Chemical and Biological Studies of Dichloro(2-((dimethylamino)methyl)phenyl)gold(III)

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Several new organogold(III) derivatives of the type $[AuX_2(damp)]$ (damp = *o*-$C_6H_4CH_2NMe_2$) have been prepared [X = CN, SCN, dtc, or X_2 = tm; dtc = R_2NCS_2 (R = Me (dmtc) or Et (detc)); tm = $SCH(CO_2)CH_2CO_2Na$] together with [AuCl(tpca)(damp)]Cl (tpca = *o*-$Ph_2PC_6H_4CO_2H$), [Au(dtc)(damp)]Y (Y = Cl, BPh_4) and K[Au-$(CN)_3$(damp)]. The ^{13}C NMR spectra of these and previous derivatives have been fully assigned. In $[Au(dtc)_2$-(damp)] and K[$Au(CN)_3$(damp)], the damp ligand is coordinated only through carbon, as shown by X-ray crystallography and/or NMR. $[Au(detc)_2(damp)]$ has space group *C*2/*c*, with *a* = 29.884(4) Å, *b* = 13.446(2) Å, *c* = 12.401(2) Å, β = 99.45(3)°, *V* = 4915 Å^3, *Z* = 8, and *R* = 0.057 for 1918 reflections. The damp and one detc ligand are monodentate, the other detc is bidentate; in solution, the complex shows dynamic behavior, with the detc ligands appearing equivalent. The crystal structure of [Au(dmtc)(damp)]BPh_4 [*Pna*2$_1$, *a* = 26.149(5) Å, *b* = 11.250(2) Å, *c* = 11.921(2) Å, *V* = 3507 Å^3, *Z* = 4, *R* = 0.073, 1772 reflections] shows both ligands to be bidentate in the cation, but the two Au−S distances are nonequivalent. The crystal structure of [Au(tm)(damp)] has also been determined [*P*2$_1$/*n*, *a* = 18.267(7) Å, *b* = 9.618(3) Å, *c* = 18.938(4) Å, β = 113.45(3)°, *V* = 3053 Å^3, *Z* = 8, *R* = 0.079, 1389 reflections]. The tm is bound through sulfur and the carboxyl group which allows five-membered ring formation. In all three structures, the *trans*-influence of the σ-bonded aryl group is apparent. $[AuCl_2(damp)]$ has been tested *in vitro* against a range of microbial strains and several human tumor lines, where it displays differential cytotoxicity similar to that of cisplatin. Against the ZR-75-1 human tumor xenograft, both $[AuCl_2(damp)]$ and cisplatin showed limited activity.

Introduction

Gold(III) is isoelectronic with platinum(II), and the complexes of both metals normally adopt a square-planar configuration. These similarities open the possibility that gold(III) complexes might have biological activity parallel to cisplatin and its homologues. Although $[AuCl_4]^-$ is widely thought to be toxic, it was used in the treatment of syphilis and alcoholism,[1] and dimethylgold(III) derivatives showed some degree of antitumor activity.[2] There have been many later studies in which gold compounds have been tested for antitumor properties, although most have involved gold(I); these studies have been reviewed recently.[3,4]

To maintain the formal resemblance to cisplatin we have chosen complexes having a single mononegative bidentate ligand together with two monodentate anionic ligands; substitution reactions with a variety of other potentially bidentate ligands of various charges have also been carried out. Previously we described complexes $[AuX_2(L-L')]$, in which L−L′ was pyridine-2-carboxylate or an analogue.[5] Unfortunately, in biological media these complexes underwent reduction to metalic gold; the implied oxidation of biological material might suggest that these materials would be toxic. We reasoned that reduction of the oxidation potential of gold(III) could be achieved by the use of softer ligands, and we now have a large range of complexes containing N−C$^-$ ligands, involving a σ-bonded phenyl, naphthyl, or similar group with various nitrogen-containing substituents. These materials are indeed more stable in reducing, biological media.

In this paper we concentrate on derivatives of the 2-((dimethylamino)methyl)phenyl ligand (−$C_6H_4CH_2NMe_2$ = damp), which forms orthometalated C,N-complexes. Such complexes have been known for about 10 years,[6] but do not seem to have been examined for biological activity. We have reprepared known complexes of the type $[AuX_2(damp)]$ and further characterized them spectroscopically; we have also obtained some new materials, of which those where the ligands X are cyanide or a dithiocarbamate are of special structural interest because the amine group is detached from the coordination sphere of the gold. This has been observed previously only for two compounds, both of which contain two damp ligands: $[AuX(damp)_2]$ (X = Cl, CN).[7] In later papers we shall describe a range of complexes containing more novel N−C$^-$ ligands.[8]

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Table 1. Selected Bond Lengths (Å) and Angles (deg)[a]

[Au(dmtc)(damp)]BPh_4		[Au(detc)$_2$(damp)]		[Au(tm)(damp)][b]	
Au−C	2.03(2)	Au−C	2.04(2)	Au−C	2.16(5), 2.04(5)
Au−N	2.23(2)	Au−S[c]	2.325(5)	Au−S	2.23(2), 2.23(2)
Au−S[d]	2.340(9)	Au−S[c,d]	2.391(5)	Au−O[d]	2.09(3), 2.12(3)
Au−S[d]	2.179(9)	Au−S	2.311(5)	Au−N	1.85(5), 2.00(5)
C−Au−S	100.0(6)	C−Au−S	95.2(3)	C−Au−S	99(2), 98(1)
S−Au−S[c]	78.6(3)	S−Au−S	74.7(2)	S−Au−O	85(1), 84(1)
S−Au−N	97.7(6)	S−Au−S	98.8(2)	O−Au−N	95(2), 97(2)
N−Au−C	81.5(8)	S−Au−C	91.3(5)	N−Au−C	80(2), 98(1)
C−Au−S	171.3(6)	C−Au−S	169.9(5)	C−Au−O	172(2), 178(1)
N−Au−S	177.6(6)	S−Au−S	173.3(2)	S−Au−N	174(2), 177(2)
S−C−S	111(2)[c]	S−C−S	120(2),[c] 127(1)[f]		

[a] Data are listed clockwise from the Au−C bond (see Figures 1, 3, and 4). [b] Two independent molecules. [c] For bidentate dtc. [d] *Trans* to C. [e] *Trans* to N. [f] For monodentate dtc.

