Cytotoxicity and Antiviral Activity of Transition-metal Salicylato Complexes and Crystal Structure of Bis(diisopropylsalicylato)(1,10-phenanthroline)copper(II) †

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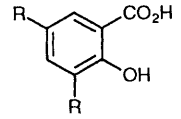
Complexes of Cu^{II}, Fe^{III}, Co^{II}, Ni^{II}, Ti^{IV} and Zn^{II} with 3,5-disubstituted salicylates, and ternary complexes of Cu^{II} containing substituted phenanthrolines have been prepared and characterised. The crystal structure of bis(diisopropylsalicylato)(1,10-phenanthroline)copper(II), [Cu(phen)(Hdips)$_2$], has been determined; Cu^{II} is in a tetragonal co-ordination environment with in-plane bonds to 2 nitrogens from phen [Cu–N 2.014(4) Å] and 2 oxygens from the carboxylates of Hdips [Cu–O 1.951(3) Å], with weaker off-axial bonds to carboxylate oxygens [Cu–O 2.557(3) Å]. The hydroxyl oxygen of Hdips is not co-ordinated. These complexes have been tested for antiviral and cytotoxic activity. Most are potently cytotoxic, especially [Cu(dmphen)(Hdips)$_2$], where dmphen is 2,9-dimethylphenanthroline.

Complexation with copper enhances the biological activity of a wide variety of organic ligands.[1,2] For example, the copper(II) complex of 2-acetyloxybenzoic acid (aspirin, Haoba), a ligand used as an analgesic since the last century, is reported to be significantly more active as an anti-inflammatory agent than the free ligand.[3] [Cu(aoba)$_2$] has also been shown to be orally effective in the treatment of rheumatoid arthritis in man.[4] Bis(salicylato)copper(II) is an analgesic and anti-inflammatory agent, being more effective in arthritic than non-arthritic rats, suggesting that two types of analgesia are involved.[5] The antibiotic bleomycin (blm) has been reported to have the following order for both antitumour activity and cytotoxicity: Cu^{II}(blm) > blm > Zn^{II}(blm) > Fe^{III}(blm) ≫ Co^{II}(blm) = non-treated control.[6] Bleomycin is isolated as its blue copper(II) complex and it is believed that the metal is essential for its biosynthesis. Also, copper(II) [and iron(III)] complexes of mono- and bis-thiosemicarbazones show markedly greater antitumour activity than the free ligands.[1,7] It has been shown that the activity of the ligand 3-ethoxy-2-oxobutyraldehyde bis(thiosemicarbazone) (H_2kts) is dependent on sequestration of copper(II) *in vivo* to form [Cu(kts)], the active species.[1,8] Thiosemicarbazones also exhibit antiviral activity, and one compound, methisazone, is in clinical use.[9] Metal activation again appears to be important. It has been proposed that the activity of thiosemicarbazones is due to the ability of their complexes to destroy the tyrosine radical in the enzyme ribonucleotide reductase.[10]

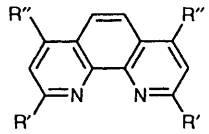
Recently there has been much intererest in the copper(II) complex of 3,5-diisopropylsalicylic acid (H_2dips)‡ [{Cu(Hdips)$_2$}$_2$] **1**, a lipophilic complex soluble in diethyl ether.[2,6,11,12] The complex exhibits anti-inflammatory, anti-neoplastic and radioprotective activities, but the modes of action are presently unknown and the chemistry of the complex is poorly understood. No crystal structures of 3,5-diisopropylsalicylato compounds appear to have been reported, and little work on complexes of other first-row transition metals has been carried out.[11]

Another series of ligands for which the biological activity is markedly influenced by metal complexation is that related to 1,10-phenanthroline.[7] Some of these ligands were shown to be bactericides nearly four decades ago, and they exhibit numerous biological activities, *e.g.* antifungal, antiviral and antimycoplasmal.[13] Antiviral activity was also studied[14] for a range of divalent metals with substituted phenanthrolines resulting in the following order of activity: Cd > Cu ≫ Zn ≫ Mn > Fe > Co > Ni > Ru. The trend in virostatic activity is similar to that for some antibacterial effects and antitumour activity.[15] The cytotoxicity of phenanthrolines is thought to depend on the chelation of trace amounts of transition metals such as copper and iron in test media, followed by transport of the metal complex into cells. In the presence of molecular oxygen and a reducing agent (*e.g.* thiol) the copper(I)–1,10-phenanthroline system has been shown to cleave DNA.[16]

In this work we have synthesised copper(II) complexes of 3,5-disubstituted salicylates and a range of first-row transition-metal complexes with H_2dips. We have also prepared ternary complexes of copper(II) with substituted phenanthrolines and salicylates (see diagram below for abbreviations and structures). One of these, [Cu(phen)(Hdips)$_2$] **4** has been studied by X-ray crystallography. The cytotoxicity and antiviral activities of a number of these complexes are also reported.



R	
Pr^i	H_2dips
Cl	H_2dcs
I	H_2dis
NO_2	H_2dns



R′	R″	
H	H	phen
Me	H	dmphen
H	Ph	dpphen

† *Supplementary data available:* see Instructions for Authors, *J. Chem. Soc., Dalton Trans.*, 1993, Issue 1, p. xxiii–xxviii.

Non-SI unit employed: $\mu_B \approx 9.274 \times 10^{-24}$ J T^{-1}.

‡ Abbreviations: H_2dips = 3,5-diisopropylsalicylic acid, H_2dis = 3,5-diiodosalicylic acid, H_2dns = 3,5-dinitrosalicylic acid, H_2dcs = 3,5-dichlorosalicylic acid, phen = 1,10-phenanthroline, dmphen = 2,9-dimethyl-1,10-phenanthroline, dpphen = 4,7-diphenyl-1,10-phenanthroline, dmso = dimethyl sulfoxide, dmf = dimethylformamide, dmap = *N*,*N*-dimethylaminopyridine, bipy = 2,2′-bipyridine, sod = superoxide dismutase.

Experimental

Materials.—All reagents were purchased from Aldrich and used as supplied.

