1,4,7-Triazacyclononane-1,4,7-triyltrimethylenetris-(phenylphosphinate) enforces Octahedral Geometry: Crystal and Solution Structures of its Metal Complexes and Comparative Biodistribution Studies of Radiolabelled Indium and Gallium Complexes†

Eleanor Cole,[a] Royston C. B. Copley,[a] Judith A. K. Howard,[a] David Parker,*,[a] George Ferguson,[b] John F. Gallagher,[b] Branko Kaitner,[b] Alice Harrison[c] and Louise Royle[a,c]
[a] *Department of Chemistry, University of Durham, South Road, Durham DH1 3LE, UK*
[b] *Department of Chemistry, University of Guelph, Guelph, Ontario, N1G 2W1, Canada*
[c] *MRC Radiobiology Unit, Chilton, Didcot, OX11 0RD, UK*

1,4,7-Triazacyclononane-1,4,7-triyltrimethylenetris(phenylphosphinate) formed C_3-symmetric complexes with the divalent ions of Co, Ni, Cu and Zn and structurally similar complexes with the trivalent ions of Fe, Co, Ga and In. For each of the eight crystal structures examined, the ligand adopts the same rigid conformation and a single chiral diastereoisomer is formed (*RRR* or *SSS* at each stereogenic phosphorus centre). The geometry around the metal centre is slightly distorted octahedral. The copper(II) complex only undergoes a Jahn–Teller distortion below 100 K, and the pink cobalt(II) complex only slowly oxidises to the dark blue cobalt(III) complex. The chiral gallium(III) complex may be resolved by preparative HPLC, and its ^1H NMR spectrum has been fully assigned with the aid of two-dimensional methods. The indium-111 and gallium-67 complexes have been examined *in vivo* and exhibit selective biliary clearance associated with their lipophilic nature.

We have begun to explore the complexation chemistry of α-aminoalkylphosphinic acids pinpointing differences from the analogous α-aminocarboxylate ligands.[1,2] There are several basic differences in the chemistry of these two systems that are particularly striking. First, the phosphinate moiety is more difficult to protonate on oxygen than is the corresponding carboxylate, *i.e.* it possesses a lower pK_a value. This applies both to the free compound and to its metal complexes, so that enhanced kinetic stability with respect to acid-catalysed metal dissociation may result, as is required for *in vivo* applications.[3] An illustration of this effect is given by the relative pK_a values of the monoanionic complexes of yttrium with 1,4,7,10-tetraazacyclododecane-*N*,*N*′,*N*″,*N*‴-tetraacetic acid (H_4L^2) and of the methylphosphinate analogue H_4L^3, 3.07 and 1.28 (298 K, $I = 0.1$ mol dm^{-3}).[4] Secondly, when one of the phosphinate oxygens binds to a metal centre, the oxygens are rendered diastereotopic because a new stereogenic centre is created at phosphorus. Thus in systems such as H_3L^1 (with three equivalent phosphorus centres), two diastereoisomers may result from the co-operative binding of all six ligand donor atoms, both of which are chiral (*i.e. RRR*/*SSS* and *RSR*/*SRS* diastereoisomers may form). Finally, the pentavalency of phosphorus allows control over complex lipophilicity (and solubility) through variation of the substituent at phosphorus, *e.g.* alkyl or aryl, in addition to providing a site for further functionalisation.[5]

This paper describes the detailed complexation chemistry of one example of this class of compounds 1,4,7-triazacyclononane-1,4,7-triyltrimethylenetris(phenylphosphinic acid) (H_3L^1). This is an example of a rigid hexadentate ligand based on the [9]aneN$_3$ skeleton and in principle its metal complexes may adopt any structure between the limiting octahedral or trigonal-prismatic geometries.[6] Complexes of this compound with iron(III), cobalt-(II) and -(III), nickel(II), copper(II), zinc(II), gallium(III) and indium(III) have been prepared and structurally characterised by X-ray and solution NMR methods. In one case, for the neutral gallium(III) complex, the chiral complex has been resolved. Part of this work has been published in a preliminary communication.[7] For both indium and gallium, radiolabelled complexes have been prepared, using ^{67}Ga (γ, $t_{\frac{1}{2}}$ 3.25 d) or ^{111}In (γ, $t_{\frac{1}{2}}$ 2.81 d), and their relative biodistribution studied in animals as a function of time.

Results and Discussion

The compound H_3L^1 may be obtained by two different syntheses. Direct reaction of 1,4,7-triazacyclononane with phenylphosphinic acid in the presence of aqueous formaldehyde, under acidic conditions, yields the product directly, but contaminated with $PhP(CH_2OH)O_2H$. A two-step reaction sequence is preferred whereby co-condensation of 1,4,7-triazacyclononane with paraformaldehyde and $PhP(OMe)_2$ in tetrahydrofuran under anhydrous conditions yields the intermediate trimethyl ester, which is readily hydrolysed (HCl–water) following purification of the ester by chromatography on neutral alumina.[5] Admixture of stoichiometric quantities of H_3L^1 with metal nitrate salts in aqueous solution led to rapid formation of the metal complexes, which crystallised upon slow evaporation. In the case of Ga^{III}, Fe^{III} and In^{III}, neutral complexes were formed, whereas for Cu^{II}, Co^{II}, Ni^{II} and Zn^{II} monoanionic complexes were formed and the counter ion in each case was the oxonium ion, H_3O^+. In the case of the cobalt(II) complex, the pink crystalline solid, either when left in contact with aerated aqueous solution over 5–6 weeks or following addition of aqueous hydrogen peroxide, changed (over 2–3 weeks) to a dark blue neutral cobalt(III) crystalline

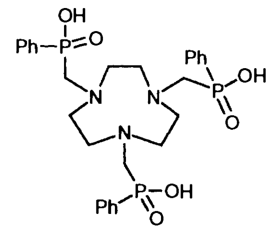
---

† *Supplementary data available:* see Instructions for Authors, *J. Chem. Soc., Dalton Trans.*, 1994, Issue 1, pp. xxiii–xxviii.

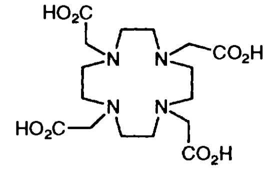
Table 1 Selected structural data for the complexes of H_3L^1 with metal ions [estimated standard deviations (e.s.d.s) in parentheses]

Complex	Twist[a] angle, α/°	M–O/Å	M–N/Å	(M–N) − (M–O)/Å	Ionic radius/Å
$[CoL^1]^{-b}$	25.3(1)	2.103(2)	2.168(3)	0.065	0.75
$[NiL^1]^-$	25.4(1)	2.083(3)	2.104(3)	0.021	0.69
$[CuL^1]^-$	25.6(2)	2.099(3)	2.134(3)	0.035	0.73
$[ZnL^1]^-$	25.4(1)	2.072(1)	2.218(1)	0.046	0.74
$[FeL^1]^c$	24.5(1)	1.932(2)	2.205(3)	0.273	0.65
$[GaL^1]^c$	26.0(2)	1.912(4)	2.135(6)	0.223	0.62
$[InL^1]^c$	23.6(1)	2.095(1)	2.303(1)	0.208	0.80

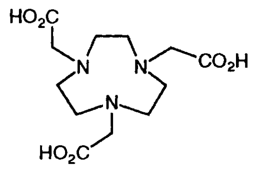
[a] Under the system adopted here, α = 0 (trigonal prismatic) and 30° (octahedral). This twist angle is therefore half the magnitude of that adopted by some workers.[8] [b] A preliminary analysis of the cobalt(III) complex gives mean bond lengths Co–O 1.93 and Co–N 1.95 Å: the effective ionic radius of Co^{III} is 0.55 Å. [c] Mean values are given.