We have also carried out a range of biological tests to evaluate [$AuCl_2$(damp)] for antimicrobial and antitumor activity. Included in these tests, as comparisons, are cisplatin and also [$AuCl_2$(ppy)] (ppy = 2-pyridylphenyl); the latter is a gold(III) complex with similar structural features.[9]

Experimental Section

The complex [$AuCl_2$(damp)] was prepared as previously described[6a] by reaction of [HgCl(damp)] and Me_4N[$AuCl_4$]. The derivatives [AuX_2(damp)] (X = Br, I, CN) were prepared by metathesis, again by literature methods.[6a] Analogous procedures were used to make complexes with X = SCN (from KSCN), dmtc, or detc (from NaS_2CNR_2, R = Me, Et) or with X_2 = mercaptosuccinate (from the corresponding silver salt). The complex [AuCl(tpca)(damp)]Cl (tpca = $Ph_2PC_6H_4CO_2H$) was prepared analogously to the corresponding PPh_3 complex.[6a] The complex [$AuCl_2$(ppy)] was prepared according to the literature method.[9] Analytical data for all materials prepared are given in the Supporting Information.

(Mercaptosuccinato)[2-((dimethylamino)methyl)phenyl]gold(III). Silver mercaptosuccinate (0.35 g, 1.0 mmol) was added in one portion to a solution of [$AuCl_2$(damp)] (0.20 g, 0.50 mmol) in acetone (30 cm^3). The mixture was stirred in the dark for 1 h, evaporated to dryness, and extracted with dichloromethane. Addition of hexane (30 cm^3) to the extract and refrigeration afforded small yellow cubes of the complex after 24 h; crystallization continued for 7 d affording a total of 0.17 g, 70%).

Potassium Tricyano[2-((dimethylamino)methyl)phenyl]aurate(III). The complex [$AuCl_2$(damp)] (0.20 g, 0.5 mmol) was dissolved in acetone (30 cm^3), and potassium cyanide (0.19 g, 3.0 mmol) was added. This suspension was stirred for 6 h and filtered. Removal of solvent gave an oil which solidified *in vacuo* after 30 min at 35 °C. The solid was washed with hexane. Yield: 0.078 g, 35%. The product was found to be highly soluble in water.

NMR measurements were made on Brucker AC250 (^{1}H, ^{13}C) and AC200 (^{31}P) spectrometers, the latter using 85% H_3PO_4 as reference. Concentrations were 0.05−0.2 mol dm^{-3}. ^{13}C spectra were measured at a flip angle of 28.2° and data point resolution of 0.137 Hz. ^{13}C DEPT90° spectra gave a negative signal for the *C*H_2 group and positive signals for *C*H and *C*H_3 groups; quaternary carbon atoms did not respond. For the ^{13}C−^{1}H shift-correlation (COSY) spectra the following pulse sequence was used:

^{1}H: D0−90−D0 D0−D3−90 BB

^{13}C: D1 180 90−D4 FID

This allowed the ^{1}H signals to be paired with the appropriate carbon signals. In ^{1}H decoupling experiments, each of the aromatic-proton doublets was irradiated in turn, allowing identification of pairs of adjacent protons. Finally, irradiation at the CH_2 frequency gave a strong NOE on the signal at δ 7.15 and a weak, negative effect at δ 7.75; the former signal was therefore attributed to H_3.

Crystallographic Studies. All measurements were performed at room temperature using graphite monochromated Mo Kα radiation (λ = 0.710 69 Å).

[Au(dmtc)(damp)]BPh_4 was examined using a Rigaken AFC6S diffractometer, and [Au(detc)$_2$(damp)] and [Au(tm)(damp)] with an Enraf-Nonius CAD-4. ω scans were used on the first two samples while [Au(detc)$_2$(damp)] was scanned by the $\omega/2\theta$ technique.

Crystal data and experimental details are given in the Supporting Information. The structures were solved by Patterson methods and refined by full-matrix least-squares using the TEXSAN suite of programs.[10] The gold, sulfur, and some terminal carbon atoms were subjected to anisotropic refinement in [Au(detc)$_2$(damp)], while only the gold and sulfur atoms were refined anisotropically in [Au(dmtc)(damp)]BPh_4 and [Au(tm)(damp)]. Hydrogen atoms were placed in chemically reasonable positions in all three cases, except for the carboxylic acid proton in [Au(tm)(damp)], which was ignored. Additionally, the phenyl ring in [Au(dmtc)(damp)]BPh_4 was constrained to be a regular hexagon of side 1.40 Å. The aromatic rings in the other compounds were accurately planar (maximum deviation from the least-squares plane: 0.03(2) and 0.14(8) Å for the detc and tm derivatives respectively).

The default TEXSAN weighting scheme of $1/\sigma 6(F_o)$ was used for all three studies.

Selected bond lengths and angles are given in Table 1; final atomic coordinates are deposited as Supporting Information and additional material is available from the Cambridge Crystallographic Data Center (atomic coordinates, thermal parameters, and the remaining bond distances and angles).

Pharmacological Studies. Microbial Strains. *In vitro* antimicrobial activity was assessed using a panel of bacteria and fungi representing microorganisms of clinical importance. The bacterial strains used were *Staphylococcus aureus* NCTC 6571, *Enterococcus faecalis* NCTC 8727, *Klebsiella pneumoniae* NCTC 9633, *Escherichia coli* NCTC 10418, and *Pseudomonas aeruginosa* NCTC 10662. The fungi consisted of *Candida albicans* NCFC 3153, *Cryptococcus neoformans* NCFC 3003, *Aspergillus fumigatus* NCFC 2140, and a strain each of *Candida albicans* and *Aspergillus niger* which were obtained from the University of Surrey.

Cell Lines. The CHO fibroblast[11] and the human tumor cell lines SW403, SW620, and SW1116 colon carcinoma,[12] HT29/219 colorectal carcinoma,[13] ZR-75-1 breast carcinoma,[14] HT1376 bladder carcinoma,[15] and the SK-OV-3 ovarian carcinoma[16] were obtained from the ECACC.