Preparation of Complexes.—Binary complexes [{Cu(Hdips)$_2$}$_2$(H$_2$O)] **1**. The addition of a solution of H$_2$dips (2.22 g, 10.0 mmol) and NaOH (0.40 g, 10 mmol) in water (40 cm^3) to a solution of copper(II) acetate hydrate (1.00 g, 5.00 mmol) in water (10 cm^3) gave the product, [{Cu(Hdips)$_2$(H$_2$O)}$_2$], as previously described,[17] which was dried *in vacuo* for 24 h to give the monohydrate. This general procedure for preparing binary complexes of 3,5-disubstituted salicylates with divalent transition metals was used in all cases with yields in the range of 40–80%.

[{Cu(Hdips)$_2$(dmso)}$_2$] **2**. Dissolution of [{Cu(Hdips)$_2$}$_2$(H$_2$O)] (100 mg, 0.20 mmol) in hot dmso (10 cm^3) gave green crystals of the product after 1 month. Yield 51 mg (45%).

[Fe(Hdips)$_3$]·1.5H$_2$O **12**. To a filtered solution of H$_2$dips (0.67 g, 3.02 mmol) in hot water (17 cm^3) and 1 mol dm^{-3} NaOH (3 cm^3) was added Fe(NO$_3$)$_3$·9H$_2$O (0.40 g, 1.00 mmol) in water (10 cm^3). The resulting brown powder was filtered off and washed with water. Yield 438 mg (59%).

[Fe(Hdis)$_3$]·2.5H$_2$O **16** *and* [Fe(Hdcs)$_3$]·2H$_2$O **17**. The previous procedure was repeated using H$_2$dis (1.18 g, 3.03 mmol) in water (100 cm^3) and 1 mol dm^{-3} NaOH (3 cm^3) or H$_2$dcs (0.64 g, 3.08 mmol) in water (17 cm^3) and 1 mol dm^{-3} NaOH (3 cm^3). Yields: 438 mg (35%) and 451 mg (64%), respectively.

[Ti(Hdips)$_2$(dips)]·2H$_2$O **11**. Addition of a solution containing Ti$_2$(SO$_4$)$_3$ (1.25 cm^3, 15% w/v, 0.98 mmol) in water (9 cm^3) to a previously filtered solution of H$_2$dips (0.70 g, 3.15 mmol) and 1 mol dm^{-3} NaOH (3.15 cm^3) in hot water (25 cm^3) gave an orange precipitate. This was filtered off and washed with water before drying under vacuum. Yield 665 mg, 91%.

[Co(Hdips)$_2$]·2H$_2$O **13**, [Ni(Hdips)$_2$]·2.5H$_2$O **14** *and* [Zn(Hdips)$_2$]·H$_2$O **15**. To a filtered, hot solution of H$_2$dips (0.70 g, 3.15 mmol) and 1 mol dm^{-3} NaOH (3.15 cm^3) was added either Co(NO$_3$)$_2$·6H$_2$O or Ni(NO$_3$)$_2$·6H$_2$O (436 mg, 1.50 mmol) or ZnCl$_2$ (204 mg, 1.50 mmol) in water (10 cm^3). The precipitate was filtered off and washed several times with water before drying *in vacuo*. Yields: 354 mg, 44%, 420 mg, 51% and 542 mg, 69%, respectively.

Ternary complexes. Changing the order of addition of the phen and H$_2$dips ligands to the copper(II) salt can result in different products being obtained.

[Cu(phen)(dips)] **3** *and* [Cu(phen)(dis)]·2H$_2$O **9**. To the royal blue solution formed from copper(II) acetate hydrate (200 mg, 1.00 mmol) in ethanol (10 cm^3) and 1,10-phenanthroline (182 mg, 1.0 mmol) in ethanol (10 cm^3) was added a filtered solution of H$_2$dips (222 mg, 1.0 mmol) or H$_2$dis (390 mg, 1.0 mmol) in ethanol (10 cm^3). After heating the resultant solution, the green product was filtered off and washed with ethanol. Yields: 148 mg, 32% and 467 mg, 70%, respectively.

[Cu(phen)(Hdips)$_2$] **4**, [Cu(dpphen)(Hdips)$_2$]·0.5H$_2$O **6** *and* [Cu(dmap)$_2$(Hdips)$_2$] **7**. To a solution of copper(II) acetate hydrate (200 mg, 1.00 mmol) in ethanol (10 cm^3) was added an excess of H$_2$dips (888 mg, 4.00 mmol) in ethanol (20 cm^3). To the clear green solution was added either phen (180 mg, 1.00 mmol), dpphen (326 mg, 1.00 mmol) or dmap (244 mg, 2.00 mmol) in ethanol (10 cm^3). With the latter ligand, a solid precipitated immediately which was filtered off, washed with ethanol, then dried *in vacuo*. Yield 524 mg, 56%. For phen and dpphen the deep green reaction solutions were filtered and left overnight, after which time crystalline solids had formed which were filtered off, washed with ethanol and dried *in vacuo*. Yields: 498 mg, 73% and 588 mg, 69%, respectively.

[Cu(dmphen)(Hdips)$_2$] **5**. Dmphen·HCl·H$_2$O (527 mg, 2.00 mmol) in ethanol (10 cm^3) was added to copper(II) acetate hydrate (400 mg, 2.00 mmol) in water (20 cm^3) to give a green solution. On addition of an excess of H$_2$dips (888 mg, 4.00 mmol) a tan-yellow precipitate was obtained which was filtered off and washed with water–ethanol (1:1) then dried *in vacuo*. Yield 707 mg, 98%. The complex was soluble in ethanol.

X-Ray Crystallography.—[Cu(phen)(Hdips)$_2$]. *Crystal data.* $C_{38}H_{42}CuN_2O_6$, monoclinic, space group $C2/c$, a = 27.123(11), b = 9.969(3), c = 13.024(3) Å, β = 107.48(2)°, U = 3359 Å^3, Z = 4, M = 686.36, D_c = 1.36 g cm^{-3}, μ(Mo-Kα) = 6.97 cm^{-1}, F(000) = 1444, crystal dimensions 0.64 × 0.78 × 0.75 mm.

