Me}\}]$ are stable at 40°C and present at the end of the reactions in equilibrium with the reactants and the products. Only the former, however, could be isolated as a pure compound.

The interaction of the anticancer drug cisplatin $\text{cis-}[\text{PtCl}_2(\text{NH}_3)_2]$ or of its analogues of general formula $\text{cis-}[\text{Pt}(\text{am})_2\text{X}_2]$ (am = an amine or $\frac{1}{2}$ chelating diamine, X = a leaving ligand) with nucleobases and DNA has been the subject of a vast number of investigations because the cytotoxic activity of these platinum complexes is believed to arise from their binding to DNA.^{1–5} However, once the platinum complex has been injected into the body it can react with any nucleophilic centre, of particular biomedical relevance being the interaction of the $\text{cis-Pt}(\text{am})_2$ moiety with the sulfur centres of biomolecules.⁶ Thus platinum–methionine complexes^{7,8} have been found as metabolites of platinum drugs, the toxicity of cisplatin may be due to its binding to thiol-rich proteins,⁹ intracellular glutathione (γ -glutamylcysteinylglycine) is responsible for inactivation,¹⁰ cell protection and resistance,¹¹ while preinjection of glutathione results in a protective action against organ-specific toxicity¹² and thiocarbamates have been proposed as rescue agents towards acute cisplatin toxicity.¹³ According to recent reports,¹⁴ even the anticancer activity of cisplatin may be due, at least in part, to the inhibition of DNA polymerase- α through the binding of Pt to the sulfur centres of the enzyme. Finally some cisplatin analogues have been proposed, in which the $\text{cis-Pt}(\text{am})_2$ moiety is bound to sulfoxides^{15–17} or thioethers^{17,18} as the leaving groups. In fact the Pt–S bonds of these ligands are relatively inert towards water or chloride,^{16,17,19} but in some instances they may be easily substituted by guanine,^{6,16,17,19–21} a model reaction of platinum binding to DNA.

It therefore appears that many biological properties of cisplatin analogues depend on the stability and reactivity of the various Pt–S bonds formed *in vivo*. Consequently a knowledge of the factors governing the competition between various sulfur ligands for the $\text{cis-Pt}(\text{am})_2$ moiety may increase our understanding of the *in vivo* fate of platinum drugs and help in designing analogues possessing improved therapeutic indices as well as potential rescue agents. As a contribution to this, we report here the results of a study on the reactions of complexes **1–6**, $[\text{Pt}(\text{en})(\text{L}-\text{S},\text{O})]^+$ (en = ethane-1,2-diamine), with L' , where both L and L' are a series of potentially chelating ligands in which a sulfur atom of a sulfanyl (thioether) or sulfinyl (sulfoxide) group is linked to an oxygen atom of either a carboxylate or phenolate anion through a methylene or phenylene group.



The moderate cytotoxicity of some of these complexes, as well as their reactivity towards Cl^- or GMP (guanosine 5'-monophosphate dianion) have been reported.^{16,17} Briefly, while methylsulfinylacetate and 2-(methylsulfinyl)benzoate are completely substituted by either Cl^- or GMP, the sulfoxide complex **6** reacts only with the nucleobase. The sulfanyl derivatives are less reactive: only the carboxylate group of **3** is replaced by chloride, yielding the monochloro derivative $[\text{PtCl}(\text{en})(\text{O}_2\text{C}-\text{C}_6\text{H}_4\text{SMe}-2)]$. The dianion GMP, which completely displaces 2-(methylsulfanyl)benzoate from **3**, gives, with **1**, a monosubstitution product with S-co-ordinated methylsulfanylacetate. Compound **5** is inert towards these reagents. All these complexes are stable in aqueous solutions.^{16,17}

Experimental

All chemicals were reagent grade. The preparation of the proligands and complexes **1–6** has been reported elsewhere.^{16,17} The complex $[\text{PtCl}(\text{dien})]\text{Cl}$ (dien = diethylenetriamine) was obtained according to a recently published method.²²