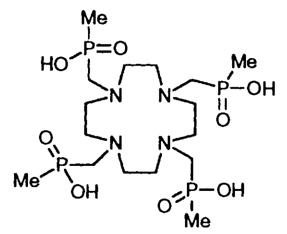
H_3L^1



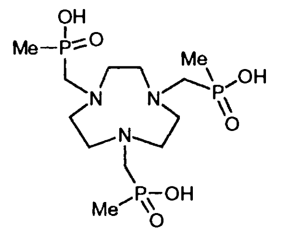
H_4L^2



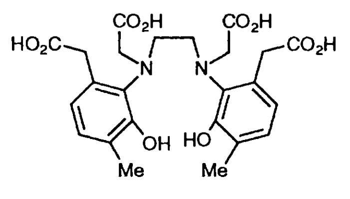
H_3L^4



H_4L^3



H_3L^5



H_4L^6

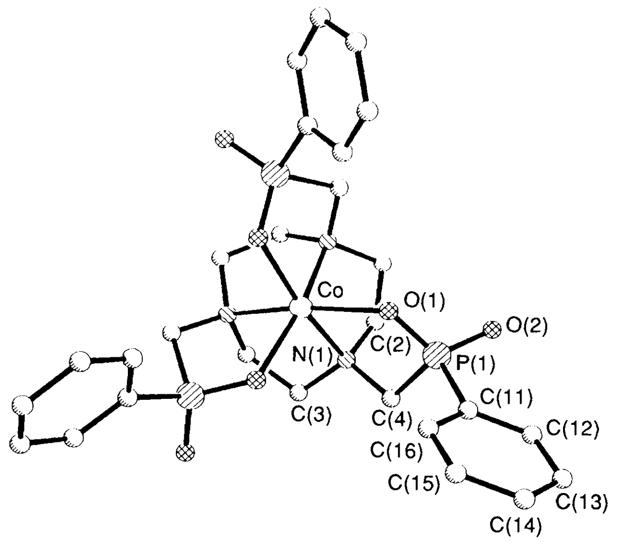


Fig. 1 View down the three-fold axis in the crystal of the anionic cobalt(II) complex. The copper, nickel and zinc complexes are isostructural

complex. This slow oxidation process was confirmed by the fact that the product was diamagnetic (d^6, spin-paired) and conductivity studies (293 K) in dry methanol solution indicated clearly that the complex product was no longer a 1 : 1 electrolyte: $[H_3O][CoL^1]$, 297; $[H_3O][CuL^1]$, 303; $[GaL^1]$, 98; and $[CoL^1]$, 96 Ω^{-1} cm^{-1}.

Structural Analyses.—In Table 1 selected molecular parameters are presented for the two sets of isostructural complexes. In the series of anionic complexes (crystallising in space group $P\bar{3}$, no. 147), the 'twist angle' [measuring the deviation of the N_3 and O_3 moieties from octahedral (α = 30°) or trigonal-prismatic geometry (α = 0°)] is essentially constant for d^7 to d^{10} complexes. A representative structure of the cobalt(II) complex is shown (Fig. 1). For the neutral complexes with iron, gallium, indium and cobalt, crystallising in space group $P\bar{1}$ [see Fig. 2 for the indium(III) complex] no real change in the twist angle is seen and all of the complexes adopt a slightly distorted-octahedral geometry.

This consistent behaviour is also apparent in the variation of the lengths for the metal–nitrogen and –oxygen bonds. In the series of anionic complexes (Co to Zn) the M–O and M–N bond lengths vary in a manner which is consistent with the differences in ionic radius, although the Zn–O and Zn–N distances are perhaps slightly longer than might have been expected based on this premise alone. For the neutral complexes, mean M–N and M–O bond lengths are given (Table 1). Although the complexes do possess an approximate three-fold axis of symmetry, for a given complex, variations in the M–N or M–O bond lengths are very small (< 0.01 Å). These distances are therefore essentially equal, given that crystal-packing forces could cause such small differences. As expected the M–O bond distances (M = Ga^{III}, Fe^{III}, In^{III} or Co^{III}) are considerably shortened with respect to the M–N bond lengths (and in comparison to the related anionic complexes), due to the difference between donor–acceptor M–N and highly ionic M–O bonds. Again, variations in the M–O distances within the group of neutral complexes echo changes in ionic radius.

These results demonstrate that the co-ordination environment around the metal centre is determined essentially by the mimimisation of intramolecular ligand interactions, involving the PPh groups. The rigid ligand is imposing its preferred geometry on the metal ion and overrides any effects on complex geometry due to either crystal-field stabilisation energies, as is commonly seen in for example hexaamine cage complexes,[9] or π-bonding effects which have been proposed, for example, to favour trigonal-prismatic geometries in certain iron(III) complexes,[10,11] although trigonal-prismatic geometry may be imposed by rigid donor-atom arrays which are unable to distort to provide octahedral co-ordination.[12,13]

Table 2 Comparison of structural parameters for complexes of H_3L^1 with those of H_3L^4

	L^1			L^4		
M	Twist angle, α/°	M–N/Å	M–O/Å	Twist angle, α/°	M–N/Å	M–O/Å
Cu^{II} [a]	25.6(1)	2.134(3)	2.099(3)	13.3(2)	2.115(3)	1.978(2)
					2.197(3)	2.205(3)
					2.039(2)	2.141(3)
Ni^{II} [b]	25.4(1)	2.104(3)	2.083(3)	22.5(9)	2.04	2.08
Fe^{III} [c]	24.5(1)	2.205(3)	1.932(2)	12.6	2.181(3)	1.962(2)
Ga^{III}	26.0(2)	2.135(6)	1.912(4)	23.8	2.104(6)	1.933(6)
In^{III} [d]	23.6(1)	2.303(1)	2.095(1)	10.4 [d]	2.258(4)	2.094(4)

[a] The complex of L^4 has undergone a Jahn–Teller distortion at 298 K.[8] [b] The nickel complex of L^4 has average distances M–N 1.93(1) and M–O 1.91(1) Å; α = 26.5°.[16] [c] The iron(III) complex of 1,4,7-triazacyclononane-1,4,7-triyltrimethylenetriphosphonate has Fe–N 2.206(2) and Fe–O 1.945(2) Å.[17] [d] For the corresponding (*RRR*)-tripropionate complex.[15]

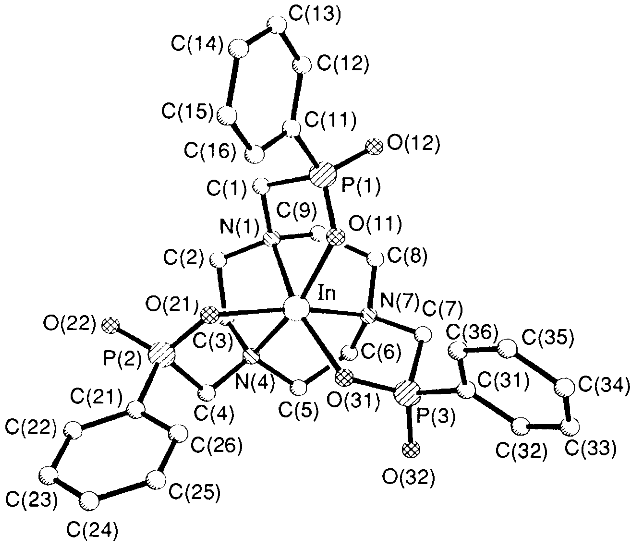
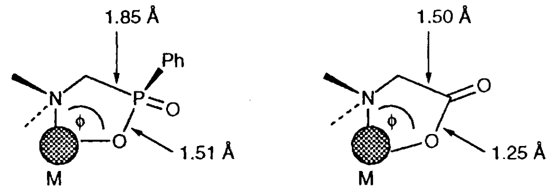


Fig. 2 Molecular structure of $[InL^1]$ at 150 K. The complexes of Ga^{III}, Co^{III} and Fe^{III} are isostructural



φ/° M	Phosphinate	Carboxylate
Co	85	
Ni	86	
Zn	85	
Cu	86	79
Ga	86	83
Fe	84	78
In	82	78

Scheme 1

Comparison with Analogous Carboxylate Complexes.—It is instructive to compare these phosphinate complexes with the corresponding complexes of 1,4,7-triazacyclononane-*N,N′,N″*-triacetic acid, H_3L^4.[8,14–16] Whilst the N_3 moiety is identical, there are significant differences in the five-membered chelates involving the anionic donors, Scheme 1, arising primarily from the longer P–C and P–O bonds compared to the corresponding C–C and C–O bonds. Thus the chelate bite angle N–M–O (ideally 90° around an octahedral centre) is more acute for the carboxylate than it is in the phosphinate series. The copper(II) and iron(III) complexes of H_3L^4,[8] as well as the related [9]aneN_3 tripropionate complex of indium(III)[15] (Table 2), possess lower twist angles (10–13°) than those found for the gallium(III) nickel-(II) and -(III) complexes of H_3L^4 (α = 22–26.5°). Thus other factors are contributing towards complex geometry in this series, such as crystal-field effects as has been discussed by other authors.[8,16]

The copper(II) complex of H_3L^4 and of the analogous trimethylenetris(phosphonic acid) analogue are not C_3-symmetric at room temperature and have undergone a Jahn–Teller distortion, so that one of the three Cu–N and Cu–O bonds is elongated (each is *ca.* 2.20 Å). In contrast, the triphosphinate copper(II) complex has not undergone such a distortion at 293 K. Furthermore a structural analysis at 123 K revealed that the complex crystallised in the same space group and no significant structural changes were observed in the Cu–N and Cu–O bond lengths or in the anisotropy of the thermal parameters for the bound O and N atoms. Examples of Cu(N–N)$_3$, CuN_6, Cu(O–O)$_3$ and CuO_6 chromophores that apparently possess an E_1 ground state at room temperature are quite rare, but have been described previously.[18–20] Although they are in apparent contradiction of the Jahn–Teller theorem, which suggests that spin or orbitally degenerate ground states should distort so as to remove the degeneracy, the observed C_3 symmetry may be considered to result from 'time averaging' of electronic–vibronic couplings. At sufficiently low temperatures a distorted structure is adopted as the 'dynamic Jahn–Teller' effect is 'frozen out'. Although not seen in the structural analyses of $[H_3O][CuL^1]$,* the onset of a Jahn–Teller distortion was revealed by variable-temperature ESR studies. At 298 K a single isotropic resonance was observed [$g = 2.22$, $\Delta H_{pp} = 185$ G (1.85×15^2 T)] whereas at 8.6 K the axial *g* tensors were resolved ($g_{\parallel} = 2.58, g_{\perp} = 2.14$) consistent with a distorted low-temperature structure.