Measurements. Refined unit-cell parameters were found by centring 30 reflections, in the range 17 ⩽ 2θ ⩽ 29° taken from a rotation photograph, on a Nicolet R3mV diffractometer. A total of 3140 data were measured, of which 2894 were unique, in the range 5 ⩽ 2θ ⩽ 50° with Mo-Kα radiation (graphite monochromator). Of these, 2280 reflections had $I \geqslant 3\sigma(I)$ and were considered to be observed for the purposes of structure solution and refinement. Three standard reflections were monitored every 97 scans and showed no significant loss during data collection. The data were corrected for Lorentz and polarisation effects, and an empirical absorption correction was applied.

Structural analysis. The asymmetric unit contains one half of the formula unit. The position of the unique copper atom was derived from direct methods and the remaining non-hydrogen atoms were found by iterative application of Fourier-difference synthesis and least-squares refinement. The hydroxyl group on the unique Hdips ligand is disordered over two sites, O(3A) and O(3B), refined occupancy 60:40. Although the disorder need not be present in the alternative lower symmetry space group, *Cc*, refinement in that non-centrosymmetric space group was less successful. In the final stages of refinement all non-hydrogen atoms were refined anisotropically, while the hydrogen atoms were included in fixed positions with idealised C–H bond lengths (0.96 Å) and a common fixed isotropic thermal parameter (U = 0.08 Å^2). The hydrogens of the hydroxyl groups were omitted from the refinement. The final cycle of refinement included 222 parameters for 2280 variables, converged to give R = 0.0624 and R' = 0.0785 [$w^{-1} = \sigma^2(F) + 0.008\,186F^2$] and did not shift any parameter by more than 0.003 times its estimated standard deviation. The final Fourier-difference map was featureless with a largest peak of 0.49 e Å^{-3}. Computations were carried out on a Microvax II computer using the SHELXTL PLUS program package.[18]

Additional material available from the Cambridge Crystallographic Data Centre comprises H-atom coordinates and thermal parameters.

Physical Measurements.—The UV/VIS transmittance spectra were recorded on a Perkin Elmer Lambda 3 spectrophotometer using Nujol mulls. Microanalyses (Table 1) were performed by the microanalysis unit at University College. Room-temperature magnetic susceptibility measurements were carried out at ambient temperature on a Johnson Matthey Magnetic Susceptibility balance with Hg[Co(SCN)$_4$] as the standard. Corrections for diamagnetism were made using Pascal's constants.[19] Conductance measurements were made using a Kyoto Electronics CM-115 conductivity meter with a Kyoto Electronics conductivity cell on *ca.* 1 mmol dm^{-3} solutions. Fast atom bombardment (FAB) mass spectra were obtained through the University of London Intercollegiate Research Service, School of Pharmacy, with *m*-nitrobenzyl alcohol as matrix.

Cell Tests.—Cell tests were carried out by the CRC Institute of Cancer Research (Sutton) using L1210 (leukaemia), ADJ/PC6 (plastocytoma) and CH1 (human ovary) cell lines under standard conditions.[20] Anti-HIV tests were carried out by the MRC Collaborative Research Centre at Mill Hill. For the latter, C8166 cells (in RPMI 1640 medium containing 10% foetal calf serum) were infected with virus (HIV-1$_{111B}$) before addition of the test complex.

Table 1 Elemental analysis, colours and effective magnetic moments of complexes

Complex	Colour	Analysis[a] (%) C	H	N	μ_{eff}[b]/μ_B
2 $[\{Cu(Hdips)_2(dmso)\}_2]$	Dark green	57.1 (57.6)	7.0 (6.9)	6.0 (5.5)[c]	1.44
3 [Cu(phen)(dips)]	Green	64.2 (64.7)	5.2 (5.2)	5.9 (6.0)	1.90
4 $[Cu(phen)(Hdips)_2]$	Dark green	66.3 (66.5)	6.2 (6.2)	4.0 (4.1)	1.91
5 $[Cu(dmphen)(Hdips)_2]$	Tan-yellow	67.3 (67.2)	6.6 (6.5)	3.9 (3.9)	1.86
6 $[Cu(dpphen)(Hdips)_2]\cdot 0.5H_2O$	Green	71.1 (70.9)	5.9 (6.1)	3.4 (3.3)	1.99
7 $[Cu(dmap)_2(Hdips)_2]$	Purple	64.0 (64.0)	7.3 (7.2)	7.5 (7.2)	1.93
8 $[\{Cu(Hdis)_2(H_2O)\}_2]\cdot 4H_2O$	Light brown	18.9 (18.8)	1.1 (1.3)	—	2.07
9 $[Cu(phen)(dis)]\cdot 2H_2O$	Light green	34.4 (34.2)	1.9 (2.3)	4.1 (4.2)	2.08
10 $[\{Cu(Hdns)_2(H_2O)\}_2]\cdot 10H_2O$	Light green	26.5 (26.9)	1.9 (2.9)	8.7 (8.9)	2.12
11 $[Ti(Hdips)_2(dips)]\cdot 2H_2O$	Orange	63.0 (62.7)	7.1 (7.4)	—	*d*
12 $[Fe(Hdips)_3]\cdot 1.5H_2O$	Brown	62.8 (62.8)	7.2 (7.3)	—	3.43
13 $[Co(Hdips)_2]\cdot 2H_2O$	Light purple	58.4 (58.1)	6.9 (7.1)	—	5.07
14 $[Ni(Hdips)_2]\cdot 2.5H_2O$	Pale green	57.1 (57.2)	6.9 (7.2)	—	3.53
15 $[Zn(Hdips)_2]\cdot H_2O$	White	59.0 (59.4)	6.8 (6.9)	—	*d*
16 $[Fe(Hdis)_3]\cdot 2.5H_2O$	Purple	19.9 (20.0)	0.8 (1.1)	—	6.06
17 $[Fe(Hdcs)_3]\cdot 2H_2O$	Purple	35.3 (35.5)	1.9 (1.9)	30.0 (30.0)[e]	4.10

[a] Calculated values given in parentheses. [b] At 293 K per metal ion. [c] % S. [d] Diamagnetic. [e] % Cl.

