Amphiphilic Bis(thiolato)-nickel(II), -palladium(II) and -platinum(II) Complexes with Diphosphine or Phosphinoarsine Ligands

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The novel complexes [M(L–L)(H_2dmsucc-*S*,*S*')] [M = Ni, Pd or Pt; L–L = 1,2-bis(diphenylphosphino)ethane, dppe; M = Pd or Pt, L–L = 1-diphenylarsino-2-diphenylphosphinoethane, dadpe; H_4dmsucc = dimercaptosuccinic acid) and [Ni(dppe)(Hmsucc)] (H_3msucc = mercaptosuccinic acid) have been prepared and characterised. The reactions of sodium 2,3-dimercaptopropanesulfonate, sodium 1-thio-β-D-glucopyranosate and dithiothreitol with [M(L–L)X_2] (M = Ni, Pd or Pt; X = Cl or Br) were investigated by ^{31}P-{^{1}H} NMR spectroscopy. The ^{31}P NMR chemical shifts, ^{31}P–^{31}P and ^{195}Pt–^{31}P coupling constants, and the conformations of chelate rings (derived from ^{1}H–^{1}H coupling constants) in mixed-ligand products from these reactions are discussed. The use of these thiolate ligands has enabled solubilisation of several complexes containing dppe or dadpe ligands in aqueous media. The cytotoxicities of dppe and dadpe complexes of Pd and Pt with dimercaptosuccinic acid were investigated.

Diphosphine complexes of Cu^I, Ag^I and Au^I exhibit anticancer activity against several types of tumours,[1,2] and consequently there is interest in investigating the anticancer activity of similar complexes of Ni^{II}, Pd^{II} and Pt^{II}. It has been reported[3,4] that [Pt(dppe)Cl_2] (dppe = $Ph_2PCH_2CH_2PPh_2$) is inactive, perhaps because the Pt–P bonds are too inert and the toxic diphosphine ligand is not released at the target site. Nickel(II) complexes are usually more labile than those of Pd^{II} or Pt^{II}, but [Ni(dppe)Cl_2] is inactive probably because it is too labile, *e.g.* it reacts rapidly with cell culture media and the oxidised diphosphine dioxide ligand is produced.[5] We have therefore investigated complexes of Ni^{II}, Pd^{II} and Pt^{II} with diphosphines and phosphinoarsines and thiolate ligands in the hope that the nickel(II) complexes would have an increased stability in comparison to chloro complexes, and that the high *trans* influence of sulfur would labilise the diphosphine in the complexes of Pd^{II} and Pt^{II}. In addition, we hoped that the aqueous solubility of complexes containing these hydrophobic diphenylphosphino- and diphenylarsinodiphenylphosphino-ethane ligands would increase on co-ordination of the thiolate. This is important for biological testing which is carried out in aqueous media, and may greatly influence the partition of the complexes *in vivo*. Increased aqueous solubility is also of interest in the area of catalysis since metal phosphine complexes are known to catalyse various reactions, *e.g.* the use of [Ni(dppp)Cl_2] (dppp = $Ph_2PCH_2CH_2CH_2PPh_2$) in the polymerisation of 3-alkylthiophenes[6] and the [Ni(PPh_3)$_2Br_2$]-catalysed preparation of polyphenylenes.[7]

There are only a few previous reports of mixed-ligand complexes of Ni^{II} with phosphine and thiolate ligands. Complexes of the type [$NiL_2(SPh)_2$] (L = PEt_3 or PMe_2Ph) tend to dissociate in solution, whereas [Ni(dppe)$(SPh)_2$] was reported to be stable.[8] Rauchfuss and Roundhill[9] have reported that complexes of Ni, Pd and Pt with ethane-1,2-dithiol (H_2edt): [{M(PPh_3)(edt)}$_2$] (M = Ni or Pd) are dimers with bridging sulfurs, whereas [Pt(PPh_3)$_2$(edt)] and [Ni(dppe)(edt)] are stable mononuclear complexes. Schmidt and Hoffman[10] have described the synthesis of [Ni(dppe)(SCH_2SCH_2S)] and [Ni(dppe)$(SCH_2CH_2CH_2S)$], although the former was unstable at room temperature. The complex [Ni(dppe)$(SH)_2$] is air-stable, but decomposes in chlorinated solvents.[11] Monothiolate complexes such as [Pt(PPh_3)$_2(SH)_2$],[12] [M(dppe){$S(CH_2)_3NHMe_2$}$_2$][BPh_4]$_2$,[13] have also been reported. Very recently complexes of Pd^{II} and Pt^{II} of 4-mercapto-1-methylpiperidine of the types [M(dppe)(SR_2)] and [{M(dppe)(SR)}$_2X_2$] have been described.[14] Other reported complexes of Ni^{II} and Pt^{II} containing P or As and S donors do not have thiolate ligands, but other S-containing ligands, *e.g.* dithiocarbamates,[15–18] dithiocarbonates,[19] dithiophosphinates[20] or thioethers.[21–25] Although all the reported nickel(II) complexes with S and P donors are diamagnetic, ^{31}P NMR data have been reported for only six of them.[10,14,15]

Results

We have synthesised and characterised 1:1 adducts of [Ni(dppe)]$^{2+}$ with *meso*-dimercaptosuccinic acid (H_4dmsucc) and mercaptosuccinic acid (H_3msucc), and similar adducts of H_2dmsucc with [M(L–L)]$^{2+}$ [M = Pd or Pt, L–L = dppe or dadpe ($Ph_2AsCH_2CH_2PPh_2$)]. Reactions of other thiols† with [Ni(dppe)Br_2] were studied in solution by ^{31}P-{^{1}H} NMR spectroscopy, as were reactions of [M(L–L)Cl_2] (M = Pd or Pt) with NaH_2dmps, NaH_4tg and Htatg. For comparison of the relative *trans* influences of P, As and S, the bis(ligand) complexes [Ni(dppe)$_2$]Br_2 and [M(L–L)$_2$]Cl_2 (M = Pd or Pt; L–L = dppe or dadpe) were prepared.

The complexes [Ni(dppe)Br_2] and [Ni(dppen)Br_2] [dppen = *cis*-1,2-bis(diphenylphosphino)ethene] were prepared as previously described;[26] [Ni(dppe)$_2$]Br_2 was prepared by a modification of the literature method.[27] Preparations of the mono(ligand) phosphine complexes [M(dppe)Cl_2] (M = Pd or Pt) and the corresponding dadpe complexes were as described in the literature for Pt,[28] *i.e.* by addition of 1 mol equivalent of the appropriate ligand to a $CHCl_3$ solution of [M(cod)Cl_2] (M = Pd or Pt; cod = cycloocta-1,5-diene). The bis(ligand) complexes [M(dppe)$_2$]Cl_2 (M = Pd or Pt) and the corresponding dadpe complexes were obtained on treatment of a

† *threo*-1,4-Dimercaptobutane-2,3-diol (dithiothreitol, H_4dtt); sodium 2,3-dimercaptopropanesulfonate (NaH_2dmps); sodium 1-thio-β-D-glucopyranosate (NaH_4tg); 2,3,4,6-tetra-*O*-acetyl-1-thio-β-D-glucopyranose (Htatg).