Another feature of the copper(II) complex of H_3L^1 that is distinct from the $[CuL^4]^-$ complexes is the protonation behaviour. The carboxylate complex protonates at low pH ($pK_a = 2.77$)[21] and the equilibrium is monitored easily by changes in the visible spectrum of the complex in solution. For $[CuL^1]^-$, not only does the complex crystallise as its oxonium ion salt in the range pH 2–5 in the presence of Na^+ or K^+ as counter ion, but also no change was discerned in the visible spectrum (293 K, $I = 0.1$ mol dm^{-3}, water) over the range pH

---

* The oxonium ion, H_3O^+, is located [as in the nickel, zinc and cobalt(II) structures] well away from the ligand heteroatoms and on the three-fold symmetry axis.

Table 3 Variation of ^{71}Ga NMR spectral parameters in six-coordinate [9]aneN$_3$-based gallium complexes

Complex[a]	δ_{Ga}[b]	$w_{\frac{1}{2}}$/Hz
[GaL^4]	171	210
[GaL^5]	139	200
[GaL^1]	132	560
[GaL^7][c]	130	1220

[a] The first three complexes were unchanged over 6 months in 6 mol dm^{-3} HNO$_3$.[23] [b] Relative to [Ga(H$_2$O)$_6$]$^{3+}$, *i.e.* Ga(NO$_3$)$_3$ in 6 mol dm^{-3} HNO$_3$(δ = 0). [c] H$_3$L^7 = 1,4,7-Triazacyclononane-1,4,7-triyltrimethylenetris(benzylphosphinic acid); the complex did appear to dissociate within 21 d at 293 K, as judged by the appearance of a singlet at δ 0 (aquagallium ion) and the disappearance of the resonance at δ +130.

2–9. This behaviour is consistent with the premise that phosphinate complexes are more difficult to protonate than are their carboxylate analogues, and has been observed previously in the behaviour of the analogous rare-earth-metal and lanthanide complexes of 1,4,7,10-tetraazacyclododecane ([12]aneN$_4$) phosphinate complexes.[1,3,22]

Solution NMR Studies.—The diamagnetic complexes of cobalt(III) (low-spin d^6), zinc(II) (d^{10}) and gallium(III) (d^{10}) have been studied by solution NMR methods. The gallium complex of H$_3$L^1 was studied by ^{71}Ga NMR ($I = \frac{3}{2}$, 39.6% natural abundance, quadrupolar moment = 0.112) spectroscopy and the observed linewidths were compared to those obtained with related complexes (Table 3). The linewidth of the ^{71}Ga resonance is a sensitive function of molecular symmetry. In the C_3-symmetric complex with H$_3$L^4 [23] the electric field gradient at the nucleus is very small and the interaction with the nuclear quadrupole moment gives rise to very little line broadening. A similar situation must be occurring with the trimethylenetris(methylphosphinate) complex GaL^5 (Table 3) which possesses a similarly sharp resonance. For [GaL^1] and the P(CH$_2$Ph) analogue slight but significant deviations from C_3 symmetry must be occurring (as confirmed by the crystal structure of [GaL^1]) so that a broadened resonance results.

The ^{1}H NMR spectra of the cobalt(III) and gallium(III) complexes were very similar. All of the proton resonances of [GaL^1] have been assigned with the aid of two-dimensional correlation spectroscopy (COSY), heteronuclear correlation spectroscopy (HETCOR) and one-dimensional nuclear Overhauser effect (NOE) experiments. In the proton-decoupled ^{13}C NMR spectrum of [GaL^1] (293 K, CD$_3$OD) the NCH$_2$P methylene group resonated as a doublet ($^1J_{CP}$ = 91 Hz) and the ring methylene carbons were distinguished by virtue of their differing carbon–phosphorus coupling constants. The resonance at δ 57.6 (corresponding to CH$_A$H$_{A'}$N in the assignment scheme used, where H$_A$ and H$_{A'}$ are on C^2) appeared as a doublet ($^3J_{PC}$ = 12.5 Hz) while the other CH$_2$N (*i.e.* for C^3) peak gave a singlet at δ 53.4. In the former case, there is a P–C–N–C^2 dihedral angle of 180° (see Figs. 3 and 4) giving rise to the significant three-bond coupling observed and in the latter case the P–C–N–C^3 dihedral angle is approximately 90° and the coupling constant is too small to be seen $^3J_{PC} \leqslant 1$ Hz.

In the ^{1}H NMR spectrum of [GaL^1] the diastereotopic methylene (NCH$_2$P) protons resonated as two doublets of doublets ($^2J_{HH}$ = −14.1 and $^2J_{PH}$ = 4.6 Hz) at δ 3.51 and 3.25. The doublet of doublets at δ 3.25 showed a strong nuclear Overhauser enhancement with the phenyl *o*-hydrogens (at δ 8.04), clearly indicating that this proton was the 'pro-*S*' hydrogen. In support of this assignment, the pro-*R* resonance (at δ 3.51) was deshielded by the proximate anisotropic phosphorus–oxygen double bond (Fig. 3), and hence resonated to higher frequency of the pro-*S* hydrogen.

For the nine-membered ring the coupling pattern observed was typical of an AA′BB′ multiplet structure (Fig. 4), wherein A and B are designated as 'axial' hydrogens and A′ and B′ the 'equatorial' hydrogens (see Fig. 3). The two 'equatorial' protons define a dihedral angle of close to 90°, so that a very small coupling constant is expected ($^3J_{HH} \leqslant 1$ Hz). Thus the 'equatorial' hydrogens H$_{A'}$ and H$_{B'}$ with two observable couplings are readily distinguished from the 'axial' hydrogens, H$_A$ and H$_B$, which possess three. Assignments made from the ^{1}H–^{1}H COSY experiment were confirmed by a ^{1}H–^{13}C HETCOR experiment.

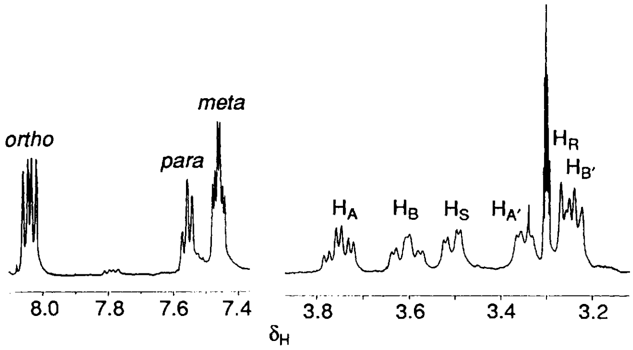


Fig. 3 Assignment of the proton NMR spectrum of [GaL^1] (293 K, CD$_3$OD) related to the crystal structure analysis. For assignments of protons see Fig. 4

Given that the gallium complex crystallises in space group $P\bar{1}$, there are two enantiomers in the unit cell in equal proportion corresponding to an *RRR* or *SSS* configuration at each phosphorus centre.* In the proton-decoupled ^{31}P NMR spectrum a single resonance was obtained, but in the presence of 2 equivalents of the chiral solvating agent 1-(9-anthryl)-2,2,2-trifluoroethanol[24] two singlets appeared in 1:1 ratio ($\Delta\delta_P$ = 0.19, 293 K, C$_6$D$_6$) consistent with the formation of the anisochronous diastereoisomeric complexes. The two enantiomers of [GaL^1] could also be resolved by chiral HPLC. Using as a chiral stationary phase the chiral triphenylmethyl methacrylate polymer [Daicel, 'Chiralcek' OT-(+); eluent MeOH], the two enantiomers eluted with a difference in retention time of 0.9 min (10 °C, t_R = 20.9 and 21.8 min). Using a semipreparative column, samples of the two enantiomers were obtained giving optical rotations of α (589 nm, 20 °C, 1.1 g 100 cm^{-3} in MeOH) = −85.7(2.0), and −87.5(2.0)° for the peaks at t_R 20.9 and 21.8 min (HPLC) respectively.