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Antimicrobial Testing. Minimum inhibitory concentration (MIC) values for each test organism were determined using the plate dilution technique[17] to assess the antimicrobial activity of [$AuCl_2$(damp)] and [$AuCl_2$(ppy)]. Iso-sensitest agar and 2% purified agar (Unipath Ltd.) supplemented with 10% yeast nitrogen base[18] were used for the bacterial and fungal MIC determinations respectively. An inoculum of 10^6 organisms mL^{-1} was applied with a multipoint inoculating device, and the plates were examined for microbial growth after incubation for either 18 h at 37 °C (bacteria) or 48 h at 30 °C (fungi). Ciprofloxacin and amphotericin B were included as controls.

Mammalian-Cell Toxicity. Comparative cytotoxicity against mammalian cells was assessed using the Chinese Hamster Ovary (CHO) fibroblast cell line.[19] The cells were seeded onto 96−well microtitre plates at a concentration of 5×10^4 cells mL^{-1}, in 200 μL of medium. After a 24−h preincubation period, the cells were treated with test compound for 2 h at concentrations of 0.1, 1.0, 10.0, and 100 μg mL^{-1}. The solution of the compound was then replaced with fresh medium and the cells were incubated for a further 48 h. Cell growth was assayed using sulforhodamine B as previously described.[20] Cell survival (%) was calculated relative to untreated control cells.

Primary *in vitro* Tumor Screen. Primary screening for antitumor activity was conducted against an *in vitro* panel of seven human tumor lines.[21] The cells were seeded onto 96-well microtitre plates at concentrations of 5×10^4 to 1×10^5 cells mL^{-1}. After a 24-hour pre-incubation period, the cells were treated with test compound for 2 h at concentrations of 0−200 μg mL^{-1}. The compound was then replaced with fresh medium and the cells were incubated for a further 72 h. Cell growth was assayed using sulforhodamine B. Cell survival (%) was calculated relative to untreated control cells. Dose/survival curves were constructed from these data, and the IC_{50} (concentration of compound giving 50% survival) was calculated.

Xenograft Study. The ZR-75-1 tumor was implanted subcutaneously in the flanks of nude mice. The tumor-bearing animals were then randomized into treatment groups of six mice and a control group of ten mice. Test compounds were administered intraperitoneally in 0.5% carboxymethylcellulose in 0.9% saline. For the experiment using [$AuCl_2$(damp)] the doses were given on days 0, 7, 14, and 21, and tumor dimensions were taken and animals weighed on days 0, 7, 14, 21, and 28. Cisplatin was also evaluated in this model using a similar procedure but with slight differences in the dosing/tumor measurement intervals, as indicated in Table 8. The tumor volume was calculated from the tumor dimensions using the formula: length × width × depth × $\pi/6$. Results are expressed as relative tumor volumes (RTV) where RTV = 100(mean volume of tumors at assessment time)/(mean volume of tumors at the start of the experiment). Results were analyzed using Student's *t* test.

The xenograft study was carried out in the Cancer Research Campaign Laboratories at the Charing Cross Hospital, London.

Results

Several complexes of the types [AuX_2(damp)] and [Au(X−X)(damp)] (X, X−X = mono- and bidentate mononegative ligands) have been obtained by procedures analogous to those reported previously,[6] of which those with X = CN, SCN, dmtc, and detc, [AuCl(tpca)(damp)]Cl (tpca = *o*-$Ph_2PC_6H_4CO_2H$); [Au(X−X)(damp)]Y (X−X = dmtc, detc, tm; Y = Cl, BPh_4), and K[Au(CN)$_3$(damp)] are new. Analytical, infrared, and conductivity data are entirely consistent with the expected formulations (Supporting Information).

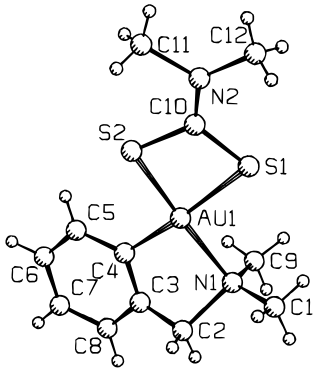

Figure 1. Structure of the cation in [Au(dmtc)(damp)]BPh_4. Bond lengths and angles are given in Table 1 and Figure 2.

The complex [AuCl(tpca)(damp)]Cl seems to be completely similar to its PPh_3 analogue,[6a] but its conductivity is low (31.2 S mol^{-1} at 10^{-3} mol dm^{-3} in $MeNO_2$); the most probable explanation for this is association between the uncoordinated carboxylic acid group and the chloride ion: $-CO_2H\cdots Cl-$. A less likely possibility is coordination of the second chloride with displacement and protonation of the amine group to form a zwitterionic complex; given the general reluctance of the amine group to be displaced, this seems unlikely. In both phosphine complexes, IR data indicate, as previously deduced,[6a] that the phosphine is *trans* to the nitrogen of damp [ν(Au-Cl) 315 and 305 cm^{-1} for PPh_3 and tpca, respectively].

The complex K[Au(CN)$_3$(damp)] is difficult to prepare reproducibly. It is a 1:1 electrolyte in acetonitrile (156 S mol^{-1} at 10^{-3} mol dm^{-3}), and NMR data (see below) indicate that the gold atom is four-coordinate and that the damp−amine group is not coordinated.

Unexpectedly, a similar detachment of the amine group occurs in [Au(detc)$_2$(damp)], as shown by X-ray crystallography (see below). In gold−damp complexes, this mode of bonding has only been previously observed in the bis(damp) compounds [$AuX(damp)_2$] (X = Cl, CN).[7] The NMR spectra show that this compound is fluxional in solution, with the damp ligands being alternately mono- and bidentate.

Crystallographic Studies

[Au(dmtc)(damp)]BPh_4. The mono(dmtc) cation has the expected structure in which gold(III) is square-planar coordinated to two chelated ligands (Figure 1 shows the cation, and Figure 2a gives a schematic of the important bond lengths and angles). The two Au−S bond lengths are appreciably different, with that *trans* to C being the longer as expected on *trans*-influence grounds. This asymmetry extends to the C−S bonds of the dmtc ligand, the longer bond being to the sulfur *trans* to N. The structure therefore approximates to that of a chelated $Me_2NC(=S)S^-$ ligand, in which the "anionic" sulfur atom is coordinated *trans* to N.