Results and Discussion

Satisfactory elemental analyses were obtained for all the salicylato and mixed-ligand salicylato–phenanthroline complexes prepared here. These are listed in Table 1 together with their colours and magnetic moments. The formulation of complexes as hydrates was confirmed by IR data. Addition of H_2dips or related 3,5-disubstituted salicylates to the appropriate metal salt in aqueous solution immediately led to precipitation of the binary complex. The complexes (except for **10**, see below), are insoluble in aqueous solution, but can generally be dissolved in dmso, dmf or diethyl ether, reflecting the lipophilic nature of the ligands.[11] Where the ligand is formulated as being singly deprotonated, *e.g.* Hdips, it is assumed that the carboxylate group co-ordinates and the hydroxyl group is not directly involved in bonding to the metal (pK_a values of salicylic acid and 3,5-substituted salicylic acids range from *ca.* 2 to 4 for the carboxyl group and *ca.* 7.5 to 13.5 for the hydroxyl group).[21] The complexes $[\{Cu(Hdips)_2\}_2(H_2O)]$ **1** and $[\{Cu(Hdips)_2(dmso)\}_2]$ **2** are formulated as dimers based on previous assignments[11] and their low magnetic moments (see below). They are assumed to have a copper(II) acetate type structure with carboxylato bridges between the two metal ions and solvent in the axial positions. The water molecules are labile, with complexes formulated as $[\{Cu(Hdips)_2\}_2(H_2O)_n]$ (where *n* is 0, 1 or 2) being formed depending on the preparation and drying procedure. The water ligands can also be displaced by other Lewis bases.[11]

Altering the order of addition of reagents during the preparation of ternary complexes resulted in different compounds being isolated. When 1 mol equivalent of phen was added to $Cu(CH_3CO_2)_2$ in ethanol, a soluble copper(II)–phen complex was formed. Further addition of 1 or 2 mol equivalents of H_2dips in the same solvent gave [Cu(phen)(dips)] **3** (*i.e.* dideprotonated H_2dips). However, when an excess of H_2dips (4 mol equivalents) was added to Cu^{II} followed by phen, $[Cu(phen)(Hdips)_2]$ **4** crystallised. This complex contains two monodeprotonated salicylates giving an $N_2O_2 + O_2$ donor set (see below for crystal structure). When 2 mol equivalents of the monodentate N donor dmap were used instead of bidentate phen derivatives, the complex $[Cu(dmap)_2(Hdips)_2]$ **7** was isolated. This, presumably, also has an $N_2O_2 + O_2$ donor set for Cu, but now with the N donors *trans* to each other.

Crystal Structure of $[Cu(phen)(Hdips)_2]$ **4**.—The structure consists of monomeric units with an N_2O_4 donor set. The unique atom labelling is shown in Fig. 1. Fractional atomic coordinates are listed in Table 2, and bond distances and angles in Table 3.

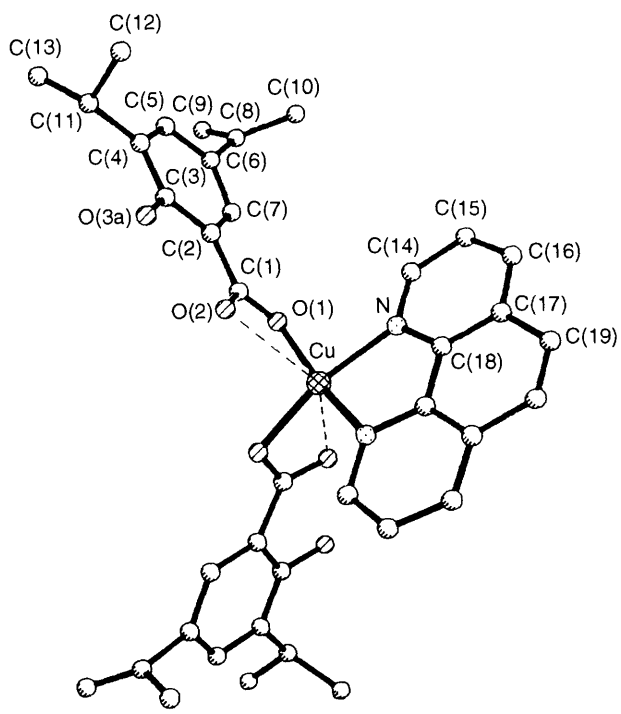


Fig. 1 The structure of $[Cu(phen)(Hdips)_2]$ **4** showing the numbering scheme. The hydroxyl group O(3a) is disordered 60:40 between C(3) and C(7) and is shown in the site of major occupancy

The copper(II) ion lies on the two-fold axis at 0, *y*, $\frac{1}{4}$ in a highly irregular octahedral geometry. The phen ligand is bisected by the two-fold axis, and chelates in the equatorial plane [Cu–N 2.014(4) Å] with the remaining two sites occupied by carboxylato oxygens from the two singly deprotonated Hdips ligands [Cu–O(1) 1.951(3) Å]. There is a tetrahedral distortion of these four donor atoms, with the distances from their mean plane being 0.16 Å for N and 0.14 Å for O(1). In the axial sites, forming four-membered chelate rings, are the other more weakly bound carboxylato oxygens [Cu–O(2) 2.557(3) Å]. A similar co-ordination sphere is found in $[Cu(sa)_2(tmen)]$[22] (where Hsa is salicylic acid and tmen is *N*,*N*,*N*′,*N*′-tetramethylethylenediamine). The angle from the O(2)–Cu bond to

Table 2 Atomic coordinates ($\times 10^4$) for [Cu(phen)(Hdips)$_2$] **4** with estimated standard deviations (e.s.d.s) in parentheses