Biodistribution Studies of [^{111}InL^1] *and* [^{67}GaL^1].—Given that the ^{71}Ga NMR studies with [GaL^1] indicated that the complex was stable with respect to dissociation for at least 6 months in 6 mol dm^{-3} nitric acid, it was thought likely that the complex would remain intact *in vivo* for at least 3 half-lives (^{67}Ga, $t_{\frac{1}{2}}$ = 3.25 d). We have previously demonstrated that there is a strong correlation between the stability *in vivo* of a radiolabelled complex and its kinetic stability with respect to acid-catalysed dissociation.[2–4,22] Accordingly the ^{67}Ga-radiolabelled complex of H$_3$L^1 was prepared and its biodistribution examined in congenitally athymic nude mice as a function of time and the results compared to those obtained with the analogous complexes [^{67}GaL^4][25] and the PMe and P(CH$_2$Ph) analogues of H$_3$L^1.

Concentrations of radioactivity (^{67}Ga) in selected tissues after administration of each of these complexes† (*ca.* 2 nmol g^{-1}

---

* In all of the X-ray and solution NMR analyses this single diastereoisomer was formed. Similar behaviour has been observed in the [12]aneN$_4$ series, where *RRRR* and *SSSS* enantiomers are preferred.[1,3,22]

† Full details of this study, including a comparison with the ^{111}In-labelled complexes, and their behaviour in tumour-bearing animals, will be published separately.

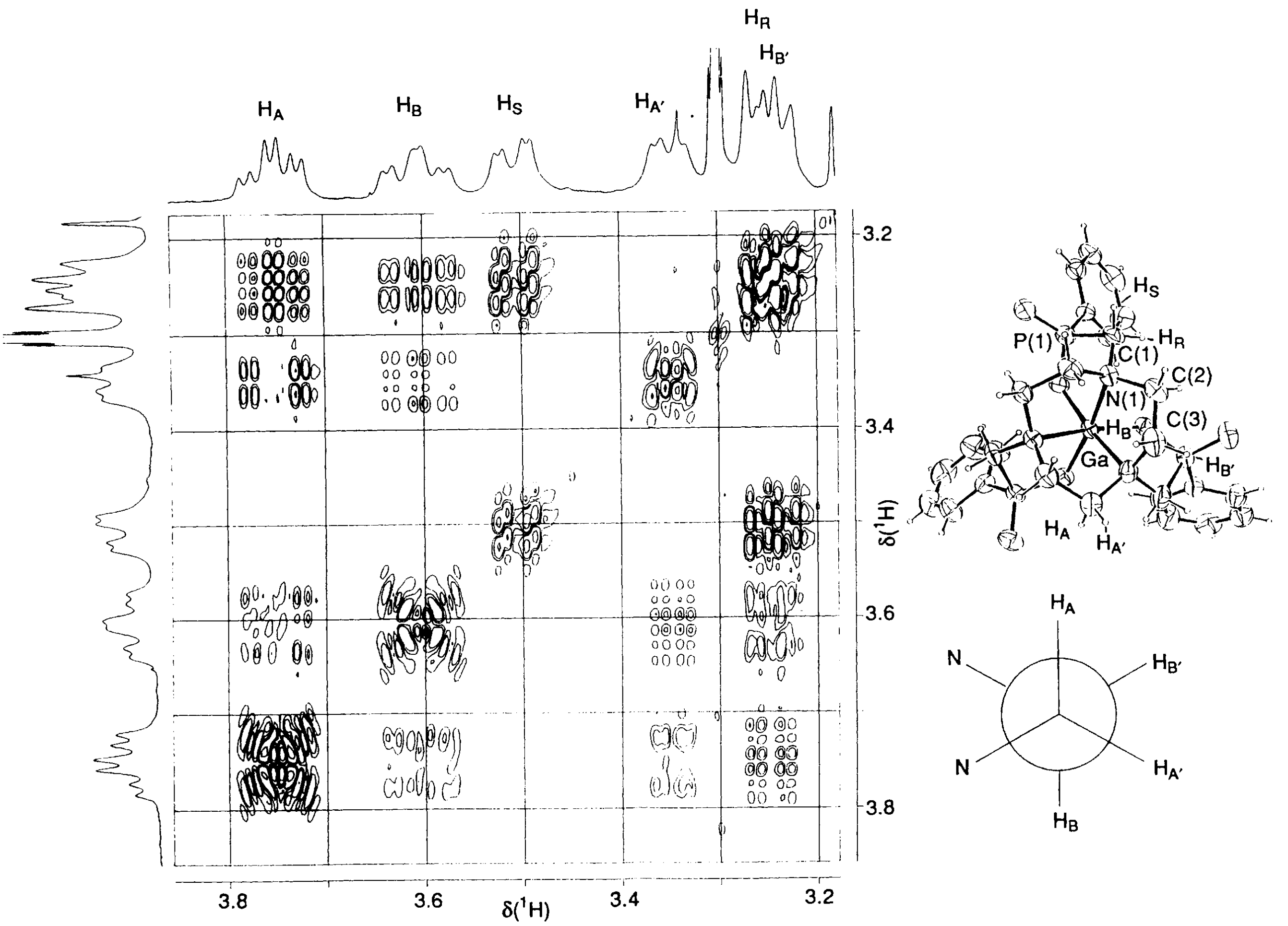


Fig. 4 The ^{1}H–^{1}H COSY NMR spectrum of [GaL^1] in the region δ 3–4 showing assignments of the AA′BB″ multiplet and of H$_S$ and H$_R$ on C(1)

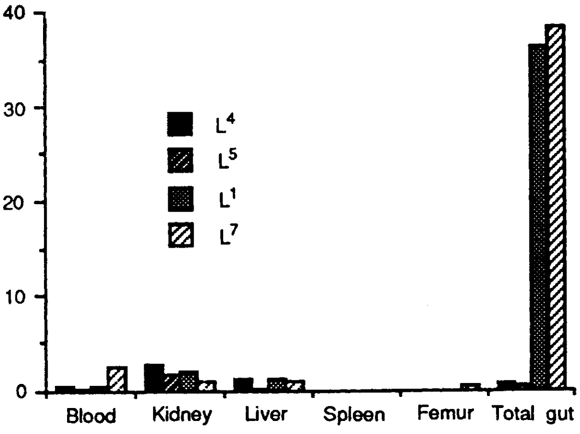


Fig. 5 Biodistribution in mice of [^{67}GaL^1] and the related complexes at 1 h in mice, compared to that of [GaL^4]

body mass, *i.e.* a tracer level) at 1 and 24 h are plotted in Figs. 5 and 6. In comparison gallium citrate clears much more slowly from the blood and non-selectively accumulates in various tissues, such as the liver, spleen and femur.[25] The high level of activity for [^{67}GaL^1] and the P(CH$_2$Ph) analogue in the biliary tract at 1 h (*e.g.* small and large intestine) is quite distinctive from the behaviour observed with the more hydrophilic complexes of H$_3$L^4 and H$_3$L^5 which clear exclusively *via* the kidney. By 24 h the activity has mostly cleared from the animal, although there is some hint that the P(CH$_2$Ph) complex is dissociating, given its higher relative concentrations in the blood, liver and spleen. The more lipophilic complexes [of L^1 and the P(CH$_2$Ph) analogue] are therefore preferentially and rapidly clearing from the animal *via* the biliary system (liver, gall bladder, intestines) and may therefore be of some interest in PET (positron emission tomography) imaging of the biliary tract with ^{68}Ga-labelled complexes (^{68}Ga, $t_{\frac{1}{2}}$ 68 min). It has previously been noted that the ^{68}Ga-labelled complex of H$_4$L^6 clears by both the kidney and the biliary route, but with little preference.[26]

Similar experiments were undertaken with ^{111}In-radiolabelled complexes. Again at 1 h (Fig. 7), the complexes of H$_3$L^1 and the P(CH$_2$Ph) analogue showed between 30 and 50% of the activity in the biliary tract whereas the hydrophilic complexes of H$_3$L^4 and the analogue H$_3$L^5 cleared *via* the renal system. However, for all the [9]aneN$_3$ 'phosphinate' indium complexes where the alkyl group R attached to P is Me, Ph, CH$_2$Ph and also Pr^i, at 24 h the biodistribution data revealed that there was significant retention of ^{111}In in the liver and femur compared to the behaviour of the carboxylate complex of H$_3$L^4. For example, for [^{111}InL^4] at 24 h, there was 0.002% of the injected dose per gram of tissue in the blood and 0.05% in both the liver and the femur. In contrast for [^{111}InL^1] there was 0.25% in the blood at this time and 0.84 and 0.80% in the liver and femur respectively. For both [^{111}InL^1] and the other phosphinate complexes there was on average 20 times as much of the radiolabel in the kidney or the liver at 24 h, compared to [^{111}InL^4]. It is apparent that, with these phosphinate complexes, premature dissociation of the ^{111}In radiolabel does occur *in vivo*, in contrast to the behaviour of the gallium-labelled complexes.