The Au-C and Au-N bond lengths are similar to, but slightly longer than, those reported for [AuCl(R)(damp)] (R = C_6H_5, C_6F_5)[22] and [Au(X−Y)(damp)] (X−Y = oxin, $H_2NC_6H_4S$).[23]

[Au(detc)$_2$(damp)]. The dimensions and structure of the bis(detc) derivative is shown in Figures 2 and 3. The gold atom appears to be approximately octahedrally coordinated: the damp-C atom, one detc-S atom of one detc and two of the other

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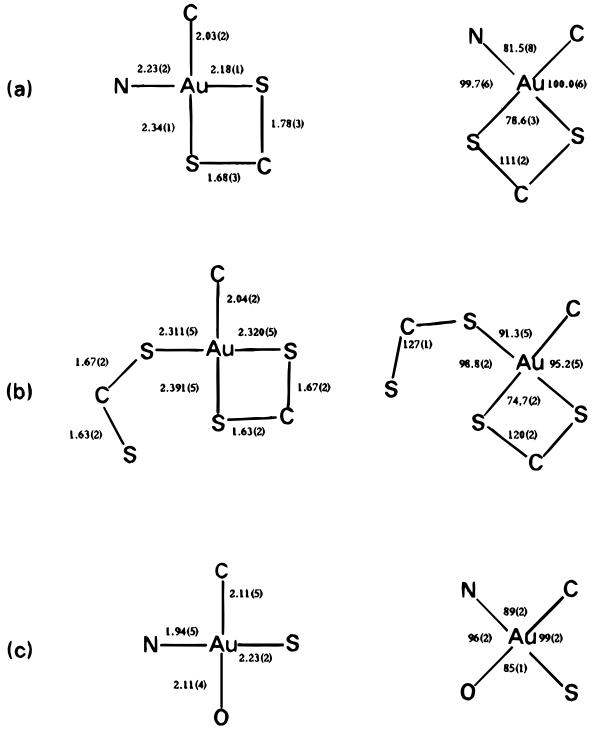

Figure 2. Schematic of principal bond lengths and bond angles for (a) [Au(dmtc)(damp)]BPh_4, (b) [Au(detc)$_2$(damp)], (c) [Au(tm)(damp)] (average of two independent molecules).

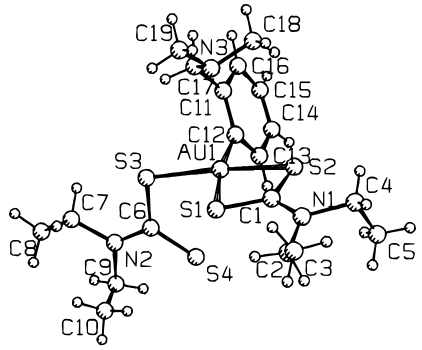

Figure 3. Molecular structure of [Au(detc)$_2$(damp)].

define a conventional square plane. The damp-N atom and the second S atom of one detc group lie above and below the $AuCS_3$ square plane (the Au−S and Au−N vectors form angles of 63.1° and 71.2° with the plane, and S−Au−N = 151.9(4)°). However, these bonds are considerably elongated: Au−N = 3.01(2) Å and Au−S = 3.196 Å. While the damp and detc ligands are not constrained to have these atoms in these positions, the interactions with gold must be very weak. The damp ligand and one detc must therefore be considered to be essentially monodentate. The other detc is bidentate and more symmetrical than that in [Au(dmtc)(damp)]BPh_4. The three Au−S bond distances are comparable to those in other gold(III) chelated-dithiocarbamate derivatives.[24] The adoption of this configuration, rather than that with two monodentate detc groups, is presumably driven by the relatively soft nature of gold(III), which favors coordination of sulfur rather than nitrogen, and

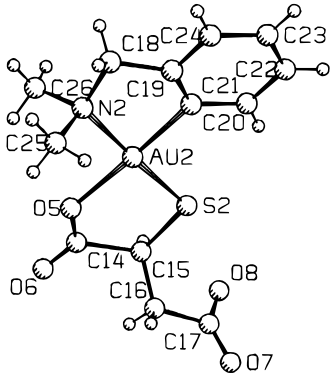

Figure 4. Molecular structure of [Au(tm)(damp)].

by the inability to have three bidentate ligands present without increasing the coordination number of the metal atom above four. The gold atom is only 0.0153 Å out of the coordination plane.

One other example of mixed coordination for dtc ligands in a gold(III) complex is known: [Au(detc)$_3$].[24e] In this case, one detc ligand is symmetrical and bidentate (Au−S = 2.333 Å), the other two are monodentate (Au−S = 2.350 Å).

[Au(tm)(damp)]. In this compound the point of interest is the coordination of the thiomalate ligand (Figure 4). The soft nature of gold(III) dictates choice of the thiolate group as one donor; it is, as expected on *trans*-influence grounds, *trans* to N. The carboxylate group bound to the carbon atom α to the thiol group also coordinates, giving a five-membered chelate ring; coordination of the other carboxylate would give a six-membered ring. The Au−S bond distance, 2.23(2) Å, is slightly shorter than for the dithiocarbamates, mainly due to the fact that it is *trans* to the nitrogen donor. In the related 2-aminobenzenethiolate derivative, the Au−S bond is 2.267 Å (*trans* to nitrogen).[23] [Au(tm)(damp)] appears to be the first example of a structure in which a gold atom is bonded to four different donor atoms.

The [Au(tm)(damp)] molecules are linked in strands by hydrogen bonding between the free carboxylate group and the carbonyl oxygen atom of the coordinated carboxyl group.