Atom	*x*	*y*	*z*
Cu	0	−3(1)	2500
O(1)	354(1)	1281(3)	1836(3)
O(2)	883(1)	1016(3)	3463(3)
O(3a)	1766(2)	1989(5)	3928(3)
O(3b)	667(3)	2343(9)	467(6)
C(1)	796(2)	1461(4)	2542(3)
C(2)	1200(2)	2149(4)	2184(3)
C(3)	1681(2)	2392(4)	2927(3)
C(4)	2076(2)	3007(5)	2614(4)
C(5)	1975(2)	3311(5)	1536(4)
C(6)	1500(2)	3063(4)	758(3)
C(7)	1112(2)	2501(4)	1114(3)
C(8)	1427(3)	3321(6)	−408(5)
C(9)	1466(6)	4531(9)	−778(7)
C(10)	1438(3)	2108(7)	−1005(5)
C(11)	2593(2)	3252(6)	3459(5)
C(12)	2938(3)	2079(8)	3527(7)
C(13)	2846(4)	4487(9)	3397(8)
N	221(1)	−1533(3)	1729(3)
C(14)	444(2)	−1503(4)	935(3)
C(15)	578(2)	−2634(6)	505(4)
C(16)	487(2)	−3875(5)	887(4)
C(17)	250(2)	−3962(4)	1691(3)
C(18)	120(1)	−2750(3)	2084(3)
C(19)	112(2)	−5197(4)	2107(5)

Table 3 Bond lengths (Å) and angles (°) for [Cu(phen)(Hdips)$_2$] **4** with e.s.d.s in parentheses. Primed atoms are generated by two-fold rotation about 0, *y*, $\frac{1}{4}$

Cu–O(1)	1.951(3)	Cu–O(2)	2.557(3)
Cu–N	2.014(4)		
O(1)–C(1)	1.284(5)	O(2)–C(1)	1.234(5)
O(3a)–C(3)	1.316(6)	O(3b)–C(7)	1.257(8)
C(1)–C(2)	1.483(6)	C(2)–C(3)	1.392(5)
C(2)–C(7)	1.387(6)	C(3)–C(4)	1.397(7)
C(4)–C(5)	1.381(7)	C(4)–C(11)	1.518(6)
C(5)–C(6)	1.401(6)	C(6)–C(7)	1.390(7)
C(6)–C(8)	1.493(8)	C(8)–C(9)	1.315(11)
C(8)–C(10)	1.443(9)	C(11)–C(12)	1.484(9)
C(11)–C(13)	1.424(11)	N–C(14)	1.345(6)
N–C(18)	1.355(5)	C(14)–C(15)	1.357(7)
C(15)–C(16)	1.383(8)	C(16)–C(17)	1.386(7)
C(17)–C(18)	1.398(6)	C(17)–C(19)	1.440(7)
C(18)–C(18′)	1.422(8)	C(19)–C(19′)	1.338(14)
O(1)–Cu–O(2)	56.2(1)	C(17)–C(19)–C(19)	121.2(3)
O(2)–Cu–N′	99.8(1)	O(1)–Cu–N	90.9(1)
O(2)–Cu–O(1′)	92.0(1)	O(1)–Cu–O(1′)	98.0(2)
N–Cu–O(1′)	167.8(1)	C(1)–Cu–O(1′)	98.0(1)
O(2)–Cu–O(2′)	133.2(1)	C(1)–Cu–O(2′)	116.0(1)
N–Cu–O(2′)	115.6(1)	O(2)–Cu–N′	115.6(1)
O(1)–Cu–N′	167.8(1)	O(1′)–Cu–N′	90.9(1)
N–Cu–N′	81.5(2)	Cu–O(1)–C(1)	104.6(3)
O(2a)–Cu–N′	99.8(1)	O(1)–C(1)–O(2)	120.8(4)
Cu–O(2)–C(1)	77.7(2)	O(2)–C(1)–C(2)	121.9(3)
O(1)–C(1)–C(2)	117.3(4)	C(1)–C(2)–C(7)	120.8(3)
C(1)–C(2)–C(3)	119.3(4)	O(3a)–C(3)–C(2)	119.0(4)
C(3)–C(2)–C(7)	119.9(4)	C(2)–C(3)–C(4)	120.9(4)
O(3a)–C(3)–C(4)	120.0(4)	C(3)–C(4)–C(11)	118.7(4)
C(3)–C(4)–C(5)	117.2(4)	C(4)–C(5)–C(6)	123.7(5)
C(5)–C(4)–C(11)	124.0(5)	C(5)–C(6)–C(8)	121.2(6)
C(5)–C(6)–C(7)	117.0(4)	O(3b)–C(7)–C(2)	118.9(5)
C(7)–C(6)–C(8)	121.7(5)	C(2)–C(7)–C(6)	121.2(3)
O(3b)–C(7)–C(6)	119.9(5)	C(6)–C(8)–C(10)	112.7(5)
C(6)–C(8)–C(9)	122.0(6)	C(4)–C(11)–C(12)	110.2(5)
C(9)–C(8)–C(10)	123.7(7)	C(12)–C(11)–C(13)	112.2(6)
C(4)–C(11)–C(13)	117.0(5)	Cu–N–C(18)	112.8(3)
Cu–N–C(14)	129.5(3)	N–C(14)–C(15)	122.5(4)
C(14)–N–C(18)	117.8(4)	C(15)–C(16)–C(17)	120.0(5)
C(14)–C(15)–C(16)	119.7(5)	C(16)–C(17)–C(19)	124.7(5)
C(16)–C(17)–C(18)	116.7(4)	N(1)–C(18)–C(17)	123.3(4)
C(18)–C(17)–C(19)	118.6(4)	C(17)–C(18)–C(18′)	120.2(2)
N–C(18)–C(18)	116.5(2)		

the mean plane of the four donor atoms about Cu in **4**, 59.8°, is comparable to values of 61.2 and 63.8° found in [Cu(sa)$_2$(tmen)]. This significantly off-axis deviation results from the restricted bite of the carboxylate and may hinder approach of any potential ligands to the apical sites. When two unidentate N donors (as opposed to the bidentate phen ligand) are co-ordinated to Cu^{II}, as in acetylsalicylatobis(pyridine)copper(II)[23] a monomeric structure is also found, only now with a *trans* arrangement of the donor atoms. Here also the carboxylato group chelates to Cu with one short [1.949(3) Å] and one long [2.623(3) Å] bond. However, it is more common to obtain carboxylato-bridged dimers in such systems rather than monomers. For example, the structures of [{Cu(phen)(sal)ClO$_4$}$_2$],[24] [{Cu(bipy)(sal)ClO$_4$}$_2$][25] (Hsal = salicylaldehyde) and [{Cu(phen)(PhCH$_2$CH$_2$CO$_2$)(H$_2$O)}$_2$][NO$_3$]$_2$[26] exist as dimers in the solid state with the carboxylate bridging between the two copper(II) centres. The factors which lead to monomeric complexes such as **4** and [Cu(sa)$_2$(tmen)] may therefore be subtle. Whether the difference is due to steric and/or electronic effects is unclear, although it has been suggested that the former are less important.[22] This implies that related complexes prepared in this work could adopt either type of structure in the solid state.