The relative lipophilicity of the indium-111 complexes was measured by studying the partition (log *P*) of the various radiolabelled complexes in water–octanol, octanol–phosphate-buffered saline, water–butanol and butanol–phosphate-buffered

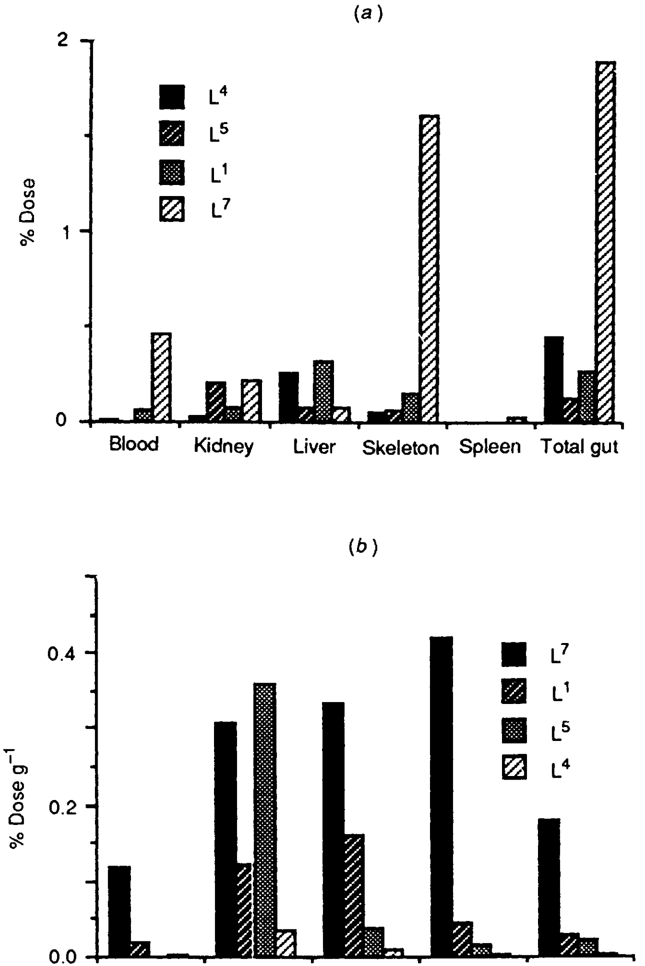


Fig. 6 (*a*) Biodistribution in mice of [^{67}GaL^1] and related complexes at 24 h. (*b*) Partial biodistribution (% injected dose per gram of tissue) in mice of [^{67}GaL^1] and related complexes at 24 h

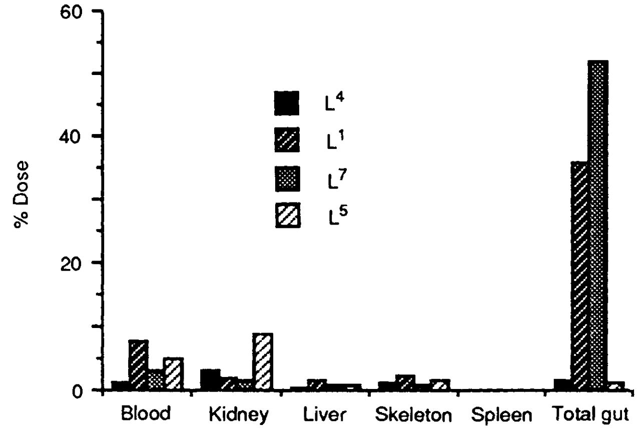


Fig. 7 Biodistribution of selected [^{111}InL] complexes at 1 h in mice

Table 4 Partition coefficient (log *P*) for ^{111}In-radiolabelled [9]aneN$_3$ macrocyclic complexes with e.s.d.s in parentheses[a]

	log *P*			
L	Octanol–water	Octanol–pbs	Butanol–water	Butanol–pbs
L^4	−4.92(29)	−4.51(46)	−2.54(04)	−2.98(04)
L^5	−3.80(11)	−3.68(31)	−1.88(02)	−2.06(01)
L$^{9\,b}$	−3.38(07)	−3.62(21)	−1.79(03)	−2.22(01)
L$^{8\,c}$	−1.92(02)	−1.89(04)	−0.98(12)	−0.99(13)
L$^{7\,d}$	+0.13(22)	+0.10(21)	+0.54(20)	+0.34(21)
L^1	+0.33(26)	+0.24(28)	+0.63(23)	+0.49(23)

[a] The correlation (linear regression, R^2) between the amount of the ^{111}In-radiolabelled complex found in the gut (at 1 h) and the measured log *P* value varied between 0.76 (octanol–water) and 0.81 (butanol–water). This was for all of the ^{111}In-labelled complexes discussed above. Full details will be reported elsewhere; pbs = phosphate-buffered saline. [b] H_3L^9 = *rac*-1,4,7-Triazacyclononane-*N*,*N*′,*N*″-tripropionic acid. [c] H_3L^8 = 1,4,7-Triazacyclononane-1,4,7-triyltrimethylenetris-(isopropylphosphinic acid). [d] H_3L^7 = 1,4,7-Triazacyclononane-1,4,7-triyltrimethylenetris(benzylphosphinic acid).

saline systems, Table 4. There is a reasonably good correlation between the log *P* values obtained and the amount of activity (^{67}Ga or ^{111}In) found in the gut at 1 h. Clearly, lipophilic *neutral* complexes of [9]aneN$_3$ derivatives clear selectively *via* the biliary system, but this mode of clearance cannot, presumably, involve the so-called 'anionic liver transporter',[22] given the charge neutrality of these complexes.

Experimental

Commercial solvents were dried from an appropriate drying agent prior to use according to standard procedures. Water was purified by the MilliQ or Purite system. Proton and carbon-13 NMR spectra were recorded on Bruker AC-250 (250.1 and 62.9 MHz respectively), Varian VXR-400 or Bruker AM 500 spectrometers, ^{31}P NMR spectra on a Bruker AC-250 spectrometer operating at 101.1 MHz. The ^{13}C and ^{1}H NMR chemical shifts are given to higher frequency of SiMe$_4$. Gallium-71 NMR spectra were recorded on the Bruker AC-250 at 76.2 MHz, with shifts given relative to [Ga(H$_2$O)$_6$]$^{3+}$ (6 mol dm^{-3} HNO$_3$, $\delta_{Ga} = 0$). Mass spectra were recorded with a VG 7070E spectrometer operating in positive-ion FAB mode, using glycerol or *m*-nitrobenzyl alcohol as the matrix. Infrared spectra were recorded as KBr discs or as a mull in Nujol with a Mattson Sirius 100 FT spectrometer. Melting points were determined on a Reichert–Köfler block and are uncorrected. Visible spectra were recorded with a Uvikon 930 spectrophotometer. The HPLC analyses and separations were effected with a Varian 5560 instrument fitted with a diode-array detector. The preparative separation of the metal complexes was carried out using a Daicel Chiralcel OT (+) column (J. T. Baker, UK).

Crystal structure data are presented in Table 5 together with the data collection, absorption correction and data analyses parameters. All data were collected with graphite-monochromated Mo-Kα radiation, λ = 0.710 73 Å. Room-temperature data for the complexes of Ni, Fe, Ga and Cu were recorded[7] on a CAD-4 diffractometer and all computations were carried out using the NCRVAX[27] system on a Silicon graphics 4D-35TG computer. The low-temperature data were measured on a Rigaku AFC-6S four-circle diffractometer fitted with an Oxford Cryostream cooling device. Structure solutions and refinements were effected using the CRYSTALS[28] program on a microVax 3300 computer, following data reductions with TEXSAN.[29] The molecular structures are shown in Figs. 1 and 2 for representative complexes giving the atomic numbering scheme. Selected molecular parameters are given in Table 6, atomic coordinates in Table 7.