Table 1 $^{31}P-\{^1H\}$ NMR data at 81 MHz, in $CHCl_3$–$CDCl_3$ (1:1); X = Cl unless otherwise stated

	[M(L–L)(H_2dmsucc-*S*,*S*′)]		[Ni(L–L)(Hmsucc-*S*,*O*)][a]		[M(L–L)Cl_2]		[M(L–L)$_2$]X_2	
	δ	*J*(PtP)/Hz	δ	*J*(PP)/Hz	δ	*J*(PtP)/Hz	δ	*J*(PtP)/Hz
L–L = dppen								
M = Ni	66.4	—	62.0, 58.0	37	64.9	—	56.4[b]	—
L–L = dppe								
M = Ni	58.2[c]	—	59.0, 47.0	53	58.2	—	49.6 (X = Br)	—
Pd	54.4	—			64.2	—	56.7	—
Pt	46.8	2817			41.9	3621	47.6	2363
L–L = dadpe								
M = Pd	57.3	—			67.5	—	62.3, 59.3[d]	—
Pt	49.9	2795			43.2	3566	53.5, 50.9[d]	2793, 2312

[a] At 24.2 MHz. [b] [Ni(dppen)$_2$Cl]Cl. [c] δ(EtOH) 58.1, (NaOH–D_2O, pH *ca.* 11) 58.6. [d] Mixture of *cis* and *trans* isomers; ratio of peaks 9:10 and 2:1 for Pd and Pt, respectively.

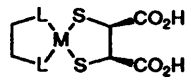

Fig. 1 Structure of [M(L–L)(H_2dmsucc-*S*,*S*′)] (L–L = dppe, M = Ni^{II} **1**, Pd^{II} **3** or Pt^{II} **5**; L–L = dadpe, M = Pd^{II} **4** or Pt^{II} **6**)

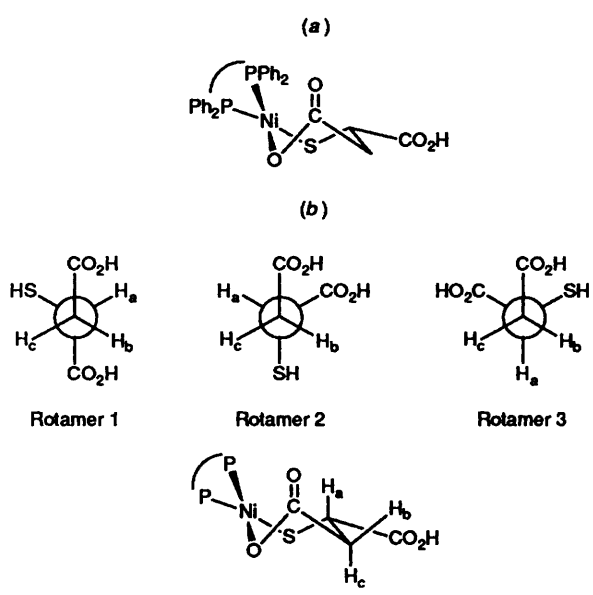

Fig. 2 (*a*) Structure of [Ni(dppe)(Hmsucc)] **2**. (*b*) Possible rotamers of H_3msucc and structure of [Ni(dppe)(Hmsucc)] showing the hydrogens involved in coupling

$CHCl_3$ solution of [M(cod)Cl_2] with 2 mol equivalents of the appopriate ligand as in the previously reported preparation of [Pt(dppe)$_2$]Cl_2.[29] The compounds of Pd and Pt were isolated by removal of the solvent *in vacuo* and purified as chloroform solvates by recrystallisation from $CHCl_3$. The $^{31}P-\{^1H\}$ NMR data were in agreement with the few literature values available.[26,28,29]

The novel complexes [Ni(dppe)(H_2dmsucc-*S*,*S*′)] **1** and [Ni(dppe)(Hmsucc-*S*,*O*)] **2** were prepared by reaction of a suspension of [Ni(dppe)Br_2] with 1 mol equivalent of the appropriate ligand in EtOH (**1**) or EtOH:water (5:1) (**2**) and purified by redissolving in aqueous NaOH and precipitating with dilute H_2SO_4. The complexes had a small residual paramagnetism (see Experimental section) and IR spectroscopy indicated the absence of S–H bands. Complex **1** was more easily isolated in pure form and was more soluble in hydrophilic solvents including 0.1 mol dm^{-3} $NaHCO_3$ (*ca.* 1.4 mg cm^{-3}). Typically, aqueous bicarbonate solutions of this complex frothed when shaken. The new complexes [M(dppe)(H_2dmsucc-*S*,*S*′)] (M = Pd **3** or Pt **5**) and [M(dadpe)(H_2dmsucc-*S*,*S*′)] (M = Pd **4** or Pt **6**) were prepared by addition of a basic solution of H_4dmsucc in ethanol to an ethanolic suspension of the appropriate [M(dppe)Cl_2] complex. After 1.5–2 h at room temperature the reaction mixtures were filtered and the products were isolated by reduction in volume of the solvent. Structures for these compounds based on ^1H and ^{31}P NMR data are shown in Figs. 1 (H_2dmsucc complexes) and 2(*a*) (Hmsucc complex). The $^{31}P-\{^1H\}$ ^1H NMR data for these compounds are presented in Tables 1 and 2. Data for the mono- and bis-(dppe) complexes of Ni, Pd and Pt and for mono- and bis-(dadpe) complexes of Pd and Pt are included for comparison.

In a variety of solvents, including aqueous alkali, the complexes [M(dppe)(H_2dmsucc)] (M = Ni, Pd or Pt) and [Ni(dppen)(H_2dmsucc)] gave singlet $^{31}P-\{^1H\}$ NMR resonances, whereas the unsymmetrical [Ni(dppe)(Hmsucc)] **2** and [Ni(dppen)(Hmsucc)] gave AB multiplets, Table 1, as expected for the structures in Figs. 1 and 2. The $^{31}P-\{^1H\}$ NMR spectra of [Pt(L–L)(H_2dmsucc)] show platinum satellites [^1J(PtP) *ca.* 2800 Hz]. The spectra remained unchanged after 24 h in a variety of solvents.

