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Studies on Pt–S bonds. Competition of chelating methylsulfanyl- or methylsulfinyl-acetate, -benzoate and -phenolate for $Pt^{II}(H_2NCH_2CH_2NH_2)$

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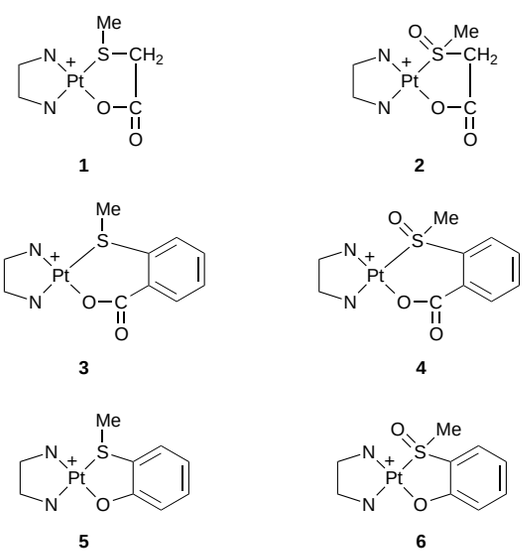
The reactions of $[Pt(en)(L\text{-}S,O)]^+$ (en = ethane-1,2-diamine) with L′, where both L and L′ are the anionic chelating ligands methylsulfanylacetate, 2-(methylsulfanyl)benzoate, 2-(methylsulfanyl)phenolate and their methylsulfinyl analogues, have been studied by ^{1}H NMR spectroscopy in D_2O solutions at 40 °C. Thioethers bind more strongly than sulfoxides to Pt(en) and within each series the order of affinity towards Pt is $^-OC_6H_4SMe$ > $^-O_2CCH_2SMe$ > $^-O_2CC_6H_4SMe$ and $^-OC_6H_4S(O)Me$ > $^-O_2CCH_2S(O)Me$ > $^-O_2CC_6H_4S(O)Me$. The first step of the reactions is substitution of the Pt–O bond of L by the Pt–S bond of L′ to give $[Pt(en)(L\text{-}S)(L'\text{-}S)]$, with both ligands monodentate, S-co-ordinated, followed by closure of the chelate ring of L′, to give $[Pt(en)(L'\text{-}S,O)]^+$, which occurs by displacement of the Pt–S bond of L by the oxygen atom of L′. The disubstituted species $[Pt(en)(O_2CCH_2SMe)_2]$, $[Pt(en)(O_2CC_6H_4SMe)_2]$ and $[Pt(en)(O_2CCH_2SMe)\{OC_6H_4S(O)Me\}]$ 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 *cis*-$[PtCl_2(NH_3)_2]$ or of its analogues of general formula *cis*-$[Pt(am)_2X_2]$ (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 *cis*-$Pt(am)_2$ 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 toxicity[12] 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 *cis*-$Pt(am)_2$ 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 *cis*-$Pt(am)_2$ 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**, $[Pt(en)(L\text{-}S,O)]^+$ (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 carboxylato group of **3** is replaced by chloride, yielding the monochloro derivative $[PtCl(en)(O_2C\text{-}C_6H_4SMe\text{-}2)]$. 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 [PtCl(dien)]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)-(O_2CCH_2SMe)]NO_3 **1** and methylsulfanylacetic acid (2.46 mmol, 1.039 and 0.2611 g respectively in 20 cm^3) together with KOH (24.6 cm^3, 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 cm^3), 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. $C_8H_{18}N_2O_4PtS_2$ requires C, 20.6; H, 3.9; N, 6.0%). IR (cm^{-1}, KBr pellets): 1586, 1379 (ionic carboxylate) *cf*. K(O_2CCH_2SMe) 1586, 1400. For ^{1}H NMR see Table 1. ^{195}Pt NMR (D_2O solution): δ −3720 *vs*. $[PtCl_6]^{2-}$ [*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 cm^3) 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 cm^3) 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. $C_7H_{20}ClN_3O_3PtS$ requires C, 18.4; H, 4.4; N, 9.2%). NMR (D_2O solution): ^{1}H (40 °C), δ 2.75 (J_{PtH} 42, CH_3S), 2.8–3.5 (CH_2 of dien) and 3.70 (J_{PtH} 37 Hz, CH_2S); ^{195}Pt, δ −3376 *vs*. $[PtCl_6]^{2-}$. IR (cm^{-1}, KBr pellets): 1605 and 1371. FAB mass spectrum (glycerol mull): $m/z = 403$, $[Pt(dien)(O_2CCH_2SMe)]^+$.