Preparations

(Ethane-1,2-diamine)bis(methylsulfanylacetato-*S*)platinum(II)

7. This compound was obtained by heating at 40 °C for 1 h an aqueous solution of equimolar amounts of [Pt(en)-(O₂CCH₂SMe)]NO₃ **1** and methylsulfanylacetic acid (2.46 mmol, 1.039 and 0.2611 g respectively in 20 cm³) together with KOH (24.6 cm³, 0.1 mol dm⁻³). The solution was evaporated to dryness under reduced pressure and the residue extracted twice with ethanol-chloroform (3:1 v/v, 50 cm³), from which the compound was obtained as a white solid by addition of diethyl ether. Yield 0.8585 g, 75% (Found: C, 20.6; H, 4.0; N, 6.1. C₈H₁₈N₂O₂PtS₂ requires C, 20.6; H, 3.9; N, 6.0%). IR (cm⁻¹, KBr pellets): 1586, 1379 (ionic carboxylate) *cf.* K(O₂CCH₂SMe) 1586, 1400. For ¹H NMR see Table 1. ¹⁹⁵Pt NMR (D₂O solution): δ -3720 *vs.* [PtCl₆]²⁻ [*cf.* ref. 8(a)].

(Diethylenetriamine)(methylsulfanylacetato-*S*)platinum(II)

chloride. A solution of [Pt(dien)Cl]Cl (0.2082 g, 0.484 mmol) and methylsulfanylacetic acid (0.0598 g) (molar ratio 1:1) in water (10 cm³) was treated with LiOH (0.0134 g) and heated at 50 °C for 5 h. The filtered solution was evaporated to dryness *in vacuo*, and the residue was dissolved in methanol (10 cm³) and stored at 5 °C overnight, giving 0.1658 g (67%) of a white precipitate of the monohydrate (Found: C, 18.4; H, 4.5; N, 9.2. C₇H₂₀ClN₃O₃PtS requires C, 18.4; H, 4.4; N, 9.2%). NMR (D₂O solution): ¹H (40 °C), δ 2.75 (*J*_{PH} 42, CH₃S), 2.8–3.5 (CH₂ of dien) and 3.70 (*J*_{PH} 37 Hz, CH₂S); ¹⁹⁵Pt, δ -3376 *vs.* [PtCl₆]²⁻. IR (cm⁻¹, KBr pellets): 1605 and 1371. FAB mass spectrum (glycerol mull): *m/z* = 403, [Pt(dien)(O₂CCH₂SMe)]⁺.

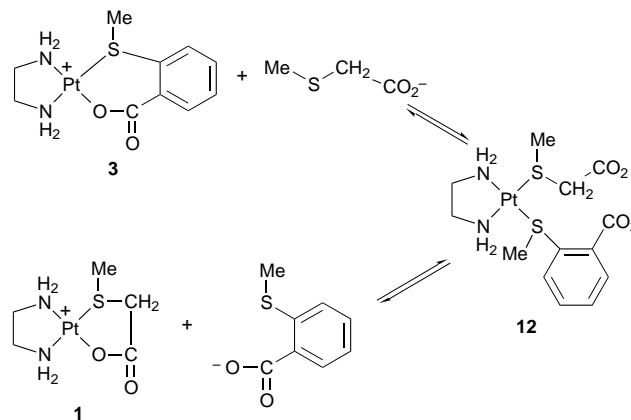
Reactivity studies

Stock D₂O solutions of known concentration of the potassium salts of the pro-ligands, to be used in these studies, were prepared by titration of the acids with 0.1 mol dm⁻³ aqueous KOH. After evaporation to dryness under reduced pressure, the residues were dissolved in known amounts of D₂O.