Additional material available from the Cambridge Crystallographic Data Centre, comprises H-atom coordinates, thermal parameters and remaining bond lengths and angles. The data for the copper(II) and gallium(III) complexes have been deposited previously.[7]

The ligand H_3L^1 was prepared as its dihydrochloride salt according to our published procedure.[5]

Complex Preparation.—Two examples are representative.

[H$_3$O][CuL^1]·4H$_2$O. To a solution of $H_3L^1 \cdot 2HCl \cdot 2H_2O$

Table 5 Summary of cell data, data collection and refinement details

Compound	$[FeL^1]\cdot 5H_2O$	$[GaL^1]\cdot 5H_2O$	$[InL^1]\cdot 5H_2O$	$[H_3O][CoL^1]\cdot 4H_2O$	$[H_3O][NiL^1]\cdot 4H_2O$	$[H_3O][CuL^1]\cdot 4H_2O$	$[H_3O][ZnL^1]\cdot 4H_2O$
Formula	$C_{27}H_{43}FeN_3O_{11}P_3$	$C_{27}H_{43}GaN_3O_{11}P_3$	$C_{27}H_{43}InN_3O_{11}P_3$	$C_{27}H_{44}CoN_3O_{11}P_3$	$C_{27}H_{44}N_3NiO_{11}P_3$	$C_{27}H_{44}CuN_3O_{11}P_3$	$C_{27}H_{44}N_3O_{11}P_3\cdot Zn$
M	734.4	748.3	793.4	738.5	738.3	743.1	744.9
Colour, habit	Yellow block	Colourless block	Colourless prism	Pink prism	Sea-blue block	Blue prism	Colourless prism
Crystal size/mm	0.15 × 0.15 × 0.20	0.25 × 0.14 × 0.10	0.30 × 0.40 × 0.45	0.25 × 0.25 × 0.25	0.15 × 0.15 × 0.20	0.09 × 0.15 × 0.22	0.35 × 0.35 × 0.35
Crystal system	Triclinic	Triclinic	Triclinic	Trigonal	Trigonal	Trigonal	Trigonal
Space group	$P\bar{1}$	$P\bar{1}$	$P\bar{1}$	$P\bar{3}$	$P\bar{3}$	$P\bar{3}$	$P\bar{3}$
a/Å	11.941(7)	11.883(3)	12.061(3)	14.426(3)	14.356(1)	14.399(3)	14.412(2)
b/Å	12.4275(8)	12.468(4)	12.261(2)	14.426(3)	14.356(1)	14.399(3)	14.412(2)
c/Å	11.9678(9)	11.842(5)	12.128(4)	8.907(4)	9.042(6)	9.023(2)	8.933(4)
α/°	98.525(6)	99.39(1)	96.69(2)	90	90	90	90
β/°	99.522(6)	98.47(1)	101.24(2)	90	90	90	90
γ/°	79.155(6)	79.97(1)	77.72(2)	120	120	120	120
U/Å^3	1707.7(2)	1691.7(4)	1713.5(7)	1605.5(7)	1613.9(2)	1620.0(4)	1607.5(6)
Z	2	2	2	2	2	2	2
F(000)	770	780	816	774	776	778	780
Molecular symmetry	Approx. three-fold	Approx. three-fold	Approx. three-fold	Three-fold	Three-fold	Three-fold	Three-fold
D_c/g cm^{-3}	1.43	1.47	1.538	1.528	1.519	1.522	1.539
μ/cm^{-1}	6.3	10.1	8.9	7.5	8.1	8.8	9.8
Minimum, maximum absorption correction	0.934, 0.998	0.870, 0.912	Empirical 0.897–1.00	Empirical 0.950–100	0.797, 0.833	0.877, 0.931	Empirical 0.939–1.00
2θ range/°	4–54	4–54	6–56	5–50	4–54	4–54	5–60
T/K	294	294	150	120	294	294	120
Reflections measured	7429	7702	8634	2153	3887	3893	3495
Reflections unique	7429	7362	8250	1896	238	2360	3133
Reflections with $I \geqslant 3\sigma(I)$	4456	3149	7456	1318	1288	1254	2403
R, *R'*, goodness of fit	0.38, 0.045, 1.24	0.051, 0.059, 1.19	0.0199, 0.0233, 1.10	0.0339, 0.0338, 1.09	0.040, 0.041, 1.32	0.040, 0.045, 1.39	0.0308, 0.0340, 1.09
Minimum, maximum density in final Δ map/e Å^{-3}	−0.39, 0.35	−0.49, 0.50	−0.27, 0.40	−0.37, 0.41	−0.39, 0.32	−0.46, 0.44	−0.67, 0.55

Table 6 Selected molecular dimensions (distances in Å, angles in °) with e.s.d.s in parentheses

(*a*) $[FeL^1]\cdot 5H_2O$							
Fe–O(11)	1.938(2)	Fe–N(7)	2.206(3)	O(11)–Fe–O(21)	100.5(1)	O(21)–Fe–O(31)	100.6(1)
Fe–O(21)	1.931(2)	P(1)–O(11)	1.535(2)	O(11)–Fe–O(31)	99.7(1)	N(1)–Fe–N(4)	79.4(1)
Fe–O(31)	1.928(2)	P(1)–O(12)	1.496(2)	O(11)–Fe–N(1)	83.7(1)	N(1)–Fe–N(7)	78.9(1)
Fe–N(1)	2.217(3)	P(1)–C(1)	1.830(3)	O(11)–Fe–N(4)	163.0(1)	N(4)–Fe–N(7)	79.6(1)
Fe–N(4)	2.192(3)			O(11–Fe–N(7)	95.4(1)		
(*b*) $[InL^1]\cdot 5H_2O$							
In–O(11)	2.0995(9)	In–N(7)	2.306(1)	O(11)–In–O(21)	101.12(4)	O(21)–In–O(31)	100.81(4)
In–O(21)	2.0927(9)	P(11)–O(11)	1.540(1)	O(11)–In–O(31)	99.95(4)	N(1)–In–N(4)	78.61(4)
In–O(31)	2.0918(9)	P(1)–O(12)	1.498(1)	O(11)–In–N(1)	82.27(4)	N(1)–In–N(7)	78.08(4)
In–N(1)	2.314(1)	P(1)–C(1)	1.843(1)	O(11)–In–N(4)	160.82(4)	N(4)–In–N(7)	78.49(4)
In–N(4)	2.289(1)			O(11)–In–N(7)	96.21(4)		
(*c*) $[GaL^1]\cdot 5H_2O$							
Ga–O(11)	1.917(4)	Ga–N(7)	2.139(5)	O(11)–Ga–O(21)	96.2(2)	O(21)–Ga–O(31)	96.5(2)
Ga–O(21)	1.908(4)	P(1)–O(11)	1.533(5)	O(11)–Ga–O(31)	95.7(2)	N(1)–Ga–N(4)	82.3(2)
Ga–O(31)	1.911(4)	P(1)–O(12)	1.489(5)	O(11)–Ga–N(1)	86.1(2)	N(1)–Ga–N(7)	82.0(2)
Ga–N(1)	2.146(5)	P(1)–C(1)	1.846(8)	O(11)–Ga–N(4)	168.3(2)	N(4)–Ga–N(7)	82.2(2)
Ga–N(4)	2.121(5)			O(11)–Ga–N(7)	94.7(2)		
(*d*) $[H_3O][CoL^1]\cdot 4H_2O$ *							
Co–O(1)	2.103(2)	P(1)–O(2)	1.511(2)	O(1)–Co–O(1A)	96.7(1)	O(1)–Co–N(1B)	167.3(1)
Co–N(1)	2.168(3)	P(1)–C(4)	1.838(3)	O(1)–Co–N(1)	85.0(1)	N(1)–Co–N(1A)	82.3(1)
P(1)–O(1)	1.525(3)	N(1)–C(2)	1.496(4)	O(1)–Co–N(1A)	95.6(1)	O(1)–P(1)–O(2)	117.7(2)
(*e*) $[H_3O][NiL^1]\cdot 4H_2O$							
Ni–O(1)	2.083(3)	P(1)–O(2)	1.506(3)	O(1)–Ni–O(1A)	94.23(12)	O(1)–Ni–N(1B)	95.29(18)
Ni–N(1)	2.104(3)	P(1)–C(4)	1.836(4)	O(1)–Ni–N(1)	86.08(11)	N(1)–Ni–N(1A)	84.36(12)
P(1)–O(1)	1.518(3)	N(1)–C(2)	1.487(5)	O(1)–Ni–N(1A)	170.43(11)	O(1)–P(1)–O(2)	117.83(16)
(*f*) $[H_3O][ZnL^1]\cdot 4H_2O$							
Zn–O(1)	2.072(1)	P(1)–O(2)	1.512(1)	O(1)–Zn–O(1A)	97.97(4)	O(1)–Zn–N(1B)	165.73(4)
Zn–N(1)	2.218(1)	P(1)–C(4)	1.842(1)	O(1)–Zn–N(1)	84.99(4)	N(1)–Zn–N(1A)	80.83(5)
P(1)–O(1)	1.529(1)	N(1)–C(2)	1.491(2)	O(1)–Zn–N(1A)	95.42(5)	O(1)–P(1)–O(2)	117.50(7)
(*g*) $[H_3O][CuL^1]\cdot 4H_2O$							
Cu–O(1)	2.099(3)	P(1)–O(2)	1.505(3)	O(1)–Cu–O(1A)	95.06(9)	N(1)–Cu–N(1A)	83.10(13)
Cu–N(1)	2.134(3)	P(1)–C(4)	1.842(4)	O(1)–Cu–N(1)	85.90(11)	O(1)–P(1)–O(2)	117.52(17)
Cu–O(W1)	3.554(8)	N(1)–C(2)	1.486(5)	O(1)–Cu–N(1A)	95.78(11)	O(1)–P(1)–C(4)	104.80(17)
P(1)–O(1)	1.515(3)			O(1)–Cu–N(1B)	168.99(11)		