The phenyl resonances in the ^1H NMR spectra of $CDCl_3$ solutions of the mixed-ligand dppe complexes, [M(dppe)(H_2dmsucc)] (M = Ni **1**, Pd **3** or Pt **5**), are all deshielded with respect to those of the free ligand dppe (δ 7.31[30]) and those of [M(dppe)X_2], Table 2(*a*). Likewise the resonances due to the methylene CH_2 protons are downfield from those of uncoordinated dppe (δ 2.09).[30] The methine protons of the complexes are also all deshielded with respect to free H_4dmsucc (δ 3.52). They are part of an AA′XX′ spin system where X = X′ = ^{31}P. In the case of [Ni(dppe)(H_2dmsucc)] **1** they give rise to an apparent singlet presumably because the couplings are too small to be resolved. For [Pd(dppe)(H_2dmsucc)] **3** and [Pt(dppe)(H_2dmsucc)] **5** these protons give rise to an apparent doublet. In 100 mmol dm^{-3} bicarbonate solutions the methine resonances are singlets with the exception of [Pt(dppe)(H_2dmsucc)] **5** which gives a doublet. Platinum-195 satellites are observed in the spectrum of **5** with ^3J(PtH) of *ca.* 42 Hz in $CDCl_3$ and *ca.* 38 Hz in bicarbonate.

Both the phenyl and CH_2 resonances of the dadpe complexes, [M(dadpe)(H_2dmsucc)] (M = Pd **4** or Pt **6**), in $CDCl_3$, are deshielded with respect to those of the free ligand dadpe (δ 7.32 and 2.16, 2.06 for Ph and CH_2 respectively),[31] Table 2(*a*). The methine resonances for all these complexes are deshielded with respect to H_4dmsucc (δ 3.52, 3.26 in $CDCl_3$, D_2O–NaOD, respectively). For these protons, two sets of doublets of doublets are observed, one set corresponding to the proton *trans* to As, the other to that *trans* to P. The spectrum of [Pt(dadpe)(H_2dmsucc)] **6** shows ^{195}Pt satellites with ^3J(PtH) values of 36 and 58 Hz. In 100 mmol dm^{-3} $NaHCO_3$, the splitting pattern of the resonances is similar though they are all shifted slightly upfield.

Table 2 Proton NMR data

(*a*) [M(L–L)(H_2dmsucc)] (at 200 MHz for M = Ni, 500 MHz for Pd and Pt), [M(L–L)X_2] (X = Br for Ni, otherwise Cl) and [M(L–L)$_2$]X_2 (at 200 MHz for M = Ni, 400 MHz for Pd and Pt), solvent $CDCl_3$

	[M(L–L)(H_2dmsucc)]		[M(L–L)$_2$]X_2	[M(L–L)$_2$]X_2	
L–L = dppe	δ	^3J(PtH)/Hz	δ	δ	*J*/Hz
M = Ni	7.75 (m)		7.99 (m)	7.32 (m)	
	7.50 (m)		7.54 (m)	7.06 (m)	
	4.07 (s)				
	2.30 (pseudo d)		2.10 (pseudo d)	2.81 (br s)	
Pd	7.676 (m)		7.86 (m)	7.64 (br)	
	7.481 (m)		7.53 (m)	7.28 (br m)	
	4.279		7.46 (m)		
	2.460		2.46	3.44 (t)	17.1
	2.360		2.40		
Pt	7.684 (br m)		7.84 (m)	7.84 (br m)	
	7.477 (m)		7.50 (m)	7.29 (m)	
	4.105	43			
	2.380 (br s)		2.38	3.36 (t)	16
			2.33		

	[M(L–L)(H_2dmsucc)]				[M(L–L)X_2]	[M(L–L)$_2$]X_2
L–L = dadpe	δ	^3J(HH)/Hz	^4J(PH)/Hz	^3J(PtH)/Hz	δ	δ
M = Pd	7.675 (m)				7.82 (m)	7.85 (m)
	7.591 (m)				7.48 (m)	7.69 (br s)
	7.472 (m)					7.60 (m)
	4.357 (d of d)	4.1	2.6			7.49 (m)
	4.232 (d of d)	4.2	2.0			7.23 (m)
	2.55 (m)				2.55 (pseudo q)	
	2.42 (m)				2.41 (unsymm. t)	4.1 (br s)
	2.32 (m)				2.34 (unsymm. t)	3.73 (br m)
Pt	7.688 (m)				7.86 (m)	7.78 (br m)
	7.619 (m)				7.49 (m)	7.64 (m)
	7.455 (m)					7.28 (m)
	4.137 (d of d)	4.2	2.4	35.8		
	3.985 (d of d)	4.1	1.5	58.1		
	2.35 (m)				2.39 (m)	4.07 (pseudo q)
	2.24 (m)				2.29 (m), 2.24 (m)	3.91 (br)
						2.70 (m)
						2.54 (d)

(*b*) H_3msucc and [Ni(dppe)(Hmsucc-*S*,*O*)] **2** (at 200 MHz)

	H_3msucc		[Ni(dppe)(Hmsucc-*S*,*O*)]	
	δ	*J*/Hz	δ	*J*/Hz
CD_3OD	3.68 (dd, H_a)	9.0, 5.9	*a*	
	2.94 (dd, H_b)	17.2, 9.0		
	2.71 (dd, H_c)	17.2, 5.9		
$CDCl_3$	*a*		7.94 (tdd, 4 H)	11.7, 7.8, 1.2
			7.72 (tdd, 4 H)	12.5, 6.2, 1.5
			7.52 (m, 12 H)	
			4.03 (dt, H_a)	11.3, *ca.* 2[b]
			2.99 (dd, H_c)	15.2, 11.3
			2.69 (ddd, H_b)	15.2, *ca.* 2, *ca.* 1[b]
			2.6–2.0 (m)	

[a] Poor solubility. [b] Possible coupling to P.

The phenyl resonances of the complex [Ni(dppe)(Hmsucc-*S*,*O*)] are deshielded with respect to free dppe, the *ortho* protons being more deshielded than the *meta* or *para*. The dppe CH_2 protons are also deshielded with respect to free dppe. The ^3J(HH) values for Hmsucc in this complex and those for the free ligand, H_3msucc, have been measured, Table 2(*b*). It is notable that the couplings observed for vicinal protons in the complex are at the extremes of ranges expected from Karplus-type relationships, *i.e.* 11.3 Hz corresponds to a dihedral angle of *ca.* 180°, 2 Hz to an angle of 60°, and therefore the ligand must have a constrained conformation in the complex. The values for the free ligand in CD_3OD are similar to those reported[32] for H_3msucc at low pH which has a *ca.* 50% population of rotamer 2 and 25% populations of rotamers 1 and 3, Fig. 2(*b*).

Reaction solutions of [Ni(dppe)Br_2] with NaH_2dmps in EtOH at a mol ratio of 1 : 1 were dark brown, and with an excess of NaH_2dmps were orange-yellow; on the basis of ^{31}P NMR shifts and ^3J(P–P) values, the main products were assigned as [Ni(dppe){Na(dmps-*S*,*S*′)}] and [Ni(dppe){NaH(dmps-*S*}$_2$], respectively, Table 3. For Pd and Pt a slight excess of a basic solution of NaH_2dmps in ethanol (ratio NaH_2dmps : NaOH 1 : 2) was added to an ethanolic suspension of [M(L–L)Cl_2] (M = Pd or Pt, L–L = dppe or dadpe), and after 4 h the reaction solutions were filtered and the filtrates concentrated, affording solid products. These were soluble in both ethanol and $CDCl_3$, and were stable in solution for 24 h. ^{31}P-{^{1}H} NMR spectroscopy showed these to be mixtures in solution ($CDCl_3$–$CHCl_3$), Table 3, with possible structures A–F given in Fig. 3.