Reactions (1)–(36) were performed directly in NMR tubes. Weighed amounts of the complexes of L were treated with appropriate volumes of the stock D₂O solutions of the potassium salts of L'. Deuterium oxide was then added to give a final concentration 2 × 10⁻² mol dm⁻³ of each reagent. The pH* (the pH-meter reading uncorrected for D₂O) was in all cases around 6.5 and remained roughly constant (±0.1) during the course of the reactions. These were performed at 40 ± 1 °C and their time course was monitored by recording ¹H NMR spectra at the same temperature (either Bruker WP80 or AC200 instrument). The chemical shifts of the reactants, intermediates and products are referred to external SiMe₄ and are reported in Table 1. The *t*_{1/2} values in Table 2 refer to the disappearance of the reagents and were calculated from the integrated intensities of their resonances.

Equilibria (37) and (38) were studied by recording the ¹H NMR spectra at various temperatures (5–85 °C) of 10⁻² mol dm⁻³ D₂O solutions of complexes **1** and **3**, containing known amounts of K(O₂CCH₂SMe) and K(O₂CC₆H₄SMe-2) respectively. Dissociation constants were calculated from the integrated intensities of the signals.

Reaction between [Pt(dien)(O₂CCH₂SMe)]Cl and GMP. The platinum complex (0.0108 g) was mixed with GMP (0.0109 g) (disodium salt, dihydrate) directly in the NMR tube and D₂O (1.0 cm³) was added, to give a final concentration of 2.46 × 10⁻² mol dm⁻³ of each reagent. The pH* was 6.8. The tube was thermostatted at 40 ± 1 °C and ¹H NMR spectra were recorded, at intervals, at the same temperature. The spectrum was unchanged for 1 d, when the peak of ⁻O₂CCH₂SMe started to grow, together with a peak at δ 8.99 (*J*_{PH} 23 Hz) attributed to

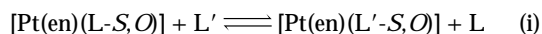


Scheme 1

H⁸ of GMP co-ordinated to Pt at the N⁷ position. After 30 d only the resonances of [Pt(dien)(GMP)] and of free ⁻O₂CCH₂SMe were observed; *t*_{1/2} 8 d.

Results and Discussion

The time course of the 36 cross-competition reactions (i)



between complexes **1**–**6** and the six anionic ligands has been monitored by ¹H NMR spectroscopy at 40 °C with equimolar concentrations (2 × 10⁻² mol dm⁻³ D₂O solutions) of the complexes and L'. The relevant ¹H NMR data are in Table 1. The nature of the products (characterized by comparison of their ¹H NMR spectra with those of authentic samples¹⁷) and the *t*_{1/2} values (corresponding to the disappearance of the reactants) are in Table 2. With few exceptions, see below, the product of the reactions is [Pt(en)(L'-S,O)]⁺, where the chelated L' has substituted L. Obviously, in these cases, when the direct reaction went to completion the reverse reaction was not observed.

Most reactions are rather fast (*t*_{1/2} ranging from 2 to 30 min), except for (20) [substitution of chelate ⁻O₂CC₆H₄S(O)Me-2 by ⁻O₂CCH₂S(O)Me, *t*_{1/2} = 5 d] and (33) [substitution of ⁻OC₆H₄-S(O)Me-2 by ⁻O₂CC₆H₄SMe-2, *t*_{1/2} = 7 d]. The order of affinity of the various pro-ligands towards the Pt(en) moiety is ⁻OC₆H₄SMe > ⁻O₂CCH₂SMe > ⁻O₂CC₆H₄SMe > ⁻OC₆H₄-S(O)Me > ⁻O₂CCH₂S(O)Me > ⁻O₂CC₆H₄S(O)Me, while for the donor atoms S > O, sulfanyl > sulfinyl and phenolato > carboxylato.

