Synthesis and biological activity of platinum(II) and palladium(II) thiosalicylate complexes with mixed ancillary donor ligands

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A series of mixed-ligand thiosalicylate complexes of the type $[M(SC_6H_4CO_2)(PPh_3)L]$ (M = Pt, L = pyridine (py), 4-methylpyridine, imidazole, 4-picolinic acid hydrazide {C₅H₄N[C(O)NHNH₂]-4}; M = Pd, L = pyridine) have been prepared by the one-pot reaction of [PtCl₂(cod)] or [PdCl₂(cod)] (cod = cycloocta-1,5-diene) with one equivalent of PPh₃ and thiosalicylic acid (HSC₆H₄CO₂H) in the presence of the nitrogen base. Single-crystal X-ray diffraction studies on [Pt(SC₆H₄CO₂)(PPh₃)(py)] and the previously reported complex [Pt(SC₆H₄CO₂)(PPh₃)(XyNC)] (Xy = 2,6xylyl) indicates that the complexes have different geometries, though in each case the two ligands of highest *trans*influence are mutually *cis*. The reaction of [PtCl₂(cod)] with PPh₃, thiosalicylic acid and ammonia led to the isolation of crystals of the dinuclear thiosalicylate-bridged complex [Pt(SC₆H₄CO₂)(PPh₃)(NH₃)Pt(SC₆H₄CO₂)(PPh₃)], which was characterised by X-ray crystallography and electrospray mass spectrometry. The conformation of the thiosalicylate ligand can vary widely with values for the dihedral angle between the ligand plane and the platinum(II) coordination plane varying from 12.4° to 70.9° in the seven complexes so far determined. The biological activities of selected platinum and palladium thiosalicylate and related complexes against P388 leukemia cells, bacteria and fungi are also reported. The complex [Pt(SCH₂CO₂)(PPh₃)] shows the highest activity against P388 cells

Introduction

 $(IC_{50} 671 \text{ ng mL}^{-1}).$

Thiosalicylic acid (o-sulfanylbenzoic acid) 1 is able to coordin-



has potent cytotoxicity towards P388 leukaemia cells.³ Since gold(III) is isoelectronic (d⁸) with platinum(II), we speculated that platinum(II) thiosalicylate complexes might also show high biological activities. In this paper, we describe the synthesis of mixed-ligand platinum(II) thiosalicylate complexes, including the formation of a thiosalicylate-bridged platinum dimer, together with the biological activity of a selection of platinum and palladium thiosalicylate complexes.

Results and discussion

Syntheses

Addition of one equivalent of PPh₃ to the complex [PtCl₂(cod)] (cod = cycloocta-1,5-diene) in methanol, followed by one equivalent of **1** and excess pyridine (py), 4-methylpyridine (Mepy), 4-picolinic acid hydrazide { $C_5H_4N[C(O)NHNH_2]-4$ } (pic) or imidazole (imid) gives the bright yellow mixed-ligand complexes **4** after refluxing, concentrating the solution, and



cooling. Similarly, reaction of $[PdCl_2(cod)]$ with PPh₃, thiosalicylic acid and pyridine gave orange crystals of **4e**. All complexes are air-stable and soluble in polar organic solvents such as chloroform, dichloromethane, *etc*. It is worth noting that pyridine is unable to displace a coordinated triphenylphosphine

ate to metal centres either through its thiolate or carboxylate groups, or both, giving rise to a range of complexes with monodentate, bidentate chelating or bridging thiosalicylate ligands.¹⁻³ It is also able to coordinate either as a monoanion or dianion. Somewhat surprisingly, the coordination chemistry of this versatile ligand is relatively undeveloped. Recently we reported the synthesis and characterisation of a series of platinum(II), palladium(II) and nickel(II) complexes containing thiosalicylate ligands, $2.^2$ We have also synthesised some organogold(III) thiosalicylate complexes 3, one of which (3b)

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ligand from 2a since the original synthesis² of this complex from *cis*-[PtCl₂(PPh₃)₂] and thiosalicylic acid used excess pyridine (as a base), under comparable reaction conditions.

In an attempt to prepare an analogous complex with triphenylphosphine and ammonia ligands, the reaction of [PtCl₂-(cod)] with one equivalent each of 1 and PPh₃, and excess ammonia in refluxing methanol was investigated, and gave a yellow solution. Electrospray mass spectrometry (ESMS) in MeCN–H₂O showed the ion [Pt(SC₆H₄CO₂)(PPh₃)₂ + H]⁺, with [Pt(SC₆H₄CO₂)(PPh₃)(NH₃) + H]⁺, [Pt(SC₆H₄CO₂)-(PPh₃)(MeCN) + H]⁺ (*m*/*z* 651) and some of the dinuclear species [Pt₂(SC₆H₄CO₂)₂(PPh₃)₂(NH₃) + H]⁺ (*m*/*z* 1236). The solution was filtered to remove a small amount of insoluble material, and after standing the filtrate for 5 weeks a small number of yellow crystals were deposited, which were poorly soluble in many common solvents. The crystals were subsequently characterised by an X-ray diffraction study (and confirmed by ESMS) to be the dimeric thiosalicylate-bridged complex **5**.



Attempts to synthesise the triphenylphosphine analogue of **5**, *i.e.* $[Pt_2(SC_6H_4CO_2)_2(PPh_3)_3]$ **6** have not been successful, though the complex can be detected in some reactions by ESMS as its $[M + H]^+$ ion at m/z 1481. For example, the species **6** has been observed as a minor ion in some syntheses of the complex $[Pt(SC_6H_4CO_2)(PPh_3)_2]$, but reaction of a 2:3:2 stoichiometric ratio of $[PtCl_2(cod)]$, PPh₃ and thiosalicylic acid in refluxing MeOH with Et₃N base for 2 days, followed by concentration of the yellow solution gave $[Pt(SC_6H_4CO_2)(PPh_3)_2]$ **2a** as the only isolated species.

Crystal structures of $[Pt(SC_6H_4CO_2)(PPh_3)(py)]$ 4a and $[Pt(SC_6H_4CO_2)(PPh_3)(XyNC)]$ 7

In order to determine the molecular geometry of complex 4a, and to compare it with other platinum(II) and gold(III) thiosalicylate complexes, a single-crystal X-ray diffraction study was carried out. For comparative purposes, the structure of the 2,6-xylyl isocyanide (XyNC) complex 7 was also determined.