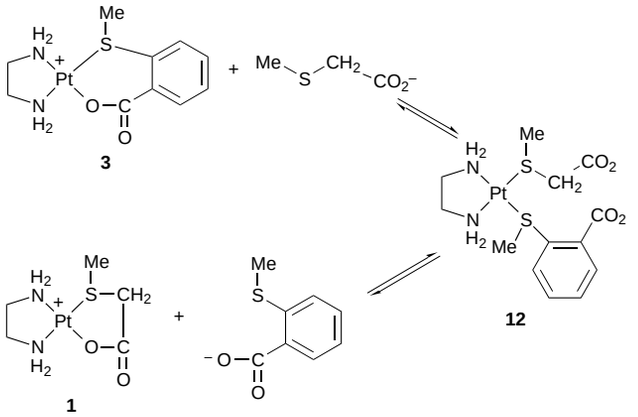
Reactivity studies

Stock D_2O 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 D_2O.

Reactions (1)–(36) were performed directly in NMR tubes. Weighed amounts of the complexes of L were treated with appropriate volumes of the stock D_2O 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 D_2O) 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 ^{1}H 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 $SiMe_4$ and are reported in Table 1. The $t_{\frac{1}{2}}$ 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 ^{1}H NMR spectra at various temperatures (5–85 °C) of 10^{-2} mol dm^{-3} D_2O solutions of complexes **1** and **3**, containing known amounts of K(O_2CCH_2SMe) and K($O_2CC_6H_4SMe$-2) respectively. Dissociation constants were calculated from the integrated intensities of the signals.

Reaction between [Pt(dien)(O_2CCH_2SMe)]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 D_2O (1.0 cm^3) 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 ^{1}H NMR spectra were recorded, at intervals, at the same temperature. The spectrum was unchanged for 1 d, when the peak of $^-O_2CCH_2SMe$ started to grow, together with a peak at δ 8.99 (J_{PtH} 23 Hz) attributed to H[8] of GMP co-ordinated to Pt at the N[7] position. After 30 d only the resonances of [Pt(dien)(GMP)] and of free $^-O_2CCH_2SMe$ were observed; $t_{\frac{1}{2}}$ 8 d.



Scheme 1

Results and Discussion

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

$$[Pt(en)(L\text{-}S,O)] + L' \rightleftharpoons [Pt(en)(L'\text{-}S,O)] + L \quad \text{(i)}$$

between complexes **1**–**6** and the six anionic ligands has been monitored by ^{1}H NMR spectroscopy at 40 °C with equimolar concentrations (2×10^{-2} mol dm^{-3} D_2O solutions) of the complexes and L′. The relevant ^{1}H NMR data are in Table 1. The nature of the products (characterized by comparison of their ^{1}H NMR spectra with those of authentic samples[17]) and the $t_{\frac{1}{2}}$ values (corresponding to the disappearance of the reactants) are in Table 2. With few exceptions, see below, the product of the reactions is $[Pt(en)(L'\text{-}S,O)]^+$, 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 ($t_{\frac{1}{2}}$ ranging from 2 to 30 min), except for (20) [substitution of chelate $^-O_2CC_6H_4S(O)Me$-2 by $^-O_2CCH_2S(O)Me$, $t_{\frac{1}{2}} = 5$ d] and (33) [substitution of $^-OC_6H_4$-S(O)Me-2 by $^-O_2CC_6H_4SMe$-2, $t_{\frac{1}{2}} = 7$ d]. The order of affinity of the various pro-ligands towards the Pt(en) moiety is $^-OC_6H_4SMe$ > $^-O_2CCH_2SMe$ > $^-O_2CC_6H_4SMe$ > $^-OC_6H_4$-S(O)Me > $^-O_2CCH_2S(O)Me$ > $^-O_2CC_6H_4S(O)Me$, while for the donor atoms S > O, sulfanyl > sulfinyl and phenolato > carboxylato.