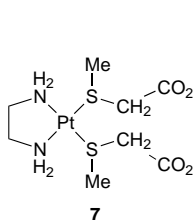
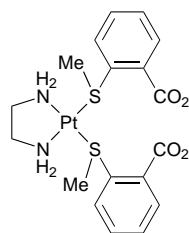
The NMR spectra, recorded during the time course of the reactions, show, in most cases, the presence of some peaks attributable to a disubstituted intermediate species of the type [Pt(en)(L-S)(L'-S)], where both L and L' are monodentate, S-co-ordinated (Pt-H coupling of the resonances of the MeS groups of both ligands, see Table 1). These species appear in the first spectra (about 2 min after mixing the reagents) their highest concentration (about 0.5 × 10⁻² mol dm⁻³) being reached at about two thirds of *t*_{1/2} and, with few exceptions, see below, are no longer visible at the end of the reaction.

A likely mechanism of these reactions is depicted in Scheme 1 for the case of reaction (13) between complex **3** and ⁻O₂CCH₂SMe which yields **1**. The spectrum recorded 2 min after mixing the reagents, shows, besides the peaks due to **3** and ⁻O₂CCH₂SMe, three peaks at δ 2.95 (*J*_{PH} 45), 3.05 (43) and 2.81 (45 Hz), in the ratio 4:3:3, which grow at the expense of those of **3**. Since these resonances are not due to **1** (see Table 1), they must be attributed to the CH₂ of en (four protons) and MeS of ⁻O₂CC₆H₄SMe and ⁻O₂CCH₂SMe (three protons each) of a new species **12**, with both ⁻O₂CCH₂SMe and ⁻O₂CC₆H₄SMe monodentate S-co-ordinated. After 10 min the peak due to MeS of ⁻O₂CC₆H₄SMe (δ 2.66) starts to grow,

Table 1 Proton NMR data for reactants, intermediates and products of reactions (1)–(36)^a

Compound	MeS	CH ₂ (en)	CH ₂ S
⁻ O ₂ CCH ₂ SMe	2.24		3.39
⁻ O ₂ CCH ₂ S(O)Me	2.94		3.75
⁻ O ₂ CC ₆ H ₄ SMe	2.66 ^b		
⁻ O ₂ CC ₆ H ₄ S(O)Me	3.08		
⁻ OC ₆ H ₄ SMe	2.54		
⁻ OC ₆ H ₄ S(O)Me	2.97		
1	2.80 (49)	2.89 (45)	3.96 ^c
2	3.92 (25)	2.99 (44)	4.74 ^c
3	2.90 (45)	2.90 (45)	
4	3.86 (23)	3.02 (44)	
5	3.00 (50)	3.00 (42)	
6	3.94 (24)	3.07 (43)	
7 [Pt(en)(O ₂ CCH ₂ SMe) ₂] [in reaction (1)]	O ₂ CCH ₂ SMe 2.81 (44)	3.08 (42)	3.95 (40)
8 [Pt(en)(O ₂ CCH ₂ SMe)(OC ₆ H ₄ SMe)] [in reaction (5)]	O ₂ CCH ₂ SMe 2.78 (44) OC ₆ H ₄ SMe 2.91 (50)	2.97 (44)	^c
9 [Pt(en)(O ₂ CCH ₂ SMe){OC ₆ H ₄ S(O)Me}] [reactions (6) and (31)]	O ₂ CCH ₂ SMe 2.78 (43) OC ₆ H ₄ S(O)Me 3.92 (24)	3.05 (43)	^c
10 [Pt(en)(O ₂ CCH ₂ SMe){O ₂ CCH ₂ S(O)Me}] [in reaction (7)]	O ₂ CCH ₂ SMe 2.60 (45) O ₂ CCH ₂ S(O)Me 3.60 (29)	3.03 (43)	^c
11 [Pt(en){O ₂ CCH ₂ S(O)Me}(O ₂ CC ₆ H ₄ SMe)] [in reaction (9)]	O ₂ CCH ₂ S(O)Me 3.81 (24) O ₂ CC ₆ H ₄ SMe 2.86 (46)	3.11 (44)	^c
12 [Pt(en)(O ₂ CCH ₂ SMe)(O ₂ CC ₆ H ₄ SMe)] [in reaction (13)]	O ₂ CCH ₂ SMe 2.81 (45) O ₂ CC ₆ H ₄ SMe 3.05 (43)	2.95 (45)	3.92 (40)
13 [Pt(en)(O ₂ CC ₆ H ₄ SMe) ₂] [in reaction (15)]	O ₂ CC ₆ H ₄ SMe 2.83 (40)	2.96 (44)	
14 [Pt(en){O ₂ CC ₆ H ₄ S(O)Me}(O ₂ CCH ₂ SMe)] [in reaction (19)]	O ₂ CC ₆ H ₄ S(O)Me 3.85 (24) O ₂ CCH ₂ SMe 2.78 (45)	3.06 (44)	^c
15 [Pt(en){O ₂ CC ₆ H ₄ S(O)Me}(O ₂ CC ₆ H ₄ SMe)] [in reaction (21)]	O ₂ CC ₆ H ₄ S(O)Me 3.84 (25) O ₂ CC ₆ H ₄ SMe 2.85 (45)	2.92 (44)	
16 [Pt(en){OC ₆ H ₄ S(O)Me}(OC ₆ H ₄ SMe)] [in reaction (35)]	OC ₆ H ₄ SMe 2.87 (48) OC ₆ H ₄ S(O)Me 3.93 (24)	3.06 (43)	