The latter complex was previously prepared by reaction of the bis(triphenylphosphine) complex 2a with XyNC.² The molecular structure of 4a is given in Fig. 1, together with the atom numbering scheme, and selected bond lengths and angles are given in Table 1. Complex 7 crystallises as an acetone solvate with two independent molecules in the asymmetric unit. The

Table 1	Selected	bond ler	ngths (Å) and ang	les (°) for [Pṫ(SC ₆ H₄CĊ)2)-
(PPh ₃)(p	y)]•H ₂ O	4a∙H ₂ O	with	estimated	standard	deviations	in
parenthe	ses						

Platinum co-ordina	tion		
Pt(1)–S(1) Pt(1)–O(1) Pt(1)–N(1)	2.255(3) 2.054(9) 2.10(2)	Pt(1)–N(1A) Pt(1)–P(1)	2.14(2) 2.231(3)
$\begin{array}{l} S(1)-Pt(1)-O(1)\\ N(1)-Pt(1)-P(1)\\ N(1A)-Pt(1)-P(1)\\ O(1)-Pt(1)-N(1) \end{array}$	94.0(3) 89.9(5) 97.4(6) 89.1(6)	O(1)-Pt(1)-N(1A) S(1)-Pt(1)-P(1) Pt(1)-S(1)-C(1) Pt(1)-O(1)-C(7)	79.7(6) 88.11(12) 109.9(4) 134.2(9)
Thiosalicylate ligar	ıd		
S(1)–C(1) C(7)–O(1) C(7)–O(2)	1.757(13) 1.28(2) 1.23(2)	C(7)-C(2) $S(1)\cdots O(1)$	1.50(2) 3.153
S(1)-C(1)-C(2) C(1)-C(2)-C(7) C(2)-C(7)-O(2)	129.3(10) 126.5(13) 118.8(14)	C(2)-C(7)-O(1) O(2)-C(7)-O(1)	122.9(13) 118.0(14)



Fig. 1 Molecular structure of $[Pt(SC_6H_4CO_2)(PPh_3)(py)]$ 4a, showing the atom numbering scheme. Only one position of the disordered pyridine ligand [incorporating nitrogen N(1)] is shown, and the water of crystallisation is omitted.



Fig. 2 Molecular structure and atom numbering scheme for molecule 2 of $[Pt(SC_6H_4CO_2)(PPh_3)(XyNC)]$ 7. The acetone of crystallisation is omitted.

molecular structure and atom numbering scheme of molecule 2 of complex 7 is shown in Fig. 2, and selected bond lengths and angles are summarised in Table 2. To the best of our knowledge, complex 4a is the first structure of a platinum compound containing the N, P, S, O donor atom set.

Both complexes contain the expected square-planar platinum(II) centre and a chelating thiosalicylate dianion ligand.

Table 2 Selected bond lengths (Å) and angles (°) for $[Pt(SC_6H_4CO_2)]$. (PPh₃)(XyNC)]·Me₂CO 7·Me₂CO^a

	Molecule 1	Molecule 2
Platinum coordinat	tion	
Pt–S	2.3490(8)	2.3395(9)
Pt-O(1)	2.024(2)	2.057(2)
Pt-C(3)	1.883(3)	1.892(3)
Pt–P	2.3068(8)	2.2962(8)
S-Pt-O(1)	87.57(6)	90.63(6)
P-Pt-C(3)	96.06(9)	94.84(9)
O(1)-Pt-P	86.45(6)	85.44(6)
S-Pt-C(3)	90.5(1)	89.2(1)
Pt-S-C(11)	95.0(1)	102.9(1)
Pt-O(1)-C(2)	125.5(2)	131.7(2)
Thiosalicylate ligar	nd	
S-C(11)	1.782(3)	1.782(3)
C(2) - O(1)	1.299(4)	1.277(4)
C(2) - O(2)	1.225(4)	1.238(4)
C(2) - C(16)	1.511(5)	1.484(5)
$S \cdots O(1)$	3.036(2)	3.132(2)
S(2)-C(11)-C(16)	123.4(3)	125.5(3)
C(11) - C(16) - C(2)	123.5(3)	125.4(3)
C(16)-C(2)-O(2)	119.2(3)	119.3(3)
C(16)-C(2)-O(1)	119.7(3)	122.3(3)
O(2)–C(2)–O(1)	121.1(3)	118.3(3)

^a Parameters are given for the two independent molecules in the asymmetric unit. Labelling is such that, for example, S refers to S(1) and S(2), and C(11) refers to C(111) and C(211), respectively in molecules 1 and 2.

However, the complexes have different arrangements of ligands; 4a has the PPh₃ ligand *cis* to the S atom and *trans* to O, while the isocyanide complex 7 has the PPh₃ ligand *trans* to S and cis to O. In both cases, the two ligand donor atoms of highest trans-influence (P and S in 4a, P and C in 7) are cis to each other, as is also the case for the gold(III) thiosalicylate complexes 3.3 This effect, antisymbiosis, has been well documented.4

It is of interest to compare the structures of 4a and 7 with that of the bis(triphenylphosphine) complex 2a. Complexes 2a and 7 have the S atom trans to a high trans-influence PPh₃ ligand, and so have similar Pt-S bond distances [2a, 2.322(2); 7, 2.3395(8) Å in molecule 2]. In contrast, the S atom in 4a is trans to a much lower trans-influence pyridine ligand, so the Pt-S bond is shorter [2.255(3) Å]. Similarly the Pt-P bond distances in 4a [trans to O, 2.231(3) Å] and in 7 [trans to S, 2.2962(8) Å in molecule 2] reflect the higher trans-influence of the thiolate ligand compared to carboxylate, as is also seen in 2a. The two bonds cis to the pyridine ligand in 4a, Pt(1)-P(1) and Pt(1)-O(1) are also shortened relative to the corresponding bonds in 2a. This is presumably because of the small size of pyridine compared to PPh3, permitting a closer approach of the PPh. and carboxylate groups. Thus, in 2a, the P(1)-Pt and O(1)-Pt bond lengths are 2.2501(11) and 2.109(3) Å, while the P(1)-Pt(1) and O(1)-Pt(1) distances in 4a are 2.231(3) and 2.054(9) Å respectively.