Spectroscopic Studies. Detailed $^1H/^{13}C$, COSY, selective decoupling, and NOE studies were made of [$AuCl_2$(damp)], in both DMSO-d_6 and $(CD_3)_2CO$, in order to determine fully the assignments for each proton and carbon atom. Eventually, the only ambiguity remaining was for C_1 and C_2, the two carbon atoms not bound to hydrogen. It was then assumed that the the atom bound to the gold atom would have the higher chemical shift. This assignment is supported by the data for [HgCl(damp)] given below, where C_1 can be unambiguously identified by its coupling to the mercury atom, and by data for a range of other aryl mercury(II) and gold(III) derivatives.[8,25−27] The final assignments are summarized diagrammatically in Figure 5. These results slightly amend those reported previously.[6] It was then assumed that the order of chemical shifts was the same for each derivative, and all the available data are summarized in Table 2.

For the damp ligand, substantial solvent shifts are observed. However, comparing data for the same solvent, large positive coordination chemical shifts are seen for C_1, as expected. Although only a limited range of data is available, the chemical

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Table 2. ^{13}C Chemical Shifts in Gold(III)−Damp Complexes

compound	solvent	C_1	C_2	C_3	C_4	C_5	C_6	CH_2	CH_3
$[AuCl_2(damp)]$	$CDCl_3$	148.2	143.9	123.5	129.2	128.2	131.3	76.0	54.0
$[AuCl_2(damp)]$	$(CD_3)_2CO$	148.9	146.9	124.2	129.4	127.8	131.1	76.0	53.9
$[AuBr_2(damp)]$	CD_2Cl_2	151.1	145.6	128.5	132.8	128.7	133.6	76.3	54.4
$[Au(CN)_2(damp)]$[a]	$(CD_3)_2SO$	152.9	151.3	127.7	132.6	131.4	139.1	78.2	57.5
$[Au(detc)(damp)]Cl$[b]	$CDCl_3$	149.1	147.3	125.1	128.1	127.8	129.1	74.0	53.4
$[Au(detc)(damp)]BPh_4$[c]	$(CD_3)_2SO$	152.8	152.2	128.7	132.0	131.7	132.9	77.1	56.6
$[Au(dmtc)(damp)]BPh_4$[d]	$(CD_3)_2SO$	153.1	152.4	129.2	133.1	131.9	131.9	77.7	56.9
$[AuCl(PPh_3)(damp)]Cl$[e]	$CDCl_3$	149.2	146.9	132.6	136.1	133.4	136.2	73.6	51.6
$[Au(tm)(damp)]$[f]	$CDCl_3$	145.0	135.0	124.1	128.7	128.4	131.1	71.6	51.3
$[Au(detc)_2(damp)]$[g]	$CDCl_3$	144.5	140.9	125.9	129.2	127.8	133.3	66.4	45.4
$K[Au(CN)_3(damp)]$[h]	$(CD_3)_2SO$	146.9	136.5	129.4	132.6	131.1	139.7	70.1	48.6
Hdamp[i]	$CDCl_3$	128.4	138.5	128.4	127.7	126.4	127.5	64.0	45.0
Hdamp[i,j]	$CDCl_3$	128.4	138.5	128.4	127.5	126.4	127.5	63.9	44.7

[a] CN signals: 144.2, 109.8. [b] detc signals: 195.5 (SS*C*N); 48.4, 47.1 (N*C*H_2CH_3); 12.7, 12.4 (NCH_2*C*H_3). [c] detc signals: 197.8 (SS*C*N); 52.2, 50.8 (N*C*H_2CH_3); 16.5, 16.2 (NCH_2*C*H_3). [d] dmtc signals: 196.9 (SS*C*N); 46.1, 44.8 (N*C*H_3). [e] PPh_3 signals at 129.6, 129.4, 128.3, 127.2, 125.7, 125.0. [f] tm signals: 183.0, 172.0 (*C* = O); 103.0 (*C*-S); 51.3 (*C*H_2). [g] detc signals: 200.5 (SS*C*N); 46.9 (N*C*H_2CH_3); 12.3 (NCH_2*C*H_3). [h] Solution containing $[Au(CN)_2(damp)$ + 2KCN; CN signals: 129.7, 118.0. [i] Numbering corresponds to that for the gold complexes. [j] From ref 26.

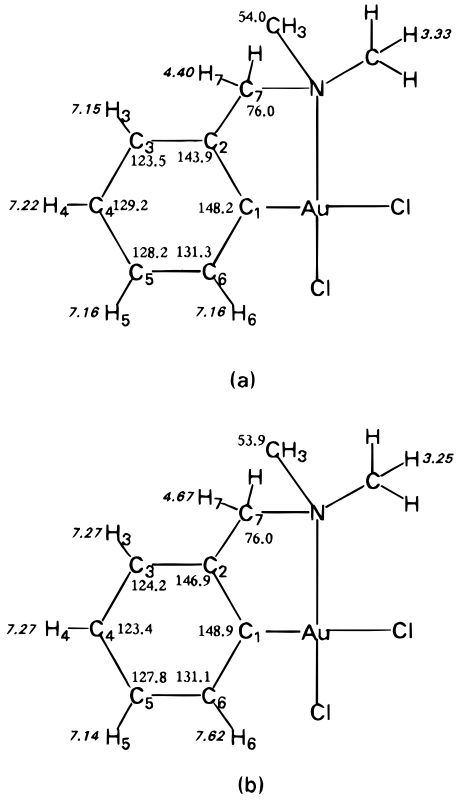


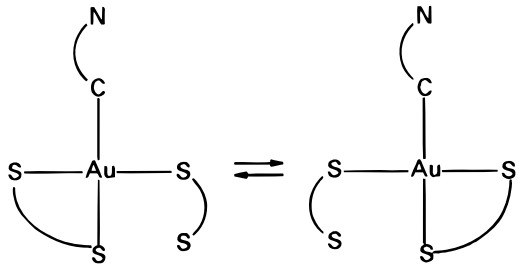
Figure 5. NMR chemical shift data for $[AuCl_2(damp)]$ in (a) $CDCl_3$ and (b) $(CD_3)_2CO$. Shifts for ^{1}H are given in italics.

shift appears to decrease as the *trans*-influence of the ligand opposite increases. Significant coordination shifts are seen for the adjacent carbon atoms, C_2 and C_6, also positive. The signals for the CH_2 and CH_3 carbon atoms show substantial positive coordination shifts in cases where the ligand is known to chelate. In other cases, these shifts are close to those of the free ligand. This a useful diagnostic criterion of chelation.