* Symmetry equivalents: A $1 - y, x - y, z$; B $1 - x + y, 1 - x, z$.

(0.23 g, 0.33 mmol) in water (2 cm^3) was added aqueous copper(II) nitrate solution (0.01 mol dm^{-3}, 33 cm^3) and the solution was heated to 60 °C for 2 min and then left to cool. On standing for 2 d, blue crystals were deposited which were filtered off and allowed to dry in air (196 mg, 80%) (Found: C, 43.4; H, 6.20; Cu, 8.25; N, 5.60; P, 12.2. $C_{27}H_{36}CuN_3O_7P_3\cdot 4H_2O$ requires C, 43.6; H, 5.95; Cu, 8.55; N, 5.65; P, 12.5%); λ_{max}(water): 700 nm (ε 82 dm^3 mol^{-1} cm^{-1}); no change in this absorption band was noted in the range pH 2.2–10.2. FAB mass spectrum (glycerol): *m*/*z* 654 (M^+).

$[GaL^1]\cdot 5H_2O$. To an aqueous solution of gallium(III) nitrate (30 cm^3, 0.01 mol dm^{-3}) was added H_3L^1 as a solid (210 mg, 0.3 mmol) and the solution was left to stand for 4 d. The colourless crystals which had formed were filtered off and dried in air (206 mg, 92%) (Found: C, 43.3; H, 5.70; N, 5.25; P, 12.0. $C_{27}H_{33}GaN_3O_6P_3\cdot 5H_2O$ requires C, 43.2; H, 5.75; N, 5.60; P, 12.4%); δ_P(CD_3OD): 27.36; δ_{Ga}(CD_3OD) 132.0 ($w_{\frac{1}{2}}$ 560 Hz); δ_C(CD_3OD) 53.36 ($CH_BH_{B'}N$ ring), 57.61 (d, $CH_AH_{A'}N$ ring, $^3J_{PC} = 12.5$), 61.6 (d, NCH_2P, $^1J = 91$), 133.8 (d, PPh, $^1J = 141$), 133.4 (m, *o*- and *p*-C of Ph) and 129.7 (d, *m*-C of Ph, $^3J = 13.4$ Hz); δ_H(CD_3OD) 8.04 (6 H, dd, *o*-H, $^3J = 7.2$, $^3J_{PH} = 12.4$), 7.56 (3 H, dt, *p*-H, $^3J = 7.1$, $^4J = 1.1$), 7.46 (6 H, dt, *m*-H, $^3J = 7.2$, $^4J_{PH} = 3.2$), 3.75 [3 H, ddd, $^2J(H_AH_{A'}) = -14$, $^3J(H_AH_B) = 13.8$, $^3J(H_AH_{B'}) = 5.5$, CH_AN part of the AA′BB′ system where A and B represent the 'axial protons': see text for a discussion], 3.61 [3 H, ddd, CH_BN, $^2J(H_BH_{B'}) = -16.8$], 3.51 (3 H, dd, NCHP, $^2J = -14.1$, $^2J_{PH} = 4.6$ Hz), 3.35 (3 H, dd, $CH_{A'}N$) and 3.25 (6 H, dd + dd, $CH_{B'}N$ + NCHP). FAB mass spectrum (*m*-nitrobenzyl alcohol): *m*/*z* 749.3 ($M^+ + 1$) and 748.2 (M^+).

The following complexes were prepared in a similar manner.

$[H_3O][NiL^1]\cdot 4H_2O$ (Found: C, 43.2; H, 6.10; N, 5.60; Ni, 7.40; P, 12.8. $C_{27}H_{36}N_3NiO_7P_3\cdot 4H_2O$ requires C, 42.9; H, 6.10; N, 5.55; Ni, 7.75; P, 12.3%). FAB mass spectrum (glycerol) *m*/*z* 648 (M^+); λ_{max}(water) 790 and 610 nm.

$[H_3O][CoL^1]\cdot 4H_2O$ (Found: C, 43.5; H, 6.05; Co, 8.55; N, 5.55; P, 12.0. $C_{27}H_{36}CoN_3O_7P_3\cdot 4H_2O$ requires C, 43.9; H, 5.95; Co, 8.00; N, 5.70; P, 12.5%): FAB mass spectrum (glycerol) *m*/*z* 648 (M^+); λ_{max}(water) 521 nm.

$[H_3O][ZnL^1]\cdot 4H_2O$ (Found: C, 43.5; H, 6.05; N, 5.65; Zn, 8.15. $C_{27}H_{36}N_3O_7P_3Zn\cdot 4H_2O$ requires C, 43.5; H, 5.90; N, 5.65; Zn, 8.75%): mass spectrum FAB (glycerol) *m*/*z* 654 (M^+); δ_P(CD_3OD) 31.2; δ_C(CD_3OD) 135.10 (d, PC, $^1J = 140$), 133.34 (d, *m*-C of Ph, $^3J_{PC} = 7$), 133.0 (br s, *p*-C), 129.5 (d, PC*C*, $^2J = 13$), 61.53 (d, NCH_2P, $^1J = 100$ Hz), 59.05 (CH_2N ring) and 53.06 (CH_2N ring); δ_H(CD_3OD) 8.00 (6 H, br, m, *o*-H of Ph), 7.4 (6 H, br m, *m*- and *p*-H of Ph), 3.32 (6 H, br dd, NCH_2P) and 2.91 (12 H, br, CH_2N).

$[FeL^1]\cdot 5H_2O$ (Found: C, 44.2; H, 5.90; Fe, 7.60; N, 5.65; P, 12.3. $C_{27}H_{33}FeN_3O_6P_3\cdot 5H_2O$ requires C, 44.1; H, 5.90; Fe, 7.60; N, 5.70; P, 12.65%); δ_P(CD_3OD) 31.4; FAB mass spectrum (glycerol) *m*/*z* 644 (M^+).

$[InL^1]\cdot 5H_2O$. (Found: C, 41.1; H, 5.80; N, 5.30; P, 11.4. $C_{27}H_{33}InN_3O_6P_3\cdot 5H_2O$ requires C, 40.8; H, 5.40; N, 5.30; P, 11.7%); δ_P(CD_3OD) 32.5; FAB mass spectrum (glycerol) *m*/*z* 704 (M^+).