The Pt-N bond involving the disordered pyridine ligand in 4a [2.12(2) Å] is longer than the Pt-N bonds trans to sulfur found in 8 [2.055(8) Å],⁵ though the SMe group is expected to have a lower trans-influence which may account for the bond





Platinum(1) co-ordin	ation		
Pt(1)-S(1)	2.3068(19)	Pt(1)-S(2)	2.3595(17)
Pt(1)–O(11)	2.068(5)	Pt(1) - P(1)	2.2124(17)
S(1)-Pt(1)-O(11) S(2)-Pt(1)-P(1) O(11)-Pt(1)-S(2)	84.69(15) 97.04(6) 89.11(14)	S(1)-Pt(1)-P(1) Pt(1)-S(1)-C(11) Pt(1)-O(11)-C(17)	89.14(7) 97.0(3) 126.9(5)
Thiosalicylate ligand	(1)		
S(1)-C(11)	1.751(9)	C(17) - O(12)	1.249(9)
C(17)–O(11)	1.270(9)	C(17)-C(16)	1.509(11)
S(1)-C(11)-C(16)	124 6(6)	C(16) = C(17) = O(11)	121 0(7)
C(11) = C(16) = C(17)	124.0(0) 121.9(7)	O(12)-C(17)-O(11)	121.0(7) 121.4(7)
C(16)-C(17)-O(12)	117.6(7)		12111(/)
Platinum(2) co-ordin	ation		
Pt(2)-S(2)	2.2799(17)	Pt(2) - N(1)	2.055(6)
Pt(2)–O(21)	2.061(4)	Pt(2)–P(2)	2.2096(17)
S(2)–Pt(2)–O(21)	90.98(14)	S(2) - Pt(2) - P(2)	88.98(6)
N(1) - Pt(2) - P(2)	97.1(2)	Pt(2)-S(2)-C(21)	100.7(2)
O(21)-Pt(2)-N(1)	82.8(2)	Pt(2)-O(21)-C(27)	130.7(4)
Bridging thiosalicylat	te ligand(2)		
S(2)–C(21)	1.785(7)	O(22)–C(27)	1.225(8)
O(21)–C(27)	1.299(8)	C(26)–C(27)	1.504(10)
S(2)-C(21)-C(26)	124.2(5)	C(26)-C(27)-O(21)	120.3(6)
C(21)–C(26)–C(27)	126.3(6)	O(22)–C(27)–O(21)	120.9(6)
C(26)–C(27)–O(22)	118.7(6)		



Fig. 3 Perspective view of the molecular structure and atom numbering scheme for [Pt₂(SC₆H₄CO₂)₂(PPh₃)₂(NH₃)] 5. The methanol of crystallisation has been omitted.

length difference. The pyridine ligand of 4a is inclined at an angle of 70.5° to the platinum coordination plane. The structure of 4a was found to contain one disordered water of crystallisation, H-bonded to the free O(2) of the carboxylate ligand. The conformation of the thiosalicylate ligand is discussed below.

Orange crystals of the palladium complex 4e (obtained from a saturated methanol solution) were examined by precession photography, and found to be isomorphous with the analogous platinum complex 4a. The palladium complex is therefore assumed to have the same geometry as the platinum one, with mutually cis PPh₃ and thiolate ligands.

Crystal structure of [Pt₂(SC₆H₄CO₂)₂(PPh₃)₂(NH₃)] 5

The molecular structure of 5 is shown in Fig. 3, together with the atom numbering scheme. Selected bond lengths and angles are given in Table 3. The complex can be viewed as the mononuclear species $[Pt(SC_6H_4CO_2)(PPh_3)(NH_3)]$ which has

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Table 4 A comparison of bond parameters for Pt(II) thiosalicylate complexes

Compound	Fold angle ^{<i>a</i>} /°	Twist angle ^b /°	Pt–S/Å	Pt–O/Å	S···O/Å	Pt-S-C/°	Pt-O-C/°	S-Pt-O/°
7 (molecule 1)	70.9	38.4	2.349	2.024	3.035	95.0	125.5	87.6
5 (Pt(2))	66.1	31.8	2.307	2.068	2.952	97.0	126.9	84.7
9	60.5	20.0	2.316	2.076	2.99	99.2	126.0	85.6
5 (Pt(1))	49.3	29.1	2.280	2.061	3.099	100.6	130.7	91.0
2a	47.2	21.1	2.322	2.109	2.99	103.7	135.8	84.7
7 (molecule 2)	40.3	32.7	2.340	2.057	3.132	102.9	131.7	90.6
4a	12.4	4.4	2.255	2.054	3.153	109.9	134.2	94.0

^a The dihedral angle between the plane of the thiosalicylate ligand (excluding the oxygen atoms) and the Pt(II) coordination plane. ^b The dihedral angle between the plane of the carboxylate group and that of the rest of the ligand.

coordinated its thiolate sulfur to a $[Pt(SC_6H_4CO_2)(PPh_3)]$ moiety. Thiolate-bridged platinum(II) complexes are very wellknown⁶ but few compounds containing a single thiolate bridge between two metal centres have been reported.⁷ However, complexes containing thiosalicylate ligands which bridge through their S atoms are known, e.g. the manganese dimer $[(CO)_3Mn-(SC_6H_4CO_2)_2Mn(CO)_3]^{2-,8}$ and complex 9 which contains two



 $[Pt(SC_6H_4CO_2)(PPh_3)_2]$ molecules coordinated to a $IHg(\mu-I)_2$ -HgI unit.9

Both platinum centres of 5 have the thiosalicylate sulfur atoms cis to the PPh₃ ligand, the same as the pyridine derivative 4a, and both PPh₃ ligands are *trans* to carboxylate oxygens, with similar bond lengths [Pt(1)-P(1) 2.2124(17), Pt(2)-P(2) 2.2096(17) Å; Pt(1)-O(11) 2.068(5), Pt(2)-O(21) 2.061(4) Å]. The two platinum coordination planes are inclined at an angle of 67.3°.