In $[Au(dtc)(damp)]^+$ (dtc = dmtc, detc), in which both ligands are chelated, the signals for the two alkyl groups of the dtc ligands are nonequivalent, reflecting the absence of a plane of symmetry between them. [^{1}H data, dtc = detc: $\delta(CH_2)$ 3.96, 3.89; $\delta(CH_3)$ 1.54, 1.50 for the chloride in $CDCl_3$; $\delta(CH_2)$ 4.81, 4.77; $\delta(CH_3)$ 1.29, 1.26 for the BPh_4 salt in DMSO-d_6.]

For the bis(dithiocarbamate) compound $[Au(detc)_2(damp)]$, the chemical shifts of the methylene and methyl groups of the damp ligand confirm that the amine group is not coordinated in solution. The shifts are quite different from those of the chelated damp complexes, but similar to those for free *N*,*N*-dimethylbenzylamine (Table 2). There is also a small shift to lower frequency for C_2. Only a single set of signals is seen for the dtc groups [^{1}H: $\delta(CH_2)$ 3.78, $\delta(CH_3)$ 1.15], even though the X-ray data show one to be bidentate and the other monodentate. The apparent equivalence is best explained by fluxionality, the two dtc ligands being alternately mono- and bidentate. This switching of coordination is fast on the NMR timescale, and it is presumably the sulfur atom *trans* to the C-bonded damp ligand which is labile (Scheme 1).

Scheme 1



In an attempt to freeze the fluxionality, the spectrum of [Au(detc)(damp)] was remeasured at −40 °C. No additional signals were seen, but the ethyl group peaks diminished in relative intensity, suggesting that they were broadened.

The ^{13}C spectrum of $[Au(CN)_2(damp)]$ contains two signals additional to those for the damp ligand; their low intensity suggests that both are for carbon atoms not bonded to hydrogen, and this is confirmed by the DEPT spectrum. A unique signal at 109.8 ppm is close to that reported for $[Au(CN)_4]^-$ (105.2 ppm in D_2O),[28] and can confidently be assigned to a bound cyanide ligand. Of the three other quaternary carbon signals, two are assigned to C_1 and C_2 of the damp ligand by comparison with the dithiocarbamate complexes; the signal at 144.2 ppm must then correspond to the second cyanide ligand. It is significantly more shielded than the other, which suggests that it is *cis* to the aryl group. The fourth coordination position is occupied by the amine group, as shown by the *C*H_2 and *C*H_3 chemical shifts.

The spectrum of $K[Au(CN)_3(damp)]$ could not be obtained directly, owing to the difficulty of synthesis. However, on addition of 2 equiv of KCN to a DMSO-d_6 solution of $[Au(CN)_2(damp)]$, extra peaks are seen in the ^{13}C spectrum, indicating the presence of a second damp-containing species. In particular, the CH_2NMe_2 chemical shifts show that the amine

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Table 3. NMR Parameters for [HgCl(damp)] in $CDCl_3$[a]

	C_1	C_2	C_3	C_4	C_5	C_6	CH_2	CH_3
$\delta(^{13}C)$	149.2	144.0 (144.5)	127.5 (127.5)	128.8 (128.7)	129.1 (129.1)	137.3 (137.3)	64.7 (64.7)	44.6 (44.6)
$J(^{199}Hg)$/Hz	2471	51.6	... (212)	31	168 (178)	141.5	102 (101)	10.6 (11.0)

[a] Numbers in parentheses are from ref 26.

Table 4. Antibacterial MIC Values (μg/mL)

compound	*S. aureus*	*E. faecalis*	*K. pneumoniae*	*E. coli*	*P. aeruginosa*
$[AuCl_2(damp)]$	1.0−2.5	1.0−2.5	10−25	10−25	10−25
$[AuCl_2(ppy)]$	1.0−2.5	2.5−10	25−100	25−100	25−100
ciprofloxacin	<0.25	1.0−2.5	<0.25	<0.25	<0.25

Table 5. Antifungal MIC Values (μg mL^{-1})

compound	*C. albicans* NCFC 3153	*C. albicans*	*C. neoformans*	*A. niger*	*A. fumigatus*
$[AuCl_2(damp)]$	10−25	25−100	2.5−100	10−25	2.5−10
$[AuCl_2(ppy)]$	25−100	25−100	1.0−2.5	25−100	25−100
amphotericin B	<0.25	<0.25	<0.25	1.25−1.0	0.25−1.0

group is not coordinated, and the C_2 shift is lower even than that for $[Au(dtc)_2(damp)]$ (Table 2); both observations show that the damp ligand is monodentate. The signals for the coordinated cyanide ligands are distinct, but have shifted toward each other (129.7, 118.0 ppm). This is consistent with an increase in shielding by the aryl group, which is now free to rotate out of the coordination plane. These observations are consistent with the presence of $[Au(CN)_3(damp)]^-$. However, no signal is seen for a free CN^- ion (variously reported at 164.1−167.4 in D_2O),[25,29] and it is possible that rapid exchange is occurring with one of the coordinated groups. Such an exchange would be expected to result in a broadening of this peak, with consequent reduction in intensity, as is seen in reactions of $[Au(OAc)_2(damp)]$ with aqueous acetate solutions;[27] this would explain the similarity in the intensities of the two cyanide signals which would otherwise be expected to be in 2:1 ratio.

When a large excess of cyanide ion is added to solutions of $[Au(CN)_2(damp)]$ or $[Au(OAc)_2(damp)]$, very complex ^{13}C spectra are observed, suggesting extensive decomposition.

The ^{13}C spectrum of the intermediate [HgCl(damp)] was also re-examined (Table 3). It was possible to see couplings to ^{199}Hg (16.8%, $I = {}^1/_2$) which had not been reported previously:[24] in particular there is a large coupling to C_1 ($^1J = 2471$ Hz), which is within the range of similar reported ^1J values.[25,30] The very small coupling for the signal at δ 128.8 indicates that this must be C_4 ($^4J = 31$ Hz); this changes the previous assignment,[26] but the new assignment conforms to the order of coupling constants seen for bis(arylmercury(II)) derivatives:[25,30] $^1J \gg {}^3J > {}^6J > {}^4J$. ^{199}Hg-coupling was also observed to the carbon atoms and the protons of the methylene group and to the carbon of the methyl groups. The first of these is similar to the value of ^3J observed for the methyl groups in bis(*o*-tolylmercury(II)).[25] The chemical shifts of these groups are similar to those of compounds in which the damp ligand is monodentate, $[Au(dtc)_2(damp)]$ and $K[Au(CN)_3(damp)]$, and to those of the free ligand.