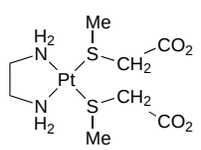
The NMR spectra, recorded during the time course of the reactions, show, in most cases, the presence of some peaks attributable to a disubstituted intermediate species of the type [Pt(en)(L-*S*)(L′-*S*)], where both L and L′ are monodentate, S-co-ordinated (Pt–H coupling of the resonances of the MeS 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 $t_{\frac{1}{2}}$ 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 $^-O_2CCH_2SMe$ which yields **1**. The spectrum recorded 2 min after mixing the reagents, shows, besides the peaks due to **3** and $^-O_2CCH_2SMe$, three peaks at δ 2.95 (J_{PtH} 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 CH_2 of en (four protons) and MeS of $^-O_2CC_6H_4SMe$ and $^-O_2CCH_2SMe$ (three protons each) of a new species **12**, with both $^-O_2CCH_2SMe$ and $^-O_2CC_6H_4SMe$ monodentate S-co-ordinated. After 10 min the peak due to MeS of $^-O_2CC_6H_4SMe$ (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_2S
$^-O_2CCH_2SMe$	2.24			3.39
$^-O_2CCH_2S(O)Me$	2.94			3.75
$^-O_2CC_6H_4SMe$	2.66[b]			
$^-O_2CC_6H_4S(O)Me$	3.08			
$^-OC_6H_4SMe$	2.54			
$^-OC_6H_4S(O)Me$	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)($O_2CCH_2SMe)_2$]	O_2CCH_2SMe	2.81 (44)	3.08 (42)	3.95 (40)
[in reaction (1)]				
8 [Pt(en)(O_2CCH_2SMe)(OC_6H_4SMe)]	O_2CCH_2SMe	2.78 (44)	2.97 (44)	*c*
[in reaction (5)]	OC_6H_4SMe	2.91 (50)		
9 [Pt(en)(O_2CCH_2SMe){$OC_6H_4S(O)Me$}]	O_2CCH_2SMe	2.78 (43)	3.05 (43)	*c*
[reactions (6) and (31)]	$OC_6H_4S(O)Me$	3.92 (24)		
10 [Pt(en)(O_2CCH_2SMe){$O_2CCH_2S(O)Me$}]	O_2CCH_2SMe	2.60 (45)	3.03 (43)	*c*
[in reaction (7)]	$O_2CCH_2S(O)Me$	3.60 (29)		
11 [Pt(en){$O_2CCH_2S(O)Me$}($O_2CC_6H_4SMe$)]	$O_2CCH_2S(O)Me$	3.81 (24)	3.11 (44)	*c*
[in reaction (9)]	$O_2CC_6H_4SMe$	2.86 (46)		
12 [Pt(en)(O_2CCH_2SMe)($O_2CC_6H_4SMe$)]	O_2CCH_2SMe	2.81 (45)	2.95 (45)	3.92 (40)
[in reaction (13)]	$O_2CC_6H_4SMe$	3.05 (43)		
13 [Pt(en)($O_2CC_6H_4SMe)_2$]	$O_2CC_6H_4SMe$	2.83 (40)	2.96 (44)	
[in reaction (15)]				
14 [Pt(en){$O_2CC_6H_4S(O)Me$}(O_2CCH_2SMe)]	$O_2CC_6H_4S(O)Me$	3.85 (24)	3.06 (44)	*c*
[in reaction (19)]	O_2CCH_2SMe	2.78 (45)		
15 [Pt(en){$O_2CC_6H_4S(O)Me$}($O_2CC_6H_4SMe$)]	$O_2CC_6H_4S(O)Me$	3.84 (25)	2.92 (44)	
[in reaction (21)]	$O_2CC_6H_4SMe$	2.85 (45)		
16 [Pt(en){$OC_6H_4S(O)Me$}(OC_6H_4SMe)]	OC_6H_4SMe	2.87 (48)	3.06 (43)	
[in reaction (35)]	$OC_6H_4S(O)Me$	3.93 (24)		

[a] In D_2O solutions at 40 °C, δ in ppm *vs.* external $SiMe_4$, 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 CH_2 groups of co-ordinated $^-O_2CCH_2SMe$ and $^-O_2CCH_2S(O)Me$ are seldom visible because of H–D exchange of these groups.[16]



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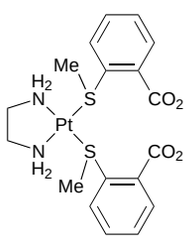

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together with those of the substitution product **1**. At $t_{\frac{1}{2}}$ (30 min) the intensities of the signals of species **12** are reduced and are no longer visible at the end of the reaction, when only the peaks of **1** and of free $^-O_2CC_6H_4SMe$ are observed.

Some disubstituted species of the type [Pt(en)(L-*S*)(L′-*S*)], *i.e.* **7** [L = L′ = $^-O_2CCH_2SMe$, reaction (1)], **9** [L = $^-O_2CCH_2$-SMe, L′ = $^-OC_6H_4S(O)Me$, reaction (6); or L = $^-OC_6H_4$-S(O)Me, L′ = $^-O_2CCH_2SMe$, reaction (31)] and **13** [L = L′ = $^-O_2CC_6H_4SMe$, 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 $^-O_2CCH_2SMe$. 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 ($t_{\frac{1}{2}} \approx 2$ min) for such an observation, for (20) [L = $^-O_2CC_6H_4S(O)Me$ and L′ = $^-O_2$-$CCH_2S(O)Me$, $t_{\frac{1}{2}}$ 5 d] and (33) [L = $^-OC_6H_4S(O)Me$, L′ = $^-O_2$-CC_6H_4SMe, $t_{\frac{1}{2}}$ 7 d] such a failure must be due to an intrinsic instability and/or reactivity of the intermediates.