^a In D₂O solutions at 40 °C, δ in ppm vs. external SiMe₄, *J*_{PtH} in Hz. The values for the pro-ligands and compounds **1**–**6** are from refs. 16 and 17. ^b The value of δ 2.41 in ref. 17 is a printing error. ^c The resonances of the CH₂ groups of co-ordinated ⁻O₂CCH₂SMe and ⁻O₂CCH₂S(O)Me are seldom visible because of H–D exchange of these groups.¹⁶

**13**

together with those of the substitution product **1**. At *t*₁ (30 min) the intensities of the signals of species **12** are reduced and are no longer visible at the end of the reaction, when only the peaks of **1** and of free ⁻O₂CC₆H₄SMe are observed.

Some disubstituted species of the type [Pt(en)(L-S)(L'-S)], *i.e.* **7** [L = L' = ⁻O₂CCH₂SMe, reaction (1)], **9** [L = ⁻O₂CCH₂SMe, L' = ⁻OC₆H₄S(O)Me, reaction (6); or L = ⁻OC₆H₄S(O)Me, L' = ⁻O₂CCH₂SMe, reaction (31)] and **13** [L = L' = ⁻O₂CC₆H₄SMe, reaction (15)] are rather stable and are found at the end of the reactions in equilibrium with both [Pt(en)-(L-S,O)]⁺ and [Pt(en)(L'-S,O)]⁺. In particular at the end of reaction (1) the spectrum shows that **7** is practically the only species present, with only traces of **1** and free ⁻O₂CCH₂SMe. Complex **7** could be isolated under preparative conditions and characterized (see Experimental section). Attempts to isolate other disubstituted species as pure compounds failed, since they tend to give rise to the chelate [Pt(en)(L-S,O)]⁺ [reactions (6) and (15)] or [Pt(en)(L'-S,O)]⁺ [reaction (31)] upon crystallization.

No intermediate species was observed during the time course of reactions (11), (12), (17), (20), (23), (24) and (33). While some of these are probably too fast (*t*₁ ≈ 2 min) for such an

observation, for (20) [L = ⁻O₂CC₆H₄S(O)Me and L' = ⁻O₂-CCH₂S(O)Me, *t*₁ 5 d] and (33) [L = ⁻OC₆H₄S(O)Me, L' = ⁻O₂-CC₆H₄SMe, *t*₁ 7 d] such a failure must be due to an intrinsic instability and/or reactivity of the intermediates.