For the mercury complex, the values are presumably time averages for the chelated and nonchelated forms;[26] this in turn implies that the coupling to the CH_2 group passes via the phenyl ring.

Table 6. Comparative Cytotoxicity against CHO Cells (% Survival)

	cytotoxicity for concn c[a]			
compound	$c = 100$	$c = 10$	$c = 1.0$	$c = 0.1$
$[AuCl_2(damp)]$	2.2	69.6	84.3	91.3
$[PtCl_2(NH_3)_2]$	26.2	89.0	92.9	96.9
ciprofloxacin	90.0	101.2	99.9	96.7
amphotericin B	2.4	72.7	88.2	102.3

[a] c in μg mL^{-1}.

Pharmacological Tests. Antimicrobial Activity. The ability of the compounds to inhibit microbial growth was determined by measuring their minimum inhibitory concentration values (MIC). The MIC was taken as the range between the highest concentration of compound which allowed growth and the lowest which inhibited growth.[31] The results (Tables 4 and 5, for bacteria and fungi, respectively) show that both $[AuCl_2(damp)]$ and $[AuCl_2(ppy)]$ have moderate, broad-spectrum antimicrobial activity; there is slightly greater specificity against the Gram positive organisms *S. aureus* and *E. faecalis*. The complex $[AuCl_2(damp)]$ was a little more potent than $[AuCl_2(ppy)]$, but neither was as active as the controls, ciprofloxacin (a quinolone antibiotic) and amphotericin B (a polyene antifungal drug).

Mammalian-Cell Toxicity. The cytotoxicity of $[AuCl_2(damp)]$ was assessed against CHO cells to obtain an indication of its toxicity against a mammalian host[32] (Table 6). Cisplatin, ciprofloxacin and amphotericin B were included, as examples of a cytotoxic metal complex, an antibacterial agent, and an antifungal agent respectively. The complex $[AuCl_2(damp)]$ has a similar cytotoxicity to cisplatin and is more cytotoxic than either ciprofloxacin or amphotericin B, with cytotoxic concentrations similar to the MIC values.

Primary *in Vitro* Antitumor Screen. The ability of the compounds to inhibit tumor-cell growth was assessed against a human tumor cell-line panel. This showed that $[AuCl_2(damp)]$ has a profile of toxicity similar to that of cisplatin, in that both show greater toxicity (lower IC_{50} values) for the breast, bladder, and ovarian tumor cell lines than for the other lines (Table 7). Such differential cytotoxicity has been used as an indicator of

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Table 7. IC_{50} Values (μg mL^{-1}) for Various Tumor-Cell Lines

compound	SW620 (colon)	SW1116 (colon)	SW403 (colon)	ZR-75-1 (breast)	HT29/219 (rectum)	HT1376 (bladder)	SK-OV-3 (ovary)
[$AuCl_2$(damp)]	50	48	56	11	22	12	18
[$AuCl_2$(ppy)]	26	35	27	20	21	9	18
[$PtCl_2(NH_3)_2$]	120	135	200	15	30	15	14

Table 8. Evaluation of [$AuCl_2$(damp)] and Cisplatin in the ZR-75-1 Human Breast Tumor Xenograft Model

group	dose mg kg^{-1}	time days	group size	RTV[a] ± SE	T/C[b]
[$AuCl_2$(damp)]	25	7	6/6	190 ± 90	0.9
		14	6/6	530 ± 220	0.8
		21	4/6	560 ± 240	0.4
		28	2/6		
	12.5	7	6/6	160 ± 50	0.7
		14	6/6	300 ± 100	0.5
		21	6/6	730 ± 280	0.5
		28	6/6	1100 ± 370	0.4
	6.25	7	6/6	230 ± 70	1.1
		14	6/6	670 ± 180	1.1
		21	6/6	1260 ± 310	0.9
		28	6/6	1840 ± 490	0.6
controls		7	10/10	220 ± 40	
		14	9/10	630 ± 130	
		21	9/10	1370 ± 340	
		28	9/10	2930 ± 880	
[$PtCl_2(NH_3)_2$]	3	8	6/6	190 ± 50	0.7
		14	6/6	360 ± 80	0.7
		21	5/6	550 ± 180	0.8
		29	4/6	870 ± 330	0.7
	1.5	8	6/6	150 ± 40	0.5
		14	6/6	240 ± 40	0.5
		21	6/6	420 ± 80	0.6
		29	5/6	650 ± 200	0.6
controls		8	9/10	280 ± 60	
		14	9/10	490 ± 130	
		21	9/10	720 ± 180	
		29	9/10	1180 ± 310	

[a] RTV = relative tumor volume = 100(mean volume of tumors at assessment time)/(mean volume of tumors at start of experiment). [b] T/C = (RTV of treated group)/(RTV of control group).

antitumor activity,[21] and the results obtained suggested that [$AuCl_2$(damp)] might have potential as an antitumor agent. However, [$AuCl_2$(ppy)] has similar toxicity toward all the cell lines with the exception of HT1376 and was not investigated further.

Xenograft Study. The *in vitro* results showed that the ZR-75-1 tumor cell line was the most sensitive to [$AuCl_2$(damp)]. This compound was therefore evaluated against the solid ZR-75-1 tumor growing as a xenograft in nude mice. The gold compound was administered to tumor-bearing mice at its previously determined maximum tolerated dose, 25 mg kg^{-1} and at two 2-fold dilutions. As a comparison, a similar experiment was conducted with cisplatin. The tumor volumes were measured at regular intervals and are expressed as a percentage of the initial volume (RTV = relative tumor volume) in Table 8 and Figure 6.