Each Hdips ligand in **4** chelates to Cu^{II} through the carboxylate oxygens O(1) and O(2). The C(1)–O(1) bond length [1.284(5) Å] is significantly longer than the C(1)–O(2) distance [1.234(5) Å] indicating more keto character in the latter in accord with its weaker bond to Cu. This is typical of asymmetrically-bonded carboxylato ligands.[23,27,28] The hydroxy group does not co-ordinate and is disordered 60:40 between C(3) and C(7). It does not form any close contacts to Cu, and the C(3)–O(3a) bond length (1.316 Å) is similar to others in non-co-ordinated salicylates and salicylic acid.[27,29] No hydrogen bond involving the hydroxy group to other donors is present. However, because of the disorder the hydrogen on O(3a) could not be accurately placed, although there is possible internal hydrogen bonding from the hydroxy H to O(2), as seen previously.[29,30] The dihedral angles between the plane of the ring and its carboxyl group, and to the ring of the other Hdips ligand, are 7.6 and 50.1°, respectively. These angles are similar to those in [Cu(sa)$_2$(tmen)].[27] Bond distances and angles for the phen moiety are normal.[26,31–33]

Physicochemical Studies.—Electronic spectral data for the complexes as Nujol mulls are given in Table 4. All complexes exhibit a band at *ca.* 320 nm assigned to a ligand charge transfer (c.t.) transition.[11] The four binary copper(II) complexes **1**, **2**, **8** and **10** have a band between 400 and 470 nm due to a ligand-to-metal charge-transfer transition, typical of carboxy-bridged dimeric copper(II) species.[34] The transitions between 704 and 735 nm for these species are very similar in energy to those observed for [{Cu(CH$_2$=CHCO$_2$)$_2$L}$_2$] (L = MeOH 710 nm, L = dmso 722 nm) and accordingly are assigned to d–d transitions. The d–d bands for the ternary complexes **3**, **4**, **6** and **9** (593–750 nm) fall within the range for tetragonal, rhombic and square-pyramidal copper(II) environments and are not definitive. The crystal structure of **4** shows Cu to have an $N_2O_2 + O_2$ tetragonal co-ordination sphere. The solid-state structures for **3**, **6** and **9** therefore appear to be more consistent with monomeric 4 + 1 or 4 + 2 co-ordination spheres, as has also been seen in [Cu(phen)(sa)]NO$_3$[32] which has $N_2O_2 + O$ co-ordination. The complex [Cu(dmphen)(Hdips)$_2$] **5** displays a very broad d–d band at 900 nm, very similar to that seen for

Table 4 Electronic absorption and conductivity data

Complex	Absorption bands (nm) c.t.[a]		d–d		Molar conductivity[b]
1	320	447	714 (br)		14
2	320	420	735 (br)		11
3	330 (br) (sh)		644		2
4	320 (sh)		652 (br) (sh)	750 (br) (sh)	14
5	420w (sh)		900 (vbr)		8
6	310	420w (sh)	609 (br)		10
7	330w (sh)	370w (sh)	558		17
8	343	470 (sh)	704 (vbr)		24
9	350 (sh)		593 (br)		2
10	400		620 (br)	730 (sh)	52
11	310 (sh)	382			4
12	322		500 (vbr)		25
13	322		557 (br)		35
14	322				40
15	338				11
16	345		537		22
17	323	538 (br)			16

[a] c.t. = Charge transfer, sh = shoulder, br = broad, w = weak, v = very. [b] In dmso; S cm^{-2} mol^{-1}.

$[Cu(dmphen)(dmc)_2]$ (Hdmc = 2,5-dimethoxycinnamic acid), for which partially resolved bands at 840 and 1280 nm were observed.[35] These data are consistent with a rhombic structure, intermediate between square pyramidal and trigonal bipyramidal. The copper(II) ion in $[Cu(dmphen)(dmc)_2]$ is five-co-ordinate and complexed by a chelating dmphen, one bidentate and one monodentate dmc ligand. The adoption of this structure, as opposed to the tetragonal symmetry for **4**, may in part arise from the steric constraints imposed by the methyl groups adjacent to the co-ordinated nitrogens of the dmphen ligand. By analogy to the purple complex $[Cu(py)_2(aoba)_2]$[22] (py = pyridine), complex **7** is assumed to have $N_2O_2 + O_2$ co-ordination for Cu^{II}, with two pyridine and two carboxylato ligands in a near square-planar arrangement. Weaker off-axial interactions to the other carboxylate oxygens would therefore complete the co-ordination sphere, with a *trans* configuration of all donor atoms (inversion centre at Cu).

The orange complex $[Ti(Hdips)_2(dips)]$ **11**, displays a c.t. band at 382 nm tailing into the visible region. No d–d bands were resolved in the solid state consistent with a d^0 Ti^{IV} configuration. Titanium(III) was used in the preparation, and the oxidant is presumably dioxygen (air).