Table 3 ^{31}P-{^1H} NMR data for products of reactions of NaH_2dmps with $[M(L–L)X_2]$ [81 MHz, solvent EtOH for M = Ni; $CHCl_3$–$CDCl_3$ (1 : 1) for M = Pd or Pt]

Reaction with	$[M(L–L)X_2]$: NaH_2dmps	δ	J(PtP)/Hz	J(PP)/Hz	Assignment	Structure*
$[Ni(dppe)Br_2]$	1 : excess	58.3	—	—	NiP_2S_2	**G**
	1 : 1	58.2 (d)	—	43	NiP_2SS'	**A**
		57.7 (d)	—	43		
		55.5, 53.1, 51.7, 50.1 (br)	—			
$[Pd(dppe)Cl_2]$	1 : 1.6	60.8	—	—	$P_2Pd(\mu\text{-}S)_2PdP_2$	**B**
		60.2 (d)	—	17	PdP_2SCl	**C** or **D**
		57.9 (d)	—	17	$PdP_2S'Cl$	**C** or **D**
		50.8, 50.9	—	—	PdP_2SS'	**A**
$[Pt(dppe)Cl_2]$	1 : 1.1	46.0	2742	—	PtP_2SS'	**A**
		44.5	3036	—	$P_2Pt(\mu\text{-}S)_2PtP_2$	**B**
		41.9	3621	—	PtP_2Cl_2	
$[Pd(dadpe)Cl_2]$	1 : 1.6	54.5	—	—	PdAsPSS'	**E** or **F**
		54.0			PdAsPSS'	**E** or **F**
	1 : 1.6	49.7	2742	—	PtAsPSS'	**E** or **F**
		49.5	2727	—	PtAsPSS'	**E** or **F**
		43.5 (minor)	—	—	$PtPAsCl_2$	

* From Fig. 3.

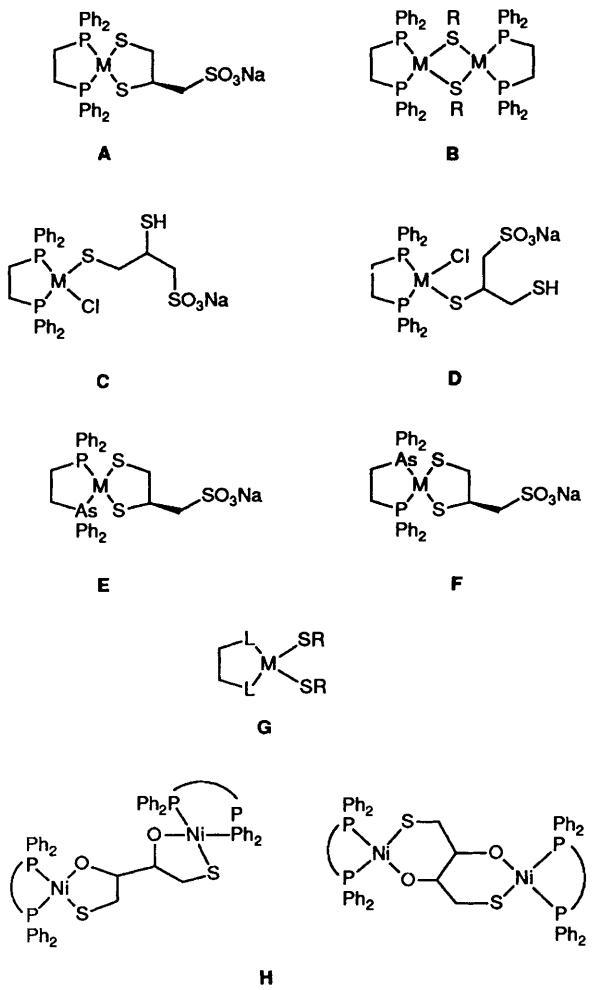

Fig. 3 Proposed structures of products from the reactions of $[M(L–L)X_2]$ (M = Ni^{II}, L–L = dppe, X = Br or I; M = Pd^{II} or Pt^{II}, L–L = dppe or dadpe, X = Cl) with sodium 2,3-dimercaptopropanesulfonate (NaH_2dmps) or dithiothreitol (H_4dtt)

The thiols H_4dtt, NaH_4tg and Htatg were treated with 1 equivalent of $[Ni(dppe)Br_2]$. With H_4dtt in ethanol yellow solutions were obtained which gave complicated ^{31}P-{^1H} NMR spectra. At low frequency (24 MHz) the major product gave a symmetrical 12-line multiplet, which at higher frequency (81 MHz) simplified to two overlapping AB quartets. The salt NaH_4tg solubilised $[Ni(dppe)Br_2]$ in water giving a yellow solution which from ^{31}P NMR spectra contained an unsymmetric $[Ni(dppe)(H_3tg\text{-}S,O)]$ species together with the diphosphine dioxide. Reactions of NaH_4tg with suspensions of $[M(L–L)Cl_2]$ (M = Pd or Pt, L–L = dppe or dadpe) in MeOH produced clear yellow (Pd) or colourless (Pt) solutions, for which ^{31}P NMR data suggested the presence of both $[M(L–L)(H_4tg\text{-}S)_2]$ and $[(L–L)M(\mu\text{-}S)_2M(L–L)]$. The only observable P-containing product from reaction of Htatg with $[Ni(dppe)Br_2]$ was the diphosphine dioxide. Complex mixtures of products were obtained in the case of the reaction of $[M(L–L)Cl_2]$ (M = Pd or Pt, L–L = dppe or dadpe) with Htatg, the spectra of which were not assigned.

The toxicities of some of the complexes against L1210 (antimetabolite-sensitive leukaemia), WS (alkylating-agent-sensitive Walker tumour) and V.79 (Chinese hamster lung) cells were investigated. The results are shown in Fig. 4. Cytotoxicity is defined in terms of IC_{50} values, *i.e.* the concentration of compound required to kill 50% of the cells. Phosphorus-31 NMR studies showed that the $H_2dmsucc$ complexes tested were stable in bovine serum (Wellcomtrol One), although the resonances were broadened ($\Delta\nu_{\frac{1}{2}}$ 230–300 Hz) suggesting that some binding to macromolecular components occurs.