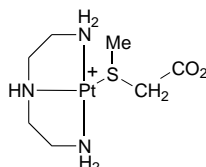
In the mechanism depicted in Scheme 1 the first step is substitution of the Pt–O bond of L-S,O by the Pt–S bond of L'. This will occur only if the balance between the stability of the chelate ring of L and the strength of the new Pt–S bond is favourable. Thus complex **5** is unreactive, while the ⁻O₂CC₆H₄S(O)Me chelate ring is easily broken and the sulfanyl groups are more 'aggressive' than the sulfinyl moieties.

The following step is, in a sense, the reverse process, in that a new Pt–O bond (of L') is formed at the expense of a bond between Pt and the soft S atom of L. This process again depends on two factors. First the relative strength and/or lability of the two Pt–S bonds of the intermediate: the platinum–sulfinyl bonds are more easily replaced by the anionic oxygen atom than are the platinum–thioether bonds. A second point is the formation of the chelate ring of L'. The thermodynamics of this process is easy to evaluate in the cases of reactions (1) and (15), where L = L', which give to the relatively stable (at 40 °C) **7** and **13**, respectively. At higher temperatures these compounds dissociate according to equilibria (37) and (38) [the reverse of reactions (1) and (15)], for which integration of the ¹H NMR peaks at various temperatures gave the following values (at 50 °C): [Pt(en)-(O₂CCH₂SMe)₂] ⇌ **1** + ⁻O₂CCH₂SMe, *K*_{dis 37} = 7.6 ± 0.9 10⁻³ mol dm⁻³, Δ*H* = 46 ± 4 kJ mol⁻¹ and Δ*S* = 101 ± 12 J K⁻¹ mol⁻¹; [Pt(en)(O₂CC₆H₄SMe)₂] ⇌ **3** + ⁻O₂CC₆H₄SMe, *K*_{dis 38} = 7.8 ± 0.1 10⁻² mol dm⁻³, Δ*H* = 31 ± 1 kJ mol⁻¹ and Δ*S* = 75 ± 4 J K⁻¹ mol⁻¹. These data, besides showing the different stabilities of the two chelate rings, clearly demonstrate the importance of chelate ring closure (the entropic

Table 2 Reaction numbering, t_r and products for the reactions $[\text{Pt}(\text{en})(\text{L}-\text{S}, \text{O})]^+ + \text{L}'^a$

L', reaction, t_r , products							
L, compound		$^-\text{O}_2\text{CCH}_2\text{SMe}$	$^-\text{O}_2\text{CCH}_2\text{S}(\text{O})\text{Me}$	$^-\text{O}_2\text{CC}_6\text{H}_4\text{SMe}$	$^-\text{O}_2\text{CC}_6\text{H}_4\text{S}(\text{O})\text{Me}$	$^-\text{OC}_6\text{H}_4\text{SMe}$	$^-\text{OC}_6\text{H}_4\text{S}(\text{O})\text{Me}$
$^-\text{O}_2\text{CCH}_2\text{SMe}$	(1)	(2)	(3)	(4)	(5)	(6)	
1	20 min	n.r.	n.r.	n.r.	3 min	12 h	
	7 + traces of 1 ^b				5	1 + 6 + 9 ^c	
$^-\text{O}_2\text{CCH}_2\text{S}(\text{O})\text{Me}$	(7)	(8)	(9)	(10)	(11) ^d	(12) ^d	
2	8 min	n.r.	15 min	n.r.	<2 min	<2 min	
	1	3	3	5	6		
$^-\text{O}_2\text{CC}_6\text{H}_4\text{SMe}$	(13)	(14)	(15)	(16)	(17) ^d	(18)	
3	30 min	n.r.	10 h	n.r.	5 min	n.r.	
	1	3 + 13 ^e	5	5			
$^-\text{O}_2\text{CC}_6\text{H}_4\text{S}(\text{O})\text{Me}$	(19)	(20) ^d	(21)	(22)	(23) ^d	(24) ^d	
4	15 min	5 d	10 min	n.r.	<2 min	<2 min	
	1	2	3	5	6		
$^-\text{OC}_6\text{H}_4\text{SMe}$	(25)	(26)	(27)	(28)	(29)	(30)	
5	n.r.	n.r.	n.r.	n.r.	n.r.	n.r.	
$^-\text{OC}_6\text{H}_4\text{S}(\text{O})\text{Me}$	(31)	(32)	(33) ^d	(34)	(35)	(36)	
6	3 h	n.r.	7 d	n.r.	15 min	n.r.	
	1 + 6 + 9 ^c	3	5				