At the two highest dose levels, the RTVs of the [$AuCl_2$(damp)]-dosed animals were lower than those of the untreated controls at all assessment times. However, there was evidence of toxicity at the highest dose, with only two animals surviving until day 28, both having lost weight over the time of the experiment. Some adhesion of the abdominal organs was also seen, which is probably a local effect associated with the intraperitoneal route of administration. This was particularly noticeable at the top dose. At a dose of 12.5 mg kg^{-1}, all of the animals survived until day 28. For this dose group the RTV ± SE ranges were outside those of the controls at 14, 21, and 28 days, and at 28 days the mean RTV was 40% of that of the control group (T/C = 0.4). However, at no single assessment time did the difference between the RTVs of the dosed and control groups reach the 5% level of significance. Thus, although the results indicate some antitumor activity for [$AuCl_2$(damp)], it must be considered as modest.

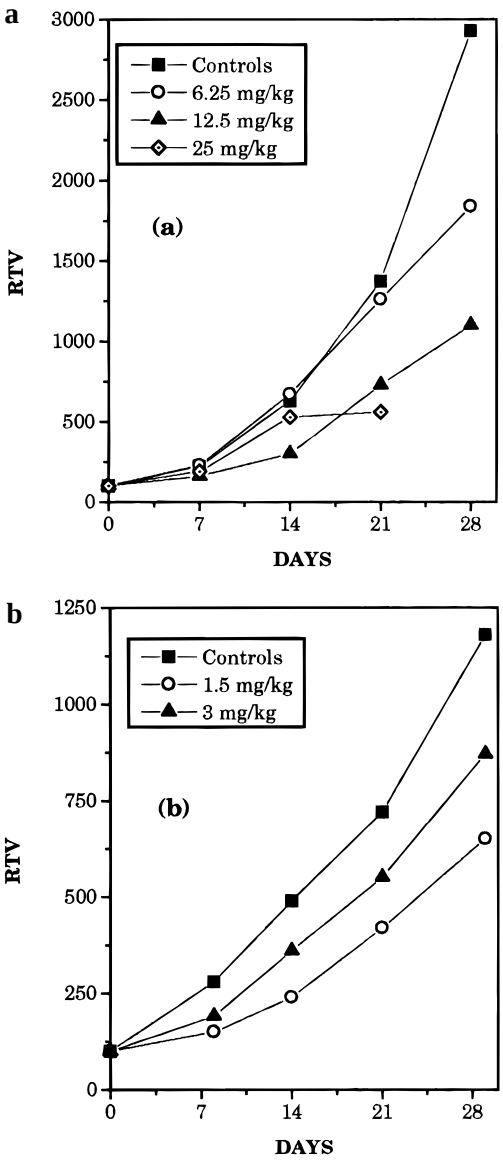

Figure 6. Growth of the ZR-75-1 breast tumor xenograft under treatment with (a) [$AuCl_2$(damp)] and (b) cisplatin. RTV = tumor volume as a percentage of the initial volume.

Cisplatin also exhibited only limited activity in this tumor model. At both dose levels the RTVs of the treated groups were below those of the controls at all times, and at 1.5 mg kg^{-1} the RTV ± SE ranges were outside those of the controls. However, at no time did the difference reach the 5% level of significance.

Discussion

Following the marked success of cisplatin and its analogues as antitumor agents, much effort has been expended in monitor-

ing other metal complexes. We considered that gold(III) complexes were worthy of attention, despite their possible greater reactivity.

Inorganic chemotherapeutic agents often act *via* substitution reactions. Thus cisplatin is hydrolyzed *in vivo* to *cis*-$[Pt(H_2O)_2(NH_3)_2]^{2+}$ and the aqua ligands can then be substituted by guanine or adenine bases of DNA.[33] The results reported above and earlier[6h] show that $[AuCl_2(damp)]$ has a rich and interesting substitution chemistry. The chloride ligands are directly replaced by softer ligands, such as the heavier halides, cyanide ion, and N- and S-donor ligands. It is therefore not surprising that this complex interacts strongly with biological systems.

Most of the substitution reactions are straightforward and involve simple replacement of chloride by another donor atom. In two cases, however, displacement of the amine donor group of the damp ligand is observed. This occurs with the two softest ligands used, cyanide ion and dithiocarbamate. For cyanide ion, the dechelation of damp is observed only when more than 2 molar equiv is used. This indicates only that the affinity of gold(III) is considerably greater for cyanide than for a simple amine, and that the difference is sufficient to outweigh the chelate effect.

The behavior with dithiocarbamates is the most interesting. A single dithiocarbamate ligand is able to displace both chlorides, and the di-chelated cation $[Au(dtc)(damp)]^+$ can be isolated with chloride as its counterion. Although chelation by dithiocarbamates is not rare, it is noteworthy that it involves a four-membered ring. The affinity of the gold(III) atom for the soft sulfur donor is sufficient to encourage formation of this tight ring. In $[Au(dtc)_2(damp)]$, the expected structure with two monodentate dtc ligands is not observed. Instead, one of the dtc ligands is bidentate, resulting in the displacement of the damp amine group. In solution, the two dtc ligands become equivalent by rapid mono- to bidentate switching, and there is no evidence for recoordination of the amine group.

When evaluated against selected microorganisms, the gold complexes demonstrated only modest activity compared to control drugs. Also, $[AuCl_2(damp)]$ displayed only marginal selectivity for the microorganisms over CHO cells. This suggests that it is not suitable as a potential antimicrobial chemotherapeutic agent. However, the broad-spectrum activity is compatible with antiseptic or biocide use.

The results from the xenograft model suggest that $[AuCl_2(damp)]$ and cisplatin have comparable activity against the ZR-75-1 tumor, although for both compounds the activity was not as marked as the *in vitro* results might have predicted. The low aqueous solubility of $[AuCl_2(damp)]$ might well have hindered its transport from the injection site to the tumor. This would have adversely affected its activity and might also have contributed to the abdominal adhesions observed.

It is also useful to consider the xenograft model. The ZR-75-1 tumor might be inherently insensitive to compounds of this type, bearing in mind the low activity found for cisplatin. Therefore another xenograft model could be more appropriate for preliminary testing.

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Supporting Information Available: Listings of analytical data, crystallographic data, atomic coordinates, *B*(eq) and *U* values, and intramolecular distances and angles (34 pages). Ordering information is given on any current masthead page.

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