Discussion

We have investigated the formation of mixed-ligand complexes of Ni^{II}, Pd^{II} and Pt^{II} with dppe and dadpe and thiolates in an attempt to increase the hydrophilicity of these complexes which are of interest as potential anticancer agents. Some of the thiols have been previously used in drugs: mercaptosuccinic acid, thioglucose and tetraacetylthioglucose are found in the antiarthritic drugs aurothiomalate, aurothioglucose and auranofin [(2,3,4,6-tetra-*O*-acetyl-1-thio-β-D-glucopyranosato)-(triethylphosphine)gold(I)], respectively, and both dimercaptopropanesulfonic acid and dimercaptosuccinic acid have been used in chelation therapy.[33] Tetracetylthioglucose is hydrolysed to thioglucose during oral absorption of auranofin,[34] and dithiothreitol (Cleland's reagent) is widely used as a reducing agent for disulfide bonds in proteins.

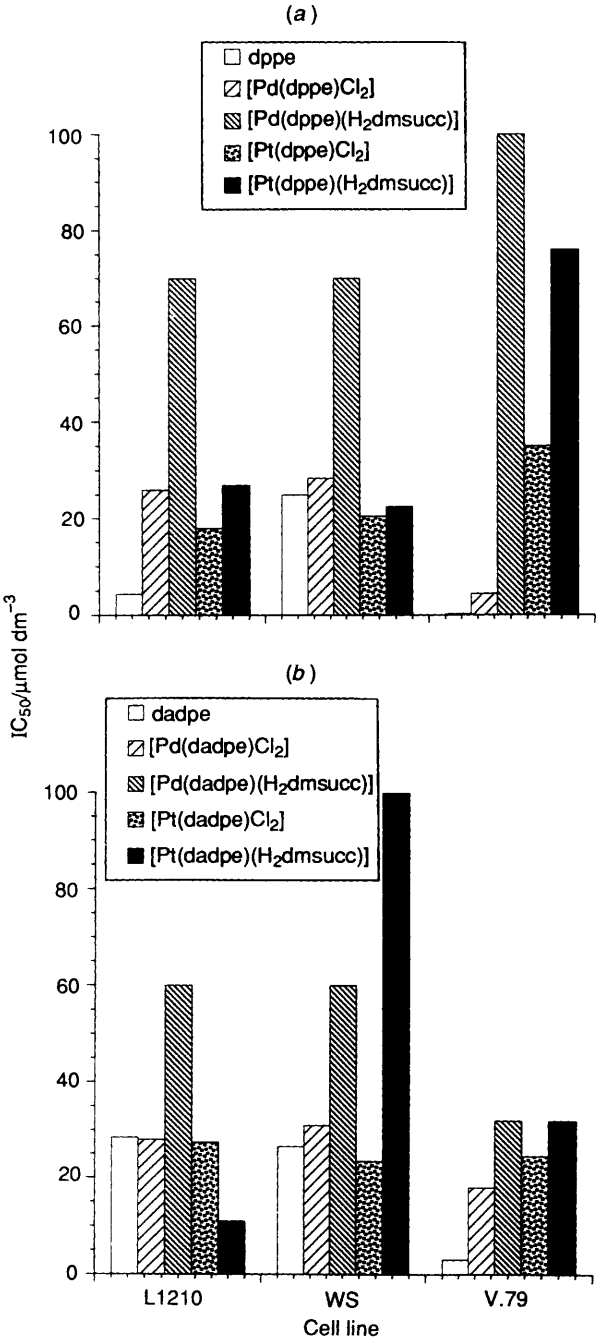

Fig. 4 Cytotoxicity towards L1210, WS, and V.79 cells

H_2dmsucc *Complexes*.—The dmsucc complexes of Ni were prepared from [Ni(dppe)Br_2] rather than [Ni(dppe)Cl_2] because of the ease of displacing Br^- from Ni^{II} compared with Cl^-.[26] It is interesting that the ^{31}P chemical shift of [Ni(dppe)(H_2dmsucc-*S*,*S*')] **1** is the same as that of the dichloro complex, while that of the bis(ligand) complex is upfield of this, Table 1. The peaks for [Pd(L–L)(H_2dmsucc-*S*,*S*')], **3** and **4**, are shifted upfield from those of the parent dichloro complexes, Table 1. A similar upfield shift is observed for the 1:2 bis(ligand) palladium complexes compared to the dichloropalladium complexes, Table 1. For the platinum complexes the reverse is the case, *i.e.* resonances for both the dmsucc and the 1:2 bis(ligand) complexes are at lower field than for the dichloro complexes. Similar trends in shifts have been reported for other thiolatephosphine complexes of Pd and Pt, *e.g.*[M(dppe)-$(SR)_2$][14] (SR = 1-methylpiperidine-4-thiolate) where δ = 54.4 (Pd) and 48.1 (Pt) in Me_2SO.

The ^1J(PtP) coupling constants for the complexes [Pt(dppe)-(H_2dmsucc-*S*,*S*')] **5** and [Pt(dadpe)(H_2dmsucc-*S*,*S*')] **6** (Table 1) are at the lower end of the range observed previously for platinum thiolates, *e.g.* 2790, 3047 and 3315 Hz for [Pt(dppe)-$\{S(CH_2)_3NMe_2\}_2$],[13] [Pt(dppe)$(SPh)_2$][35] and [Pt(dadpe)$\{S_2$-$P(OEt)_2\}$]$^+$,[20] respectively, and are less than that observed for P *trans* to O, *e.g.* ^1J(PtP) 3628 Hz for [Pt(dppe)(C_2O_4)],[36] confirming co-ordination of dmsucc through thiolate rather than carboxylate. As expected, the values of ^1J for the dmsucc complexes are less than those for the corresponding dichloro complexes, Table 1, since the *trans* influence of Cl^- is less than that of S.[37] The values are comparable to that of *cis*-$[Pt(dadpe)_2]^{2+}$, Table 1, suggesting that the *trans* influence of S in co-ordinated H_4dmsucc is similar to that of As in dadpe.

The splittings observed for the methine proton resonances of dadpe complexes of dmsucc arise from ^1H–^1H and ^1H–^{31}P couplings. The larger coupling constant (4.2 Hz) is assigned as ^3J(HH). Smaller splittings (2.4 and 1.5 Hz) are assigned to ^4J(PH). Assignments of the downfield resonance to the CH group *cis* to P can be made on the basis of the similarity of ^3J(PtH) coupling constant (37 Hz) to that previously reported for [Pt$(PPh_3)_2(SCH_2S)$][38] [^3J(PtH) = 43 Hz]; this coupling is greater for the upfield CH resonance (58 Hz), Table 2(*a*).

Unlike the parent dihalogeno compounds, the complexes are soluble in hydrophilic solvents (EtOH, 100 mmol dm^{-3} $NaHCO_3$). However, they retain some lipophilic character, as shown by their solubility in $CHCl_3$. The frothing behaviour of the nickel complex in aqueous bicarbonate is typical of detergent-like molecules.