The occurrence of a broad transition at 557 nm for $[Co(Hdips)_2]\cdot 2H_2O$ **13** is consistent with an octahedral[34] or a trigonal-bipyramidal[36] structure. Weak bands which might have been expected to lower energy were not observed. Similarly, for the pale green complex $[Ni(Hdips)_2]\cdot 2.5H_2O$ **14**, no d–d bands were resolved, suggesting an octahedral structure. The white complex $[Zn(Hdips)_2]\cdot H_2O$ **15** shows only one band at 338 nm, confirming that this is a charge-transfer transition. The three iron(III) complexes **12**, **16** and **17** are brown or red powders and display a broad d–d absorption at *ca.* 530 nm typical of an octahedral O_6 donor set.[34]

The effective magnetic moment for **2** of 1.44 μ_B indicates some degree of spin-pairing at ambient temperature as found previously for this complex.[11] Assignment of a copper(II) acetate type structure with axial dmso co-ordination is consistent with this value. There has been considerable interest in the magnetic properties of copper(II) carboxylates and there have been attempts to correlate these with structural features in a wide range of substituted benzoates and salicylates.[37] Complexes **8** and **10** have magnetic moments close to the spin-only value. Apparently changing the isopropyl groups to iodo or nitro groups results in a reduced Cu–Cu interaction or a change in structure; however these complexes need further investigation.

The ternary copper compounds exhibit normal spin-only magnetic moments consistent with magnetically dilute species. However, this does not rule out dimeric or oligomeric complexes since related compounds have been shown to adopt an array of structures in the solid state, *e.g.* $[\{Cu(phen)(PhCH_2CH_2CO_2)(H_2O)\}_2][NO_3]_2$ exists as a dimer with the two phenylpropionato ligands bridging the copper(II) centres and the chelated phen on each Cu involved in π–π interactions.[26] The magnetic moments of 5.07 and 3.53 μ_B for **13** and **14**, respectively, are normal for octahedral high-spin cobalt(II) and nickel(II) species, respectively, and **11** is diamagnetic as expected for Ti^{IV}. The value of 6.06 μ_B for the iron complex **16** is typical of high-spin iron(III). However, both **12** and **17** have lower values of 3.43 and 4.10 μ_B, respectively, indicative of some antiferromagnetic behaviour.

Molar conductance values in dmso, in all but one case, fall below the range expected for 1:1 electrolytes (50–70 S cm^2 mol^{-1}) and suggest that the salicylato ligand remains bound even in such a strongly co-ordinating solvent. The exception, **10** (52 S cm^2 mol^{-1}) probably results from the ionisation of a phenolate proton due to its greater acidity relative to the other salicylates employed. For example, the pK_a values[21] for the carboxylate and phenolate protons of 3,5-diiodosalicylic acid are 3.8 and 11.2, respectively, whereas for 3,5-dinitrosalicylic acid the corresponding values are reduced to *ca.* 2 and 7. This may also account for the fact that **10** is the only complex prepared here which has any appreciable aqueous solubility.

The FAB mass spectra for complexes **3** and **4** were identical, with peaks at *m/z* 243 [Cu(phen) 100], 423 $[Cu(phen)_2$ 33], 464 [Cu(phen)(dips) 8], 708 $[Cu_2(phen)_2(dips)$ 11] and 990 $[Cu_3(phen)_2(Hdips)_2$ 2%]. These results suggest that product rearrangement occurs in the spectrometer to give oligomeric materials, and therefore the technique was of limited use in differentiating between the ternary adducts. All peaks showed the expected isotopic pattern for Cu.

Biological Activity.—The results of cytotoxicity (L1210, ADJ/PC6, CH1 cell lines) and anti-HIV activity are presented in Table 5. By changing the substituents on H_2dips, changing the metal and also incorporating phenanthrolines (which are known to possess antitumour activity) in ternary adducts, we hoped to optimise the biological activity of these complexes.

From Table 5 it can be seen that all binary complexes gave IC_{50} values (concentration of complex required to inhibit growth of 50% of the cells) of *ca.* 30 μmol dm^{-3} for the ADJ/PC6 tumour cell line. There is little differentiation between the

Table 5 Cytotoxicity and antiviral data

	IC_{50}[a]/μmol dm^{-3} cell line			C8166 (HIV-1)[b]		
					Cell viability (%)	
Complex	L1210	ADJ/PC6	CH1	c/μg cm^{-3}	Infected	Uninfected
1	4.5	26.0	10.0	—	—	—
4	0.52	3.2	0.3	—	—	—
3	0.40	0.72	0.84	—	—	—
5[c]	0.27	0.38	0.037	—	—	—
12	5.8	31.0	3.0	20	20	69
	—	—	—	2	30	72
14	39.0	100.0	31.5	50	10	11
	—	—	—	5	31	100
13	14.0	28.0	27.0	50	1	6
	—	—	—	5	43	87
15	40.0	30.0	31.0	50	18	13
	—	—	—	5	41	90
11	31.0	26.0	21.5	50	0	0
	—	—	—	5	44	74
8	2.8	24.5	3.1	100	0	0
	—	—	—	10	23	100
9	0.19	1.9	0.32	5	0	0
	—	—	—	0.5	14	81
				0.05	27	100
10	2.5	20.5	2.4	100	0	45
	—	—	—	10	24	100

[a] IC_{50}, concentration required to inhibit cell growth by 50%. [b] None showed any significant anti-HIV activity under the conditions used for the tests. For comparison, AZT reduces the virus population of these infected cells by 50% at a concentration of 0.01 μg cm^{-3} and is non-toxic at 1000 μg cm^{-3}. Cell viability is given as % of control. [c] LD_{50} for mice bearing the murine ADJ/PC6 plasmacytoma of 14.7 mg kg^{-1}. No appreciable antitumour effect observed at this dose.