The bridging thiolate is not symmetrically bonded to both platinum centres, with Pt(1)-S(2) [2.3595(17) Å] somewhat longer than Pt(2)-S(2) [2.2799(17) Å] and Pt(1)-S(1)[2.3068(19) Å], indicating primary coordination of this thiosalicylate ligand in S,O chelate fashion to Pt(2). The Pt(2)-S(2) bond [2.2799(17) Å] is shorter than the corresponding bond in 9 [2.3159(14) Å], where the S is *trans* to a (high *trans*-influence) PPh₃ ligand, compared to a low *trans*-influence NH₃ in 5. The Pt(2)-S(2)-C(21) and Pt(1)-S(2)-C(21) bond angles of 5 [100.7(2) and 107.5(2)° respectively] are similar to the corresponding Pt-S-C and Pt-S-Hg bond angles [99.2(2) and $105.78(18)^{\circ}$ in 9, but the Pt(2)–S(2)–Pt(1) bond angle $[104.77(7)^{\circ}]$ is wider than the Pt–S–Hg angle $[96.51(5)^{\circ}]$.

With the structures reported here, there are now seven distinct examples of Pt(II)-thiosalicylate complexes for which parameters are determined. It is immediately apparent that the conformation of the thiosalicylate ligand varies widely within this set, as indicated by the dihedral angles between the ligand and coordination planes. In Table 4 are summarised the relevant details.

The "fold angle" between the plane defined by the ligand (excluding the oxygen atoms) and the Pt(II) coordination plane varies from 12.4° in 4a to 70.9° in one of the independent molecules of 7. It is clear that this folding is flexible, since the two independent molecules of 7 have dihedral angles of 40.3° and 70.9°, showing that the crystal packing effects can induce

large changes. The relative conformation has little effect on the Pt-S $(2.31 \pm 0.05 \text{ Å})$, Pt-O $(2.07 \pm 0.04 \text{ Å})$ and S···O $(3.05 \pm 0.10 \text{ Å})$ distances which remain reasonably constant given the different co-ligands present. (Surprisingly, further coordination of the sulfur atom to another metal, as in 5 or 9, has little consequence for the chelation interaction with Pt(II).)

The increase in the fold angle is accommodated by a twisting of the carboxylate group out of the plane of the rest of the thiosalicylate ligand (by 4-38°), and leads to a decrease in the Pt-S-C (109.9 to 95.0°) and Pt-O-C (134.2-125.5°) angles. Increased folding also correlates with a decrease in the S-Pt-O angle, although this relationship is less regular. A nickel complex related to 2a also falls into this general pattern.²

The overall picture of the thiosalicylate ligand is therefore one of a relatively rigid unit with a constant $S \cdots O$ bite distance, which can however be readily folded about the S and O chelating atoms by other interactions, either intra- or intermolecular. Changes in conformation and metal size are accommodated mainly by variations in the angles at the chelating S and O atoms.

NMR spectroscopic analysis

³¹P-{¹H} NMR spectroscopy of the platinum complexes 4 gives a single resonance with ¹⁹⁵Pt satellites, with ${}^{1}J(PtP)$ values in the range 4146-4201 Hz, showing that the isomer formed in each case has the phosphine ligand trans to the carboxylate. By comparison, ${}^{1}J(PtP)$ for the PPh₃ trans to carboxylate for **2a** is 3899 Hz; the low *cis*-influence of the nitrogen ligands is presumably responsible. Values of ${}^{1}J(PtP)$ for phosphines *trans* to thiolate ligands are of the order of 3000 Hz, e.g. 3047 Hz for [Pt(SPh)2-(Ph₂PCH₂CH₂PPh₂)]¹⁰ and 2884 Hz for the phosphine *trans* to S in $2a^2$.

The ³¹P NMR spectra of several batches of the palladium complex 4e always showed (in addition to the major product at δ 34.9) a small singlet at δ 26.7, which may be the other isomer having the PPh₃ ligand *trans* to sulfur. Consistent with this, excellent microanalytical data were obtained for this complex. Furthermore, for the bis(triphenylphosphine) palladium complex 2d, the PPh₃ ligand *trans* to S has a higher chemical shift (δ 36.5), similar to the major peak observed for 4e, while the PPh₃ trans to O has a lower chemical shift (δ 25.2), similar to the minor peak observed for 4e at δ 26.7.²

The ¹³C-{¹H} NMR spectrum of **4a** shows a singlet resonance for the coordinated carboxylate at δ 169.4. Complex 2a also displayed a broadened singlet at δ 168.0,² indicating that phosphorus coupling is small.

Electrospray mass spectrometry (ESMS)

ESMS is becoming a routine technique for the characterisation of coordination complexes,¹¹ and can provide information on fragmentation processes, by the use of high cone voltages. We have described the use of ESMS in characterisation of the thiosalicylate complexes of Ni, Pd and Pt,² and of Au.³ The ease of fragmentation of these complexes is highly dependent on the nature of the ancillary ligands. Thus the organogold(III)

Table 5	Selected electrospray m	nass spectrometric data for	the mixed-ligand thiosali	cylate complexes in N	$4 eCN - H_2O(1:1 v/v)$
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Complex	Ion mode	Cone voltage/V	Ions $(m/z, \%)^b$
4 a	Positive	20	$[M + H]^+$ (689, 100), $[2M + H]^+$ (1377, 73)
		80	$[M + H - py]^+$ (610, 28), $[M + H - py + MeCN]^+$ (651, 12), $[M + H]^+$ (689, 100), $[2M + H]^+$
			$H - 2py]^+$ (1219, 28), $[2M + H - py]^+$ (1298, 32), $[2M + H]^+$ (1377, 100)
4b	Positive	20	$[M + H]^+$ (703, 100), $[2M + H]^+$ (1405, 68)
		60	$[M + H - (Mepy)]^+$ (610, 68), $[M + H - (Mepy) + MeCN]^+$ (651, 20), $[M + H]^+$ (703, 43),
			$[2M + H - (Mepy)]^+$ (1313, 20), $[2M + H]^+$ (1405, 100)
4c	Positive	20	$[M + H]^+$ (747, 100), $[2M + H]^+$ (1493, 40)
4d	Positive	20	$[M + H]^+$ (678, 100), $[2M + H]^+$ (1355, 25)
4 e	Positive	20	$[M + H]^+$ (600, 100), $[2M + H - py]^+$ (1122, 50), $[2M + H]^+$ (1201, 20)
5 <i>ª</i>	Positive	40	$[M + H]^+$ (1236, 100), $[M + NH_4]^+$ (1253, 45), $[3M + NH_4 + Na]^{2+}$ (1874, 80), $[2M + NH_4]^+$
			(2489, 60)
	Negative	60	$[Pt(SC_6H_4CO_2)(PPh_3)Cl]^-$ (645, 70), $[Pt(SC_6H_4CO_2)(PPh_3)(MeOH)Cl]^-$ (677, 30), $[M-PPh_3-NH_3+Cl]^-$ (991, 40), $[M-NH_3+Cl]^-$ (1254, 100)

^a Sample dissolved in CH₂Cl₂ and analysed with methanol. ^b m/z values refer to the most intense peak in the isotope distribution pattern.

complexes, containing two chelate ring systems, are highly resistant towards fragmentation, and the parent $[M + H]^+$ ion was the base peak even at a cone voltage of 200 V. In contrast, complexes containing PPh₃ ligands fragment by means of a cyclometallation process. Thus, it was of interest to examine the mixed-ligand complexes described herein, which contain a relatively weakly coordinated nitrogen-donor ligand, which is expected to be easily lost at elevated cone voltages.