Hmsucc *Complexes*.—The vicinal ^1H–^1H couplings (*ca.* 2 and 11.3 Hz) observed for [Ni(dppe)(Hmsucc)] **2** are at the extremes of the normal range of values, suggesting that the conformation of the ligand is highly constrained. This could be achieved by co-ordination through S and the two carboxyl groups giving square- or trigonal-pyramidal complexes. However, models indicate that this would lead to dihedral angles of *ca.* 30–50 and 70–90° corresponding to coupling constants of 6–4 and 0–1 Hz. If co-ordination is through S and one carboxyl, then the complex is free to adopt a stable 'boat' conformation, in which H_a and H_c are diaxial and H_a and H_b axial–equatorial, Fig. 2(*b*), giving the observed couplings, Table 2(*b*). In this conformation the bulky carboxyl group is equatorial and unable to interact with Ni.

NaH_2dmps *Reactions*.—Reaction of [Ni(dppe)Br_2] with an excess of NaH_2dmps in EtOH afforded a product with a singlet ^{31}P NMR resonance, Table 3, assignable to a complex with symmetric NiP_2S_2 co-ordination as in structures **B** or **G**, Fig. 3. With a 1:1 ratio of reactants, the spectrum not only contained an AB quartet assignable to [Ni(dppe)$\{$Na(dmps)$\}$] with NiP_2SS' co-ordination, **A** in Fig. 3, but also four broad peaks ($\Delta\nu_{\frac{1}{2}}$ 50–60 Hz) to high frequency which may arise from species with sulfonate-*O* co-ordination and/or involve bridging thiolate-*S* ligands. Bridging thiolate sulfurs are known to occur in [Ni$\{$Ni(2-aet)$_2\}_2$]Cl_2,[39] (aet = 2-aminoethanethiolate) and the presence of a complex such as [$\{$Ni(dppe)Cl$\}_2\{$Na(dmps)$\}$] together with chemical exchange broadening due to the presence of different structural forms may account for the observed spectrum.

The major feature in the spectrum of the product from the reaction of [Pd(dppe)Cl_2] with NaH_2dmps is a pair of resonances at δ 50.8 and 50.9, Table 3. These are tentatively assigned to the structure **A**, Fig. 3. Only two peaks are observed suggesting that they may belong to an AB system, the weaker outer resonances not being seen. Two less-intense doublets are assigned as arising from structure **C** or **D**, which again have non-equivalent P groups. The singlet resonance at δ 60.8 may be due to a bridging species of type **B**. Assignments of the resonances are made on the basis of the ^1J(PtP) values, that at δ 46.0 with ^1J(PtP) 2742 Hz being assigned to [Pt(dppe)$\{$Na(dmps)$\}$]

(structure **A**, Fig. 3) by analogy with [Pt(dppe)(H_2dmsucc-*S*,*S*')] [δ 46.8, ^1J(PtP) 2817 Hz, Table 1]. No splittings attributable to P–P coupling are seen for the platinum species, Table 3, possibly because the coupling is too small. The major resonance (δ 44.5) has a greater ^1J(PtP) coupling constant (3036 Hz) and is assigned to structure **B** with bridging S groups. Couplings of this size have been observed previously, for example $[(dppe)Pt\{\mu\text{-}S(CH_2)_3NMe_2\}_2Pt(dppe)]^{2+}$,[13] ^1J(PtP) = 3046 Hz, and compounds containing a four-membered chelate ring, *e.g.* $[Pt(dadpe)(S_2CNEt_2)]BPh_4$,[18] ^1J(PtP) = 3115 Hz. The magnitude of the coupling constants is consistent with S rather than O co-ordination. The other species present in solution is $[Pt(dppe)Cl_2]$, perhaps arising from reaction of one of the products with $CHCl_3$, rather than unreacted starting material, since $[Pt(dppe)Cl_2]$ is not soluble in ethanol from which the product mixture was obtained.

For the dadpe complexes, [M(dadpe){Na(dmps)}], two isomeric products are possible if the dithiol is bidentate, structures **E** or **F**, Fig. 3 and $^{31}P\text{-}\{^1H\}$ NMR spectroscopy shows that two products are indeed formed, Table 3. The mean ^1J(PtP) value observed for [Pt(dadpe){Na(dmps)}] (2735 Hz) is comparable to that observed for the dmsucc analogue [^1J(PtP) = 2795 Hz], thus confirming the assignments of the two isomers. In both cases there are minor species present having unassigned broad resonances.

The $|^3J(P\text{–}P)|$ values for dmps complexes follow the order $Ni^{II} > Pd^{II} > Pt^{II}$, Table 3. With chelating diphosphines two coupling pathways have been recognised; through the metal and through the ligand. In some complexes, *e.g.* $[M\{Ph_2P(CH_2)_nPRR'\}(CO)_4]$ (*n* = 1–3; M = Cr, Mo or W),[40] these appear to be additive, whereas in others, *e.g.* $[M\{cis\text{-}Ph_2PCH{=}C(R)PR'R''\}Cl_2]$ (M = Ni, Pd or Pt; R = CF_3, Ph or Bu^t; R' = R'' = Ph or C_2H_4CN, R' = Et, R'' = Ph),[41] ^3J(P–P) is determined largely by the metal. For the latter complexes, values of 63–71, 13–21 and < 2 Hz have been reported for Ni^{II}, Pd^{II} and Pt^{II} respectively,[41] the same trend as that observed here.

Thioglucose and Tetraacetylthioglucose Reactions.—The results from the reaction of thioglucose with $[Ni(dppe)Br_2]$ are more complex than those for Pd or Pt reflecting the ability of Ni to bind an O of the thioglucose as well as S. An aqueous solution of $[Ni(dppe)Br_2]$ containing 1 mol equivalent of NaH_4tg gave rise to a singlet for the diphosphine dioxide and a ^{31}P NMR AB quartet with chemical shifts which seem too low for Br to be a *trans* ligand, but comparable to those of [Ni(dppe)(Hmsucc)], and so a NiP_2OS configuration is assigned to this complex. For the platinum reaction products the structures were assigned as bridged or unbridged based on the relative magnitudes of the PtP coupling constants, *e.g.* for $[Pt(dppe)Cl_2]$ with 2 mol NaH_4tg, the signal at δ 47.5 with ^1J(PtP) = 2903 Hz is assigned to a dithiolate structure *cf.* [Pt(dppe)(H_2dmsucc)] [δ 46.8, ^1J(PtP) = 2817 Hz], while the other species present [δ 46.2, ^1J(PtP) = 3024 Hz] may be a S-bridged species by analogy with other S-bridged platinum phosphines such as $[(dppe)Pt\{\mu\text{-}S(CH_2)_3NMe_2\}_2Pt(dppe)]^{2+}$[13] [$^1J$(PtP) = 3046 Hz]. At a $[Pt(dadpe)Cl_2]$:NaH_4tg ratio of 1:1, two signals are observed with ^1J(PtP) of *ca.* 3000 Hz indicating two isomeric bridged structures. The palladium 1:1 complexes may contain bridging S by analogy with those of Pt, and the major resonances at higher ratios of Pd to NaH_4tg are assigned as monometal 1:2 complexes, $[Pd(L\text{–}L)(H_4tg\text{-}S)_2]$.