^a n.r. = No reaction. For conditions see text. ^b See text. ^c In the ratio 1:0.1:1. ^d No intermediate species was observed during this reaction. ^e In the ratio 1:0.26.



factor) in this step of the reactions. Unfortunately no similar data could be obtained for the other cases with $\text{L} = \text{L}'$ [i.e. reactions (8), (22), (29) and (36)], since we could detect traces of the disubstituted products only by performing the reactions with a very high excess (15-fold) of the pro-ligands, when integration of the NMR peaks was unreliable for any quantitative measurement.

In conclusion certain Pt-bound sulfur ligands can be substituted by other sulfur nucleophiles. In the cases discussed in this paper, formation of a S,O-chelate ring favours such substitution and we believe these results may form the basis of the design of effective rescue agents towards acute platinum toxicity.

A final point is worth discussing. The potential reversibility of Pt–S bonds in the presence of other sulfur ligands suggests that, *in vivo*, Pt can be transferred between various S-containing biomolecules, which can thus act as effective depot and/or transport systems for platinum drugs, as has been suggested.^{20,21} However, if such a transport/depot system is operative, the question then arises whether such Pt–S species can react with the target guanine base of DNA. This has been discussed in some cases.^{16,17,21,23} Thus GMP displaces only the carboxylato group in **1**, yielding¹⁷ the monofunctional adduct $[\text{Pt}(\text{en})(\text{GMP}-N^7)(\text{O}_2\text{CCH}_2\text{SMe})]^+$, a compound similar to that obtained from reaction of GMP with acetylmethionine complexes of Pt(en).²³ [In the case of the *cis*-Pt(NH₃)₂ analogue extensive decomposition was observed.^{21b}] In contrast to the stability of the Pt–S bond in these thioether complexes of Pt(en)(GMP), methionine is displaced²¹ by GMP from $[\text{Pt}(\text{dien})(\text{Hmet}-\text{S})]^{2+}$ (Hmet = methionine). We have therefore synthesized $[\text{Pt}(\text{dien})(\text{O}_2\text{CCH}_2\text{SMe})]^+$ and found that also the platinum–thioether bond of this complex is substituted, slowly, by GMP (t_r 7 d at 40 °C, see Experimental section). The reversibility of such a bond in the presence of nucleobases therefore depends on different factors which need further investigation, currently underway in our laboratory.

Acknowledgements

This work was supported by MURST (Ministero dell'Università e della Ricerca Scientifica e Tecnologica).