Positive-ion ESMS data for the complexes reported in this paper are given in Table 5. At a relatively low cone voltage (20 V) the platinum complex 4a yields the expected strong pseudoparent $[M + H]^+$ ion (*m*/*z* 689), together with an aggregate ion $[2M + H]^+$ (*m*/*z* 1377); such behaviour is typical for this class of complex and is observed for 4b-4d and other platinum, palladium and nickel thiosalicylate complexes reported previously.² On increasing the cone voltage above 40 V, pyridine is lost preferentially, resulting in the formation of ions $[M + H - py]^+$, $[2M + H - py]^+$, $[2M + H - 2py]^+$ and the solvated analogue $[M + H - py + MeCN]^+$. It is noteworthy that there are no ions containing two platinum atoms together with MeCN, corresponding to the mono-platinum ion $[M + H - py + MeCN]^+$, possibly suggesting the presence of bridging thiosalicylate ligands which would block any vacant coordination sites. The palladium complex 4e showed similar behaviour, except for the presence of a reasonably intense ion $[2M + H - py]^+$, formed by loss of pyridine, and which could contain a bridging thiosalicylate ligand, analogous to 5 and 6. The higher lability of palladium compared to platinum complexes might account for this difference.

The dinuclear complex 5 was poorly soluble in methanol and 1:1 MeCN-H₂O, but can be successfully analysed by dissolving a few small crystals of the complex in CH2Cl2 before diluting with methanol, using pure methanol mobile phase in the spectrometer. The spectra are consistent with the dinuclear nature of the complex (Fig. 4). The positive ion spectrum at 20 V shows a number of ions, all consistent with the dinuclear complex (M) remaining intact: $[M + H]^+$ (*m*/*z* 1236), $[M + NH_4]^+$ $(m/z \ 1253), [3M + NH_4 + Na]^{2+} (m/z \ 1874), and [2M + NH_4]^{+}$ (m/z 2489). Confirmation of the m/z 1874 ion as a dication was readily obtained from the isotope pattern. Increasing the cone voltage to 40 V increased the intensity of the $[M + H]^+$ ion at the expense of the aggregate ions, while at 60 V, fragmentation of the parent begins to occur, with observation of [M + H - NH_3]⁺ (m/z 1219) and [2M - 2NH₃ + MeOH + H]⁺ (m/z 2470). Addition of KCl to the solution of 5 resulted in the observation of analogous potassiated ions, viz. $[M + K]^+$ (m/z 1274), $[3M + K + H]^{2+}$ (*m*/*z* 1874), $[3M + 2K]^{2+}$ (*m*/*z* 1893), and $[2M + K]^+$ (m/z 2511), lending additional support to the ion assignments. However, interestingly, addition of NH₄[HCO₂] to the solution only resulted in increasing the intensity of the $[M + H]^+$ (m/z 1236) ion, such that few other



Fig. 4 Electrospray mass spectra of the dinuclear complex $[Pt_2-(SC_6H_4CO_2)_2(PPh_3)_2(NH_3)]$ 5 (=M) in CH₂Cl₂-MeOH: (a) positive ion, cone voltage 40 V and (b) negative ion, cone voltage 60 V, showing ion assignments.

ions were observed. At 80 V, the same loss of NH₃ is observed, giving $[M + H - NH_3]^+$ (*m*/*z* 1219). Analysis of **5** in the more strongly coordinating MeCN-H₂O solvent at cone voltages in the range 20–50 V showed the $[M + H]^+$ ion (*m*/*z* 1236), together with an ion at *m*/*z* 651, assigned as $[Pt(SC_6H_4CO_2)-(PPh_3)(MeCN) + H]^+$, and a weak ion at *m*/*z* 627 assigned as $[Pt(SC_6H_4CO_2)(PPh_3)(NH_3) + H]^+$. These ions are presumably formed by cleavage of the thiolate bridge by the solvent MeCN, giving the two mononuclear species.

Complex 5 also gives reasonably strong ions in negative ion mode, with $[M - NH_3 + Cl]^-$ (*m*/*z* 1254) being the base peak at a cone voltage of 20 V, together with the lower intensity ion $[Pt(SC_6H_4CO_2)(PPh_3)Cl]^-$ (*m*/*z* 645), formed from adventitious chloride ions. Increasing the cone voltage to 60 V effects further fragmentation, with $[Pt(SC_6H_4CO_2)(PPh_3)Cl]^-$ increasing in intensity relative to the base peak of $[M - NH_3 + Cl]^-$, and observation of $[M - NH_3 - PPh_3 + Cl]^-$ (*m*/*z* 991), and

Table 6 Antitumour (P388), antiviral/cytotoxicity assay results and antimicrobial/antifungal^e activities^d for platinum(II) and palladium(II) thiosalicylate and related complexes