Similar reactions of tetraacetylthioglucose with dppe or dadpe complexes of Pd or Pt afforded mixtures of products which were too complicated to analyse by ^{31}P NMR spectroscopy. Inspection of space-filling models suggests that complexes such as $[M(L\text{–}L)(tatg)_2]$ may not form because of severe steric interactions between the adjacent bulky thiolate ligands. It seems likely that a variety of S-bridged complexes are formed instead.

Dithiothreitol–Nickel Reactions.—Dithiothreitol (H_4dtt, Cleland's reagent) is widely used in biochemistry as a reducing agent for disulfide bonds. One of the few reported structures of metal–dtt complexes is that of $[Mo^{VI}_2O_5(dtt)]^{2-}$, in which the tetradentate ligand provides two deprotonated bridging oxygens and two deprotonated thiolate sulfurs.[42]

Intriguing $^{31}P\text{-}\{^1H\}$ NMR spectra were obtained from reaction of dtt with $[Ni(dppe)Br_2]$. At 24 MHz a symmetrical 12-line multiplet was observed, and at 81 MHz the peaks appeared to be two overlapping AB quartets. To give rise to such a complicated multiplet the species must contain more than two ^{31}P nuclei and structures such as those shown as **H** in Fig. 3 seem likely. Indeed, the most intense peak in the mass spectrum (fast atom bombardment) of an orange-red solid isolated from such reactions[43] was at m/z = 1065. Calculations for $[Ni_2(dppe)_2(dtt)] + H^+$ (1065) reproduced the observed isotope ratio well.[43] Such an arrangement of phosphorus nuclei would give rise to AB quartets if they do not interact, but if they do then the AA'BB' spin system could give up to 24 lines.[44]

Cytotoxicity Studies.—From Fig. 4(*a*) it can be seen that the palladium(II) complexes of dppe are less toxic than is the free ligand against all three cell lines. It is clear that the introduction of the chelating dithiolate, H_2dmsucc, greatly reduces the cytotoxicity. This suggests that the dppe ligand is not a good leaving group in these complexes, *i.e.* they are more stable than the more highly cytotoxic Group 11 complex, $[Au(dppe)_2]^+$.[1] Alternatively the increased hydrophilicity of the dmsucc complex may reduce cell uptake. Similarly, the presence of H_2dmsucc as a ligand in palladium(II) dadpe complexes reduces their cytotoxicity (the carboxylate groups may be ionised at pH 7.4, but their pK_a values were not determined).

The trends in cytotoxicity on introduction of dmsucc are not so clear for Pt^{II}. In one case (L1210 cells) with dadpe, [Pd(dadpe)(H_2dmsucc)], the complex is more cytotoxic than either the free ligand or the dichloro complex, while for the dppe complex [Pd(dppe)(H_2dmsucc)] the cytotoxicity against WS cells is comparable to those of both the free ligand and the dichloro complex. In general, the platinum(II) complexes are more cytotoxic than the palladium(II) complexes, as has been previously found for amine complexes.[45] This is usually rationalised on the basis of the higher kinetic lability of Pd^{II}.

Thus both the metal and the cell line have significant influences on the observed cytotoxicities.

Conclusion

The present work has involved the preparation of amphiphilic phosphine and phosphinoarsine complexes of Ni, Pd and Pt with bidentate thiol ligands. Complexes of the type [M(L–L)(H_2dmsucc)] (M = Ni, Pd or Pt, L–L = dppe; M = Pd or Pt, L–L = dadpe), and [Ni(dppe)(Hmsucc)] were isolated and characterised. These are all square-planar complexes, and, in general, are stable and soluble in a range of solvents including both $NaHCO_3$ and the lipophilic $CHCl_3$. These solubility properties are a consequence of the presence of both hydrophobic Ph groups and hydrophilic carboxylic acid groups in each complex. In general, the introduction of dithiolates decreased the cytotoxicity of this series of complexes, although there was some cell-line dependence, and the platinum(II) complexes were more cytotoxic than the palladium(II) complexes.

Experimental

Sources of Chemicals and Reagents.—1,2-Bis(diphenylphosphino)ethane, *cis*-1,2-bis(diphenylphosphino)ethene and 1-diphenylarsino-2-diphenylphosphinoethane were purchased from Strem Chemicals. Dichloro(cycloocta-1,5-diene)platinum(II) and -palladium(II) were obtained from Aldrich as were *meso*-dimercaptosuccinic acid, tetraacetylthioglucose, dithiothreitol

and sodium 2,3-dimercaptopropanesulfonate. Sodium 1-thio-β-D-glucopyranosate and mercaptosuccinic acid were obtained from Sigma, and Hg[Co(NCS)$_4$] from Alfa. The compounds [M(L–L)Cl$_2$], [M(L–L)$_2$]Cl$_2$ (M = Pd or Pt, L = dppe, or dadpe), [Ni(dppe)Cl$_2$], [Ni(dppen)Cl$_2$], [Ni(dppe)$_2$]Br$_2$ and [Ni(dppen)$_2$Cl]Cl were prepared as previously described.[26–28] The complexes of Pd and Pt were isolated as CHCl$_3$ solvates: 2.0 mol equivalent for the monoligand complexes and [Pt(dppe)$_2$]Cl$_2$, and 0.25, 0.75 and 0.5 mol equivalent for [Pd(dppe)$_2$]Cl$_2$, [Pd(dadpe)$_2$]Cl$_2$ and [Pt(dadpe)$_2$]Cl$_2$ respectively.

Physical Measurements.—The ^{31}P-{^{1}H} NMR spectra were obtained on a Bruker WM200 spectrometer at 81 MHz, or a JEOL FX60 at 24.15 MHz, using 5 or 15 mm tubes. The shift reference was 85% H_3PO_4 (external). Proton NMR spectra were recorded on JEOL FX200, GSX270, GSX500 or Bruker AM400 spectrometers in 5 mm tubes, and electronic spectra on a Perkin Elmer Lambda 5 instrument using cells of 1 cm pathlength. Elemental analyses were carried out by the microanalysis service at University College London. Melting points were determined on a Mettler FP800 apparatus with an FP82 hot stage. Magnetic susceptibilities were measured using a JME magnetic susceptibility balance, calibrated with Hg[Co(NCS)$_4$].[46] Diamagnetic corrections for ligands were measured, and those for Ni^{II} and halides were taken from standard tables.[47]

Preparations.—[Ni(dppe)(H$_2$dmsucc-*S*,*S*′)] **1**. The complex [Ni(dppe)Br$_2$] (0.31 g, 0.5 mmol) was added to H$_4$dmsucc (0.091 g, 0.5 mmol) in EtOH (25 cm^3), and stirred for 2 h, during which time the solution turned from orange to yellow. The crude orange-yellow product was filtered off, and purified by redissolving in aqueous NaOH (pH 10) and reprecipitating with dilute H_2SO_4. The yield of yellow crystalline *solid* was 0.18 g (54.2%), m.p. 154–156 °C (Found: C, 53.5; H, 4.6; P, 9.1; S, 9.3. Calc. for $C_{30}H_{28}NiO_4P_2S_2{\cdot}2H_2O$: C, 53.5; H, 4.8; P, 9.2; S, 9.5%). Electronic spectra (0.1–0.6 mmol dm^{-3}); (CHCl$_3$): λ_{max}/nm 540 (sh) and 432 (sh) (ε/dm^3 mol^{-1} cm^{-1} 250 and 920); (acetone) 520 (sh) and 432 (sh) (ε/dm^3 mol^{-1} cm^{-1} 210 and 560); ν_{max}(CO) 1720 cm^{-1}; μ_{eff} 0.53 ± 0.05. Insoluble in water, soluble in 0.1 mol dm^{-3} NaHCO$_3$ (1.4 mg cm^{-3}), EtOH, CHCl$_3$, dimethylacetamide (dma), tetrahydrofuran (thf) and acetone.