References

- B. Lippert, *Prog. Inorg. Chem.*, 1987, **37**, 1.
- W. I. Sundquist and S. J. Lippard, *Coord. Chem. Rev.*, 1990, **100**, 293.
- S. L. Bruhn, J. H. Toney and S. J. Lippard, *Prog. Inorg. Chem.*, 1990, **38**, 477.
- J. Reedijk, *Chem. Commun.*, 1996, 801.
- M. J. Bloemink and J. Reedijk, *Met. Ions Biol. Syst.*, 1996, **32**, 641.
- E. L. M. Lempers and J. Reedijk, *Adv. Inorg. Chem.*, 1991, **37**, 175.
- C. M. Riley, L. A. Sternson, A. J. Repta and S. A. Slyter, *Anal. Biochem.*, 1983, **130**, 203.
- R. E. Norman, J. D. Ranford and P. J. Sadler, *Inorg. Chem.*, 1992, **31**, 877; P. d. S. Murdoch, J. D. Ranford, P. J. Sadler and S. J. Berners-Price, *Inorg. Chem.*, 1993, **32**, 2249; K. J. Barnham, U. Frey, P. d. S. Murdoch, J. D. Ranford and P. J. Sadler, *J. Am. Chem. Soc.*, 1994, **116**, 11 175.
- S. V. Pizzo, M. W. Swaim, P. A. Roche and S. L. Gonias, *J. Inorg. Biochem.*, 1988, **33**, 67; J. Bongers, J. U. Bell and D. E. Richardson, *J. Inorg. Biochem.*, 1988, **34**, 55.
- E. Eastman and M. A. Barry, *Biochemistry*, 1987, **26**, 3303.
- S. J. Berners-Price and P. W. Kuchel, *J. Inorg. Biochem.*, 1990, **38**, 327.
- M. Tedeschi, A. De Cesare, S. Oriana, P. Perego, A. Silva, P. Venturino and F. Zunino, *Cancer Treat. Rev.*, 1991, **18**, 253; F. Zunino, G. Pratesi, A. Micheloni, E. Cavalletti, F. Sala and O. Tofanetti, *Chem.-Biol. Interact.*, 1989, **70**, 89.
- P. C. Dedon, R. Quaziand and F. R. Borch, in *Biochemical Mechanism of Platinum Antitumor Drugs*, eds. D. C. H. McBrien and T. F. Slater, IRL, Oxford, 1986, p. 199.
- T. J. Kelley, S. Moghaddas, R. N. Bose and S. Basu, *Cancer Biochem. Biophys.*, 1993, **13**, 135; R. N. Bose, D. Li, M. Kennedy and S. Basu, *J. Chem. Soc., Chem. Commun.*, 1995, 1731.
- N. Farrell, *J. Chem. Soc., Chem. Commun.*, 1982, 331; N. Farrell, D. M. Kiley, W. Schmidt and M. P. Hacker, *Inorg. Chem.*, 1990, **29**, 397; J. Landi, M. P. Hacker and N. Farrell, *Inorg. Chim. Acta*, 1992, **202**, 79.
- A. Pasini, G. D'Alfonso, C. Manzotti, M. Moret, S. Spinelli and M. Valsecchi, *Inorg. Chem.*, 1994, **33**, 4140.
- A. Pasini, P. Perego, M. Balconi and M. Lupatini, *J. Chem. Soc., Dalton Trans.*, 1995, 579.
- S. Shamsuddin, S. Al-Baker, Z. H. Siddik and A. R. Khokhar, *Inorg. Chim. Acta*, 1996, **241**, 101.
- E. L. M. Lempers, M. J. Bloemink and J. Reedijk, *Inorg. Chem.*, 1991, **30**, 201.

- 20 S. S. G. E. van Boom and J. Reedijk, *J. Chem. Soc., Chem. Commun.*, 1993, 1397.
- 21 (a) K. J. Barnham, M. I. Djuran, P. d. S. Murdoch and P. J. Sadler, *J. Chem. Soc., Chem. Commun.*, 1994, 721; (b) K. J. Barnham, M. I. Djuran, P. d. S. Murdoch, J. D. Ranford and P. J. Sadler, *J. Chem. Soc., Dalton Trans.*, 1995, 3721.
- 22 G. Annibale, M. Brandolisio and B. Pitteri, *Polyhedron*, 1995, **14**, 451.
- 23 K. J. Barnham, Z. Guo and P. J. Sadler, *J. Chem. Soc., Dalton Trans.*, 1996, 2867.

Received 5th August 1996; Paper 6/05475G