salicylate ligands or between the metal ions in the complexes, the only exception being $[Ni(Hdips)_2]\cdot 2.5H_2O$, **14**, which is less toxic with an IC_{50} value of 100 μmol dm^{-3}. In contrast, the binary complexes exhibit significant differences in their toxicities towards the L1210 and CH1 cell lines. Complexes **8** and **10** are *ca.* 2–4 times as toxic as **1**. This result is unexpected as it has been assumed that the lipophilicity of **1** is the dominating feature of its activity,[11] yet **8** and **10** are predicted to be less lipid soluble. For the calculation of lipophilicities, each Cu can be considered to have four substituents associated with it (two ligands with two substituents in the 3- and 5-positions) giving π values* for **1**, **8** and **10** of 6.1, 4.5 and −1.1 respectively.[38] This spans an octanol–water partitioning of 1.7×10^7 and indicates that if lipophilicity is the dominant property which determines cytotoxicity, then **10** should not be active. Other properties of these complexes must therefore be important for their activity. Steric effects can be estimated from E_s parameters[38] and those for Pr^i and I are −1.7 and −1.4, respectively, with values for NO_2 of −1.0 and −2.5 due to its two possible orientations. On average these are quite similar and may be more important than previously thought, due to steric interactions of the 3-position on the hydroxyl group or possibly steric effects at the site of activity. A measure of the electronegativity is the Hammett σ parameter,[38] with values for Pr^i, I and NO_2 in the *para* position being −0.15, 0.18 and 0.78, respectively. These σ values on their own cannot explain the difference in activity observed, but in combination with lipophilic and steric factors may be important. Ligand exchange and redox reactions must also be considered, including those with the culture medium. We have shown[39] by NMR studies of blood plasma that Cu^{II} can be transferred from $[\{Cu(Hdips)_2\}_2]$ onto the strong N-terminal binding site of albumin. Lactate was displaced from binding to protein during this process and the diisopropylsalicylate ligand was not seen in the spectrum and so was probably bound to protein. Arena *et al.*[40] have recently noted for a series of hydrophilic complexes that cytotoxic activity correlated merely with the amount of Cu^{II} administered because all their complexes underwent ligand exchange reactions with the cell culture media. For hydrophobic complexes it now becomes important to investigate further the relative rates of partitioning (into lipophilic compartments such as lipoproteins and cell membranes), as well as ligand exchange and redox reactions.

Binary complexes of metals other than copper, with the exception of the iron complex **12**, are up to an order of magnitude less toxic. In view of their contrasting kinetic, thermodynamic and stereochemical properties, the mode of action of **12** may be different and therefore this could represent a new type of agent. It would then be interesting to prepare ternary complexes of iron for comparison with those of copper. The zinc complex **15** is worthy of comment as its toxicity is similar to the other less active binary complexes (*e.g.* **11**, **13**). The Hdips ligands bound to zinc would be expected to be labile, therefore this result would seem to confirm previous findings that the free ligand is not the active species and the preformed copper (iron) complex is needed for activity.

Incorporation of a phen ligand increases the cytotoxicity of the copper complexes by an order of magnitude. For example when phen is incorporated into **1** to give **4**, the IC_{50} value for L1210 cells decreases from 4.5 to 0.52 μmol dm^{-3}. Incorporation of dmphen causes an even bigger increase in toxicity: the IC_{50} values of **1**, **4** and **5** are 10.0, 0.3 and 0.037 μmol dm^{-3}, respectively, for CH1 cells. Differences in biological activity between phen and dmphen have been noted previously, see below. Because of the potent *in vitro* cytotoxicity of **5**, this complex was further tested for *in vivo* antitumour activity (Table 5). It was inactive suggesting that it is destroyed by interaction with biofluids and is not stable enough to reach the tumour cells *in vivo*. A possible advantage of the ternary

* π is a measure of substituent lipophilicity based on octanol–water partitioning of a parent compound and its substituted analogue. More positive values of π indicate greater octanol solubility, therefore increased lipophilicity. If an inverse parabolic or bilinear dependence on π existed, the range of octanol–water partition values is so large that it would still be expected to differentiate between the complexes.[38]

adducts, if they remain intact, when compared to species such as $[Cu(phen)_n]^{m+}$ ($n = 1$ or 2, $m = 1$ or 2), is that they are electrically neutral, and this may aid their transport across cell membranes.

The complex $[\{Cu(Hdips)_2\}_2]$ **1** has been reported to exhibit a wide variety of bioactivities, including antiinflammatory, anticancer, anticarcinogenic, antimutagenic, anticonvulsant, antidiabetic and radiation protection. It can act as a superoxide dismutase (sod) mimic. This may be important for radiation protection, but is not sufficient to explain the observed range of activity, and other mechanisms must also operate. For example the lipophilic complex may deliver Cu and activate enzymes involved in protection and repair. However, a study of the tissue distribution and *in vivo* stability of $[\{^{67}Cu(Hdips)_2\}_2]$ carbon-14 labelled at the carboxy sites has shown the coincident appearance and persistence of both radioisotopes at multiple sites in mice.[41] Rapid partitioning of this complex into lipophilic compartments may therefore be important since the complex would be expected to be thermodynamically unstable in biological media due to the abundance of potential donors.[39] The close association between Cu and Hdips suggests that the intact complex could be a biologically important species. Incorporation of a phen ligand in the ternary complexes prepared here may favour DNA intercalation, with the salicylate ligand aiding transportation of the complex to the nucleus, but further studies are needed to elucidate the mechanism of action.

Several of the complexes were tested for activity against the human immunodeficiency virus (HIV), but none displayed anything other than marginal activity, Table 5. The major problem was the high toxicity against the cell lines used in these tests, *i.e.* it was difficult to differentiate between cell-kills and virus depletion.

Conclusion

Binary complexes of first-row transition metals with several 3,5-disubstituted salicylates have been isolated and characterised. Several of these exhibited magnetic exchange coupling in the solid state. Ternary complexes of copper(II) with substituted phenanthrolines and salicylates were also isolated and two different stoichiometries were obtained, depending upon the synthetic conditions employed: either two mono-deprotonated salicylates or one dideprotonated salicylate per Cu^{II}. The crystal structure of $[Cu(phen)(Hdips)_2]$ was determined, the first of a 3,5-diisopropylsalicylato complex. This revealed Cu^{II} in a tetragonal environment with in-plane bonds from nitrogens of phen and 2 oxygens of the Hdips carboxylates, and weaker off-axial bonds to (chelated) carboxylate oxygens.

Cytotoxicity and antiviral testing revealed that most complexes were cytotoxic. There was little correlation between cytotoxicity and lipophilicity for the binary copper–salicylates, and ternary complexes incorporating phenanthrolines were *ca.* ten times as cytotoxic as their binary analogues. Most potently cytotoxic were the ternary complexes [Cu(phen)X], X = $(Hdips)_2$, dips or dis, which had cytotoxicities comparable with the anticancer drug cisplatin *cis*-$[PtCl_2(NH_3)_2]$.

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