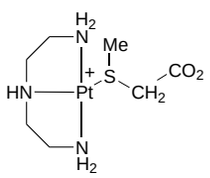
In the mechanism depicted in Scheme 1 the first step is substitution of the Pt–O bond of L-*S*,*O* by the Pt–S bond of L′. This will occur only if the balance between the stability of the chelate ring of L and the strength of the new Pt–S bond is favourable. Thus complex **5** is unreactive, while the $^-O_2CC_6H_4S(O)Me$ 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 ^{1}H NMR peaks at various temperatures gave the following values (at 50 °C): [Pt(en)-($O_2CCH_2SMe)_2$] $\rightleftharpoons$ **1** + $^-O_2CCH_2SMe$, $K_{dis\ 37} = 7.6 \pm 0.9$ 10^{-3} mol dm^{-3}, $\Delta H = 46 \pm 4$ kJ mol^{-1} and $\Delta S = 101 \pm 12$ J K^{-1} mol^{-1}; [Pt(en)($O_2CC_6H_4SMe)_2$] $\rightleftharpoons$ **3** + $^-O_2CC_6H_4SMe$, $K_{dis\ 38} = 7.8 \pm 0.1$ 10^{-2} mol dm^{-3}, $\Delta H = 31 \pm 1$ kJ mol^{-1} and $\Delta S = 75 \pm 4$ 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, $t_{\frac{1}{2}}$ and products for the reactions $[Pt(en)(L\text{-}S,O)]^+ + L'$ [a]

	L′, reaction, $t_{\frac{1}{2}}$, products					
L, compound	$^-O_2CCH_2SMe$	$^-O_2CCH_2S(O)Me$	$^-O_2CC_6H_4SMe$	$^-O_2CC_6H_4S(O)Me$	$^-OC_6H_4SMe$	$^-OC_6H_4S(O)Me$
$^-O_2CCH_2SMe$	(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]
$^-O_2CCH_2S(O)Me$	(7)	(8)	(9)	(10)	(11) [d]	(12) [d]
2	8 min	n.r.	15 min	n.r.	<2 min	<2 min
	1		**3**		**5**	**6**
$^-O_2CC_6H_4SMe$	(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**	
$^-O_2CC_6H_4S(O)Me$	(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**
$^-OC_6H_4SMe$	(25)	(26)	(27)	(28)	(29)	(30)
5	n.r.	n.r.	n.r.	n.r.	n.r.	n.r.
$^-OC_6H_4S(O)Me$	(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 L = 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**, yielding[17] the monofunctional adduct $[Pt(en)(GMP\text{-}N^7)(O_2CCH_2SMe)]^-$, a compound similar to that obtained from reaction of GMP with acetylmethionine complexes of Pt(en).[23] [In the case of the *cis*-$Pt(NH_3)_2$ 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 displaced[21] by GMP from $[Pt(dien)(Hmet\text{-}S)]^{2+}$ (Hmet = methionine). We have therefore synthesized $[Pt(dien)(O_2CCH_2SMe)]^+$ and found that also the platinum–thioether bond of this complex is substituted, slowly, by GMP ($t_{\frac{1}{2}}$ 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.

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References

1 B. Lippert, *Prog. Inorg. Chem.*, 1987, **37**, 1.
2 W. I. Sundquist and S. J. Lippard, *Coord. Chem. Rev.*, 1990, **100**, 293.
3 S. L. Bruhn, J. H. Toney and S. J. Lippard, *Prog. Inorg. Chem.*, 1990, **38**, 477.
4 J. Reedijk, *Chem. Commun.*, 1996, 801.
5 M. J. Bloemink and J. Reedijk, *Met. Ions Biol. Syst.*, 1996, **32**, 641.
6 E. L. M. Lempers and J. Reedijk, *Adv. Inorg. Chem.*, 1991, **37**, 175.
7 C. M. Riley, L. A. Sternson, A. J. Repta and S. A. Slyter, *Anal. Biochem.*, 1983, **130**, 203.
8 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.
9 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.
10 E. Eastman and M. A. Barry, *Biochemistry*, 1987, **26**, 3303.
11 S. J. Berners-Price and P. W. Kuchel, *J. Inorg. Biochem.*, 1990, **38**, 327.
12 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.
13 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.
14 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.
15 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.
16 A. Pasini, G. D'Alfonso, C. Manzotti, M. Moret, S. Spinelli and M. Valsecchi, *Inorg. Chem.*, 1994, **33**, 4140.
17 A. Pasini, P. Perego, M. Balconi and M. Lupatini, *J. Chem. Soc., Dalton Trans.*, 1995, 579.
18 S. Shamsuddin, S. Al-Baker, Z. H. Siddik and A. R. Khokhar, *Inorg. Chim. Acta*, 1996, **241**, 101.
19 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.

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