Compound	IC ₅₀ ^{<i>a</i>}	Cyt ^{<i>b</i>}	Ec	Bs	Ра	Ca	Tm	Cr
$[Pt(SC_6H_4CO_2)(PPh_3)_2] 2a^g$	2506	4+	12	15	9	13	18	24
$[Pt(SC_6H_4CO_2)(pta)_2] \mathbf{2b}^g$	49680	2+	2	7			_	_
$[Pt(SC_6H_4CO_2)(dppe)] 2c^g$	799	ND	_				_	_
$[Pd(SC_6H_4CO_2)(PPh_3)_2] 2d^g$	2506	+	—	1	—	—		
$[Pt(SC_6H_4CO_3)(PPh_3)(py)]$ 4a	1294	3+	1	7	_			_
$[Pt(SC_6H_4CO_2)(PPh_3)(pic)]$ 4c	>62500	f	f	f	f	f	f	f
$[Pt(SC_6H_4CO_2)(PPh_3)(imid)]$ 4d	8653	f	f	f	f	f	f	f
$[Pd(SC_6H_4CO_2)(PPh_3)(py)] 4e$	11483	+-	—	2	_	_	—	
$[Pt(OC_6H_4CO_2)(PPh_3)_2]$ 12 ^g	6291	ND		5		1	4	_
[Pt(SCH ₂ CO ₂)(PPh ₃) ₂] 13 ^g	671	+		_	_	_	_	_
$[\{C_6H_4(CH_2NMe_2)-2\}Au\{SC_6H_4CO_2\}] 3a^e$	1937	4+	4	10	4	6	12	4
$[\{C_{6}H_{3}(CH_{2}NMe_{2})-2-(OMe)-5\}Au\{SC_{6}H_{4}CO_{2}\}] \mathbf{3b}^{e}$	301	3+	2	6	3	5	4	7

^{*a*} The concentration of sample in ng mL⁻¹ required to reduce the cell growth of the P388 leukemia cell line (ATCC CCL 46) by 50%. ^{*b*} Cytotoxicity to BSC cells; ND denotes no discernible antiviral or cytotoxic effects, + – denotes minor effects located under the disc, + denotes antiviral or cytotoxic zone 1–2 mm excess radius from disc (25% zone), 2+ denotes antiviral or cytotoxic zone 2–4 mm excess radius from the disc (50% zone), 3+ denotes antiviral or cytotoxic zone 4–6 mm excess radius from the disc (75% zone), 4+ denotes antiviral or cytotoxic zone over the whole well (100% zone). ^{*c*} Ec = *Escherichia coli*, Bs = *Bacillus subtilis*, Pa = *Pseudomonas aeruginosa*, Ca = *Candida albicans*, Tm = *Trichophyton mentagrophytes*, Cr = *Cladosporium resinae*. ^{*d*} Inhibition zone as excess radius (mm) from a 6 mm (diameter) disc containing 2 µg of sample. ^{*e*} Data from ref. 3. ^{*f*} Not determined. ^{*g*} Synthesised according to ref. 2.

 $[Pt(SC_6H_4CO_2)(PPh_3)(MeOH)Cl]^-$ (*m/z* 677). At 80 V, $[Pt(SC_6H_4CO_2)(PPh_3)Cl]^-$ is the base peak, suggesting that the dinuclear species is undergoing fragmentation across the bridging thiolate–Pt bond, generating $[Pt(SC_6H_4CO_2)(PPh_3)Cl]^-$, and the neutral fragment $[Pt(SC_6H_4CO_2)(PPh_3)(NH_3)].$

Biological activity of thiosalicylate complexes

We have previously reported that the gold(III) thiosalicylate complexes, in particular the methoxy-functionalised complex **3b**, show marked antitumour and antimicrobial activity.³ The platinum and palladium thiosalicylate complexes **4** have a similar arrangement of two mutually *cis*, high *trans*-influence ligands which are *trans* to two mutually *cis*, low *trans*-influence ligands. The related gold complex **10** has shown appreciable



activity against Chinese hamster ovary cells, comparable to that shown by the clinical drug cisplatin, *cis*-[PtCl₂(NH₃)₂].¹² Further impetus for studying the biological activities of these thiosalicylate complexes comes from the observation that platinum(II) complexes containing methylsulfinyl and methyl-sulfanyl derivatives of thiosalicylate (*e.g.* **8**) have been found to show antitumour activity.^{5,13} However, platinum(II) and palladium(II) complexes (11) with dithiolate-containing ligands such as dimercaptosuccinate show reduced cytotoxicity,¹⁴ suggesting that the presence of a labile carboxylate ligand might be useful in increasing the activity of this class of complex.

The biological activities of a number of thiosalicylate complexes have been determined, in order to compare: (i) platinum with palladium complexes; (ii) the effect of phosphine *versus* pyridine ligands; (iii) thiosalicylate *versus* salicylate and mer-



captoacetate (SCH₂CO₂) ligands (in complexes **12** and **13** respectively); and (iv) the effect of a bidentate chelating ligand (dppe). The phosphatriazaadamantane (pta) complex **2b** was also included in the study because of the water-solubility of pta complexes.¹⁵ Assay data are summarised in Table 6.

Against P388 leukemia cells, the complexes $[Pt(SCH_2CO_2)-(PPh_3)_2]$ **13** and $[Pt(SC_6H_4CO_2)(dppe)]$ **2c** exhibit low IC₅₀ values (the amount required to inhibit cell growth by 50%) of 671 and 799 ng mL⁻¹ respectively, which equates to very high activity. These two complexes were the most active of those tested, but they are still less effective than the gold(III) thiosalicylate complex **3b**, which has an IC₅₀ of 301 ng mL^{-1.3} Moderate antitumour activity is exhibited by the complexes $[Pt(SC_6H_4CO_2)(PPh_3)(py)]$ **4a**, $[Pt(SC_6H_4CO_2)(PPh_3)_2]$ **2a**, and $[Pd(SC_6H_4CO_2)(PPh_3)_2]$ **2d**, all three of which have an IC₅₀ value between 1200 and 2600 ng mL⁻¹. The remaining compounds were not significantly active.

In the antimicrobial assay, seven of the compounds tested showed little activity against the bacteria *Escherichia coli, Bacillus subtilis* and *Pseudomonas aeruginosa*, and the fungi *Candida albicans, Trichophyton mentagrophytes* and *Cladosporium resinae*. However, the complex $[Pt(SC_6H_4CO_2)(PPh_3)_2]$ **2a** showed extremely high activity against the microbes tested, unusually high values for these types of tests. The complex has even higher activity than the gold(III) complex **3b**, which also displayed high antimicrobial and antifungal activities. The antimicrobial minimum inhibitory concentration (MIC; range between the highest concentration allowing growth and the lowest inhibiting growth) for $[Pt(SC_6H_4CO_2)(PPh_3)_2]$ **2a** against the bacterium *Bacillus subtilis* was measured at 3–6 µg mL⁻¹ (3.4–6.9 µmol L⁻¹), this being one of the most sensitive

Experimental

Materials and methods

General experimental procedures and instrumentation were as described previously.² Electrospray mass spectra were recorded in positive-ion mode in MeCN-H₂O (1:1 v/v) solution (unless otherwise stated), and ion assignment was aided by comparison of experimental and calculated isotope patterns, the latter obtained using the Isotope program.¹⁶ NMR spectra were recorded in CDCl₃ solution unless otherwise stated. The following compounds were used as supplied from commercial sources: pyridine (BDH), 4-methylpyridine (BDH), triphenylphosphine (Pressure Chemical Co.), thiosalicylic acid (Sigma), 4-picolinic acid hydrazide (Merck), imidazole (Aldrich). The compounds [PtCl₂(cod)],¹⁷ [PdCl₂(cod)],¹⁸ 2a-2d, 12 and 13 were synthesised by the literature procedures.² Assays for biological activity were carried out by Gill Ellis of the Marine Chemistry Group, University of Canterbury. Reactions were carried out in LR grade methanol solvent, without exclusion of air.