[Ni(dppe)(Hmsucc-*S*,*O*)] **2**. This was prepared by the above procedure, except that the solvent was EtOH–water (5:1). The yield was 0.10 g (64%), m.p. 210–220 °C. The ^{31}P-{^{1}H} NMR spectrum showed that it contained residual [Ni(dppe)Br$_2$] {Found: C, 55.5; H, 4.9; Br, 0.6; P, 9.6; S, 5.1. Calc. for $C_{30}H_{28}NiO_4P_2S{\cdot}2H_2O$ + 2.49% [Ni(dppe)Br$_2$]: C, 56.05; H, 5.0; Br, 0.6; P, 9.7; S, 4.9%}. Electronic spectra (0.1–0.6 mmol dm^{-3}): (CHCl$_3$) λ_{max}/nm 398 (ε/dm^3 mol^{-1} cm^{-1} 600); (acetone) 400 (ε/dm^3 mol^{-1} cm^{-1} 650); ν_{max}(CO) 1735 and 1595 cm^{-1}; μ_{eff} 1.13 ± 0.05. Insoluble in water, soluble in 0.1 mol dm^{-3} NaHCO$_3$ (0.2 mg cm^{-3}), CHCl$_3$, dma, thf and acetone.

[Pd(dppe)(H$_2$dmsucc-*S*,*S*′)] **3**. Aqueous sodium hydroxide (0.5 mmol, 1 cm^3 of a 0.5 mol dm^{-3} solution) was added to a solution of H$_4$dmsucc (0.087 g, 0.478 mmol), in EtOH–water (5:1, 30 cm^3). After 10 min this was added to a suspension of [Pd(dppe)Cl$_2$]·2CHCl$_3$ (0.235 g, 0.29 mmol) in EtOH (30 cm^3). After 2 h the solution had become clear. Concentration of it afforded 0.127 g of yellow *crystals* (64% yield), m.p. 192.1–193.3 °C (decomp.) (Found: C, 52.4; H, 4.7. Calc. for $C_{30}H_{30}O_4P_2PdS_2{\cdot}C_2H_5OH$: C, 52.6; H, 4.7%). Electronic spectrum (CHCl$_3$): λ_{max}/nm *ca.* 340 (sh), 280, 258 and 245 (sh) (ε/dm^3 mol^{-1} cm^{-1} 1000, 57 700, 53 750 and 49 300).

[Pd(dadpe)(H$_2$dmsucc-*S*,*S*′)] **4**. Aqueous sodium hydroxide (0.38 mmol, 0.77 cm^3 of a 0.5 mol dm^{-3} solution) was added to a solution of H$_4$dmsucc (0.037 g, 0.20 mmol), in EtOH–water (5:1, 30 cm^3). After 10 min this was added to a suspension of [Pd(dadpe)Cl$_2$]·2CHCl$_3$ (0.15 g, 0.17 mmol) in EtOH (30 cm^3). After 2 h the solution had become clear. Concentration of it afforded 0.086 g of yellow *crystals* (69% yield), m.p. 182–183.8 °C (decomp.) (Found: C, 48.9; H, 4.1. Calc. for $C_{30}H_{30}AsO_4PdS_2{\cdot}0.5C_2H_5OH$: C, 49.5; H, 4.2%). Electronic spectrum (CHCl$_3$): λ_{max}/nm *ca.* 368 (sh), 324 (sh), 288 (sh), 272 (sh) and 243 (sh) (ε/dm^3 mol^{-1} cm^{-1} 52, 353, 1743, 1722, 1701 and 1560).

[Pt(dppe)(H$_2$dmsucc-*S*,*S*′)] **5**. Aqueous sodium hydroxide (0.32 mmol, 0.25 cm^3 of a 1.27 mol dm^{-3} solution) was added to a solution of H$_4$dmsucc (0.063 g, 0.35 mmol), in EtOH–water (3:1, 20 cm^3). After 10 min this was added to a suspension of [Pt(dppe)Cl$_2$]·2CHCl$_3$ (0.25 g, 0.29 mmol) in EtOH (30 cm^3). After 1.5 h the still cloudy reaction solution was filtered and the filtrate concentrated affording 0.15 g of white *crystals* (68% yield), m.p. 205–206 °C (decomp.) (Found: C, 46.6; H, 3.55. Calc. for $C_{30}H_{30}O_4P_2PtS_2$: C, 46.6; H, 3.65%). Electronic spectrum (CHCl$_3$): λ_{max}/nm 312 (sh) and 246 (sh) (ε/dm^3 mol^{-1} cm^{-1} 2064 and 19 266).

[Pt(dadpe)(H$_2$dmsucc-*S*,*S*′)] **6**. Aqueous sodium hydroxide (0.16 mmol, 0.26 cm^3 of a 0.6 mol dm^{-3} solution) was added to a solution of H$_4$dmsucc (0.029 g, 0.16 mmol), in EtOH–water (3:1, 30 cm^3). After 10 min this was added to a suspension of [Pt(dadpe)Cl$_2$]·2CHCl$_3$ (0.15 g, 0.15 mmol) in EtOH (30 cm^3). After 2 h the reaction solution was almost clear. It was filtered and the filtrate concentrated affording 0.082 g of white *crystals* (62.5% yield), m.p. 151.5–152.7 °C (Found: C, 44.2; H, 3.7. Calc. for $C_{30}H_{30}AsO_4PtS_2{\cdot}C_2H_5OH$: C, 44.2; H, 3.7%). Electronic spectrum (CHCl$_3$): λ_{max}/nm 332 (sh), 304, 272 (sh), 280 (sh) and 252 (ε/dm^3 mol^{-1} cm^{-1} 710, 2787, 5419 and 33 424).

Reaction of [M(L–L)Cl$_2$] (M = Pd *or* Pt, L–L = dppe *or* dadpe) *with* NaH$_2$dmps.—These reactions were carried out by addition of a basic solution of NaH$_2$dmps (slight excess) to a suspension of the appropriate dichloro complex in ethanol. The crude product was isolated from ethanol, redissolved in CDCl$_3$ and spectroscopically analysed.

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