Syntheses

[Pt(SC₆H₄CO₂)(PPh₃)(py)] 4a. A mixture of [PtCl₂(cod)] (605 mg, 1.616 mmol), triphenylphosphine (424 mg, 1.616 mmol), thiosalicylic acid 1 (249 mg, 1.616 mmol) and pyridine (10 drops, excess) in methanol (30 mL) was heated under reflux for 20 min giving a bright yellow solution. The volume was reduced to one-third, refrigerated overnight, and the resulting bright yellow microcrystals were filtered off, washed with methanol (5 mL), diethyl ether (20 mL) and dried under vacuum for 2 h to give 641 mg (58%) of **4a**. From a separate preparation, crystals of the monohydrate suitable for an X-ray diffraction study were obtained. A sample for elemental analysis was recrystallised from CH₂Cl₂–diethyl ether. Mp 230–232 °C (decomp.). Found: C, 52.1; H, 3.6; N, 2.1. C₃₀H₂₄-NO₂PPtS requires C, 52.3; H, 3.5; N, 2.0%. ³¹P-{¹H} NMR, δ 10.0, [s, ¹*J*(PtP) 4146]. IR, ν(C=O) 1596(vs), 1575(s, sh) cm⁻¹.

[Pt(SC₆H₄CO₂)(PPh₃)(Mepy)] 4b. Following the method for 4a, yellow crystals (75 mg, 40%) of 4b were obtained starting from [PtCl₂(cod)] (101 mg, 0.269 mmol), triphenylphosphine (71 mg, 0.269 mmol), thiosalicylic acid (42 mg, 0.269 mmol) and 4-methylpyridine (10 drops, excess). Mp >230 °C (decomp.). Found: C, 50.5; H, 3.7; N, 1.9. $C_{31}H_{26}NO_2PPtS$ requires C, 53.0; H, 3.7, N, 2.0%. $C_{31}H_{26}NO_2PPtS \cdot 2H_2O$ requires C, 50.4; H, 4.1; N, 1.9%. NMR: ³¹P-{¹H}, δ 9.9 [s, ¹J(PtP) 4160]. IR, ν(C=O) 1618(s, sh), 1591(vs) cm⁻¹.

[Pt(SC₆H₄CO₂)(PPh₃)(pic)] 4c. A mixture of [PtCl₂(cod)] (300 mg, 0.802 mmol), PPh₃ (210 mg, 0.802 mmol), thiosalicylic acid (124 mg, 0.805 mmol) and 4-picolinic acid hydrazide (pic) (600 mg, excess) in methanol (20 mL) was heated under reflux for 20 min giving a clear deep yellow solution. After cooling and standing overnight yellow microcrystals had formed, which were filtered off, washed with methanol–water (1:1, 15 mL) and dried to give **4c** (200 mg, 33%). Found: C, 49.2; H, 3.5; N, 5.65. C₃₁H₂₆N₃O₃PPtS requires C, 49.9; H, 3.5; N, 5.6%. Mp 230–234 °C. ³¹P-{¹H} NMR, δ 9.8 [s, ¹*J*(PtP) 4201].

 $[Pt(SC_6H_4CO_2)(PPh_3)(imid)]$ 4d. A mixture of $[PtCl_2(cod)]$ (300 mg, 0.802 mmol), PPh₃ (210 mg, 0.802 mmol), thiosalicylic acid (124 mg, 0.805 mmol) and imidazole (600 mg, excess) in methanol (25 mL) rapidly gave a clear, bright yellow solution. After heating under reflux for 2 h the mixture was cooled to room temperature, and the yellow precipitate filtered off, washed with cold methanol (3 mL), water (5 mL), ethanol (5 mL) and diethyl ether (2 × 5 mL), and dried. Yield 340 mg (63%). Found: C, 49.5; H, 3.4; N, 4.2. $C_{28}H_{22}N_2O_2PPtS$ requires C, 49.7; H, 3.3; N, 4.1%. Mp 236–239 °C. ³¹P-{¹H} NMR, δ 8.4 [s, ¹*J*(PtP) 4196].

[Pd(SC₆H₄CO₂)(PPh₃)(py)] 4e. [PdCl₂(cod)] (400 mg, 1.40 mmol), triphenylphosphine (366 mg, 1.40 mmol), thiosalicylic acid (215 mg, 1.40 mmol) and pyridine (1 mL, excess) were heated under reflux in methanol (30 mL) for 20 min. Evaporation to *ca.* one-third gave orange crystals, which were filtered off, washed with cold methanol (5 mL), water (10 mL), and diethyl ether (10 mL) and vacuum dried to give 700 mg (84%) of **4e.** Found: C, 60.0; H, 4.05; N, 2.3. $C_{30}H_{24}NO_2PPdS$ requires C, 60.1; H, 4.0; N, 2.3%. Mp 210–216 °C. ³¹P-{¹H} NMR, δ 34.9 (s), plus a small peak at δ 26.7 (s). IR, ν (C=O) 1592 (vs), 1570 (vs) cm⁻¹.

[Pt₂(SC₆H₄CO₂)₂(PPh₃)₂(NH₃)]·1.5MeOH 5·1.5MeOH. A mixture of [PtCl₂(cod)] (101 mg, 0.270 mmol), PPh₃ (71 mg, 0.271 mmol), thiosalicylic acid (41.8 mg, 0.271 mmol) and conc. NH₃ solution (10 drops, excess) in methanol (30 mL) was heated at reflux for 20 min to give a pale yellow solution, and the volume reduced to ca. one-third. ESMS showed the formation of $[Pt(SC_6H_4CO_2)(PPh_3)_2]$ and some $[Pt(SC_6H_4CO_2)-$ (PPh₃)(NH₃)], so the reaction was continued for 24 h with fresh conc. NH₃ (1 mL) and additional MeOH (20 mL). ESMS again showed mainly $[Pt(SC_6H_4CO_2)(PPh_3)_2]$, together with more $[Pt(SC_6H_4CO_2)(PPh_3)(NH_3)]$ and $[Pt_2(SC_6H_4CO_2)_2-$ (PPh₃)₂(NH₃)]. The volume was reduced to one-third, stored at -18 °C for 2 days, whereupon some greenish-grey precipitate was deposited. The solution was filtered and the filtrate allowed to stand for 5 weeks. A small quantity of yellow plates (28 mg) formed, and one was characterised as 5 by a single-crystal X-ray diffraction study. The crystals appear to lose solvent when air dried. Found: C, 46.7; H, 3.5; N, 1.3. C₅₀H₄₁NO₄-P₂Pt₂S₂·1.5MeOH requires C, 48.1; H, 3.6; N, 1.1%. Mp decomp. >250 °C with gas evolution.

Crystallography

Crystal data, collection and refinement details are summarised in Table 7. Non-routine features are as follows.

Structure determination of [Pt(SC₆H₄CO₂)(PPh₃)(py)]·H₂O $4a \cdot H_2O$. Data were collected to 56° but the higher angle data were very weak because of the small crystal size, so only the data below 48° were used in the refinement. Refinement was complicated by disorder of the pyridine ring, which was modelled as two half-occupied sites with isotropic thermal parameters. Both disordered components were co-planar, one displaced upwards and one downwards with respect to the platinum coordination plane. There was also concomitant disorder of the carboxylate part of the thiosalicylate ligand, but this was less pronounced so was absorbed into the anisotropy of the atoms in this region. A penultimate difference map revealed a double peak assigned as a disordered water of crystallisation H-bonded to the free O(2) of the thiosalicylate ligand. Hydrogen atoms were included in their calculated positions only for the phenyl and thiosalicylate rings.

Structure determination of $[Pt(SC_6H_4CO_2)(PPh_3)(XyNC)]$ · Me₂CO 7·Me₂CO. The complex was prepared as a mixture of *cis/trans* isomers (7 is the major isomer) by the literature

Table 7 Crystal and refinement data for [Pt(SC₆H₄CO₂)(PPh₃)(py)]·H₂O 4a·H₂O, [Pt(SC₆H₄CO₂)(PPh₃)(XyNC)]·Me₂CO 7·Me₂CO, and [Pt₂(SC₆H₄CO₂)₂(PPh₃)₂(NH₃)]·1.5MeOH **5**·1.5MeOH

	4a ∙H ₂ O	7∙Me₂CO	5 •1.5H ₂ O
Empirical formula Formula weight Crystal system Space group <i>a</i> /Å <i>b</i> /Å <i>c</i> /Å <i>a</i> /° β/° γ/° Volume/Å ³ <i>T/</i> K <i>Z</i> Absorption coefficient/mm ⁻¹ Reflections collected	4a •H ₂ O C ₃₀ H ₂₄ NO ₂ PPtS•H ₂ O 706.64 Monoclinic <i>C2/c</i> 18.7231(10) 17.3019(10) 17.6543(10) 90 103.360(10) 90 5564.25(5) 203(2) 8 5.208 27133	7•Me ₂ CO C ₃₄ H ₂₈ NO ₂ PPtS•C ₂ H ₆ CO 798.77 Triclinic <i>P</i> Ī 10.5158(10) 15.1613(2) 21.4698(2) 73.346(10) 85.576(10) 87.630(10) 3268.98(6) 203(2) 4 4.442 27558	$ \begin{array}{c} \textbf{5.1.5H}_2\textbf{O} \\ \hline \textbf{C}_{50}\textbf{H}_{41}\textbf{NO}_4\textbf{P}_2\textbf{P}_2\textbf{S}_2\textbf{\cdot}\textbf{1.5CH}_3\textbf{OH} \\ 1284.14 \\ \textbf{Monoclinic} \\ \textbf{C}_2/c \\ 31.5133(19) \\ 11.2727(6) \\ 26.8046(14) \\ 90 \\ 90.062(2) \\ 90 \\ 9522.1(9) \\ 203(2) \\ 8 \\ 6.075 \\ 25267 \\ \end{array} $
Independent reflections Final <i>R</i> indices $[I > 2\sigma(I)]$	$4377 [R_{(int)} = 0.045]$ $R_1 = 0.0703$ $R_1 = 0.0200 \text{ m} R_2 = 0.1410$	$12946 [R_{(int)} = 0.0228]$ $R_1 = 0.0244$ $R_2 = 0.0205 m R_2 = 0.0582$	9574 $[R_{(int)} = 0.0485]$ $R_1 = 0.0472$ $R_1 = 0.0551$ mB = 0.0065
Independent reflections Final <i>R</i> indices $[I > 2\sigma(I)]$ <i>R</i> indices (all data)	$4377 [R_{(int)} = 0.045]$ $R_1 = 0.0703$ $R_1 = 0.0999, wR_2 = 0.1410$	12946 $[R_{(int)} = 0.0228]$ $R_1 = 0.0244$ $R_1 = 0.0295$, w $R_2 = 0.0583$	9574 [$R_{(int)} = 0.0485$] $R_1 = 0.0472$ $R_1 = 0.0561$, w $R_2 = 0.0965$

procedure,² starting from [Pt(SC₆H₄CO₂)(PPh₃)₂] and XyNC. Recrystallisation from a mixture of chloroform, acetone and diethyl ether by slow evaporation at 4 °C gave very pale yellow tablets of the major isomer 7.

Structure determination of [Pt₂(SC₆H₄CO₂)₂(PPh₃)₂-(NH₃)]·1.5MeOH 5·1.5MeOH. Penultimate difference maps showed two solvent (methanol) regions, one ordered, and one disordered and lying on a two-fold axis, giving 1.5 MeOH overall. All non-hydrogen atoms were assigned anisotropic thermal parameters except for those of the disordered methanol. The H atoms associated with the solvent molecules were not included. CCDC reference number 186/2072.

See http://www.rsc.org/suppdata/dt/b0/b003619f/ for crystallographic files in .cif format.

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