Table 7 Fractional atomic coordinates

Atom	x	y	z	Atom	x	y	z
(*a*) $[\mathrm{FeL^1}]\cdot5\mathrm{H_2O}$							
Fe	0.199 86(4)	0.233 70(4)	0.158 97(4)	C(8)	0.417 24(28)	0.080 78(27)	0.113 15(31)
P(1)	0.183 90(8)	0.135 57(7)	−0.091 6(7)	C(9)	0.337 14(31)	−0.001 8(27)	0.111 23(31)
P(2)	−0.013 53(8)	0.257 36(8)	0.276 72(8)	C(11)	0.060 13(29)	0.172 65(26)	−0.194 00(28)
P(3)	0.359 43(8)	0.404 33(7)	0.230 97(7)	C(12)	0.054 07(32)	0.121 36(30)	−0.305 28(31)
O(11)	0.198 83(20)	0.236 29(17)	−0.002 69(18)	C(13)	−0.039 83(37)	0.151 35(35)	−0.385 21(33)
O(12)	0.286 89(20)	0.083 61(19)	−0.148 31(20)	C(14)	−0.127 9(36)	0.232 31(38)	−0.354 68(39)
O(21)	0.036 53(18)	0.259 31(18)	0.166 33(19)	C(15)	−0.123 61(37)	0.281 92(38)	−0.245 01(43)
O(22)	−0.078 88(21)	0.166 60(20)	0.275 92(24)	C(16)	−0.030 36(35)	0.253 57(33)	−0.163 90(35)
O(31)	0.236 22(19)	0.378 21(17)	0.216 49(18)	C(21)	−0.097 34(29)	0.390 52(29)	0.310 89(29)
O(32)	0.411 07(22)	0.440 14(19)	0.349 07(20)	C(22)	−0.198 54(34)	0.399 13(32)	0.356 67(34)
N(1)	0.214 24(23)	0.052 92(21)	0.110 44(23)	C(23)	−0.266 29(38)	0.501 33(36)	0.377 08(38)
N(4)	0.213 647(23)	0.178 00(22)	0.326 91(22)	C(24)	−0.234 72(42)	0.593 25(34)	0.352 13(39)
N(7)	0.387 77(22)	0.180 38(21)	0.195 08(22)	C(25)	−0.133 74(47)	0.586 62(36)	0.309 65(46)
C(1)	0.145 68(30)	0.041 70(27)	−0.005 28(30)	C(26)	−0.064 64(38)	0.484 89(33)	0.288 89(40)
C(2)	0.158 91(31)	0.013 39(27)	0.195 54(32)	C(31)	0.359 55(29)	0.504 14(26)	0.136 72(28)
C(3)	0.207 03(32)	0.057 50(29)	0.315 64(31)	C(32)	0.433 08(36)	0.579 56(35)	0.165 30(35)
C(4)	0.117 21(30)	0.248 11(30)	0.381 2(29)	C(33)	0.428 51(44)	0.660 31(38)	0.094 08(44)
C(5)	0.327 1(29)	0.202 16(29)	0.388 67(28)	C(34)	0.353 26(47)	0.664 63(38)	−0.001 60(42)
C(6)	0.421 72(29)	0.155 87(29)	0.316 27(30)	C(35)	0.280 07(48)	0.588 96(45)	−0.032 33(39)
C(7)	0.438 78(28)	0.274 05(27)	0.171 29(29)	C(36)	0.283 39(39)	0.507 60(36)	0.036 90(34)
(*b*) $[\mathrm{InL^1}]\cdot5\mathrm{H_2O}$							
In	0.189 863(7)	0.244 941(7)	0.151 288(7)	C(12)	0.052 1(1)	0.117 0(1)	−0.317 3(1)
P(1)	0.177 50(3)	0.141 15(3)	−0.100 86(3)	C(13)	−0.043 9(1)	0.143 7(1)	−0.401 5(1)
P(2)	−0.024 62(3)	0.262 85(3)	0.270 35(3)	C(14)	−0.137 5(1)	0.224 7(1)	−0.378 5(1)
P(3)	0.356 60(3)	0.416 02(3)	0.230 75(3)	C(15)	−0.136 5(1)	0.278 9(1)	−0.271 2(2)
O(11)	0.184 29(8)	0.248 63(8)	−0.022 36(8)	C(16)	−0.041 5(1)	0.253 2(1)	−0.186 6(1)
O(12)	0.283 73(8)	0.088 01(9)	−0.148 45(8)	C(21)	−0.109 5(1)	0.395 2(1)	0.310 4(1)
O(21)	0.014 04(8)	0.276 21(9)	0.159 33(8)	C(22)	−0.204 1(1)	0.399 4(1)	0.362 1(1)
O(22)	−0.085 41(9)	0.168 37(9)	0.268 1(1)	C(23)	−0.272 6(1)	0.502 2(1)	0.388 3(1)
O(31)	0.229 89(8)	0.401 94(8)	0.208 72(8)	C(24)	−0.247 7(2)	0.600 0(1)	0.363 2(1)
O(32)	0.407 63(9)	0.444 76(8)	0.350 56(8)	C(25)	−0.152 6(2)	0.596 3(2)	0.314 1(2)
N(1)	0.211 18(9)	0.054 25(9)	0.103 79(9)	C(26)	−0.083 1(2)	0.494 6(2)	0.287 9(2)
N(4)	0.207 76(9)	0.178 19(9)	0.323 77(9)	C(31)	0.365 5(1)	0.519 1(1)	0.140 9(1)
N(7)	0.386 73(9)	0.186 00(9)	0.196 94(9)	C(32)	0.446 6(1)	0.587 0(1)	0.172 7(1)
C(1)	0.144 1(1)	0.044 0(1)	−0.012 6(1)	C(33)	0.449 1(2)	0.670 3(2)	0.104 9(2)
C(2)	0.156 8(1)	0.014 6(1)	0.188 6(1)	C(34)	0.372 0(2)	0.684 9(1)	0.005 9(2)
C(3)	0.204 8(1)	0.055 8(1)	0.309 1(1)	C(35)	0.292 6(2)	0.617 2(2)	−0.026 9(2)
C(4)	0.110 2(1)	0.246 9(1)	0.374 9(1)	C(36)	0.288 6(2)	0.533 6(2)	0.040 0(1)
C(5)	0.321 2(1)	0.201 3(1)	0.385 6(1)	O(100)	0.303 08(9)	−0.133 09(9)	−0.246 9(1)
C(6)	0.418 3(1)	0.156 9(1)	0.317 1(1)	O(200)	0.573 2(1)	0.353 07(9)	0.525 0(1)
C(7)	0.435 6(1)	0.281 8(1)	0.175 8(1)	O(300)	0.583 9(1)	0.156 8(1)	0.613 9(1)
C(8)	0.414 6(1)	0.087 1(1)	0.116 2(1)	O(400)	0.297 1(1)	−0.039 5(1)	−0.448 7(1)
C(9)	0.336 4(1)	0.002 0(1)	0.112 2(1)	O(500)	0.393 2(1)	0.124 1(1)	−0.316 7(1)
C(11)	0.053 5(1)	0.172 4(1)	−0.209 6(1)				
(*c*) $[\mathrm{GaL^1}]\cdot5\mathrm{H_2O}$							
Ga	0.207 63(6)	0.224 13(6)	0.165 63(7)	C(12)	−0.025 0(7)	−0.252 6(7)	−0.152 7(7)
P(1)	0.187 1(2)	0.134 6(2)	−0.086 7	C(13)	−0.118 9(7)	−0.281 6(7)	−0.231 3(8)
P(2)	−0.010 2(2)	0.256 2(2)	0.227 2(2)	C(14)	−0.124 3(7)	0.232 9(8)	−0.343 1(8)
P(3)	0.357 6(2)	0.400 8(2)	0.232 3(2)	C(15)	−0.036 8(7)	0.152 5(7)	−0.378 8(7)
O(11)	0.206 1(4)	0.233 7(4)	0.005 4(4)	C(16)	0.058 1(6)	0.122 2(6)	−0.300 2(7)
O(12)	0.288 5(4)	0.082 9(4)	−0.148 4(4)	C(21)	−0.093 3(6)	0.388 8(6)	0.307 9(6)
O(21)	0.044 6(3)	0.253 2(4)	0.165 9(4)	C(22)	−0.197(7)	0.399 7(7)	0.353 6(7)
O(22)	−0.078 1(4)	0.167 2(4)	0.278 1(5)	C(23)	−0.265 0(7)	0.501 2(8)	0.327 0(8)
O(31)	0.234 7(4)	0.371 5(3)	0.220 2(4)	C(24)	−0.231 6(8)	0.591 5(7)	0.345 0(8)
O(32)	0.408 8(4)	0.439 0(4)	0.349 8(4)	C(25)	−0.128 2(9)	0.583 2(7)	0.302 1(9)
N(1)	0.215 4(4)	0.050 1(4)	0.113 7(5)	C(26)	0.058 5(7)	0.481 9(7)	0.283 8(8)
N(4)	0.215 8(5)	0.178 5(5)	0.331 8(5)	C(31)	0.355 6(6)	0.499 1(6)	0.136 4(6)
N(7)	0.390 4(4)	0.178 7(4)	0.196 7(5)	C(32)	0.430 0(7)	0.576 3(7)	0.164 3(7)
C(1)	0.148 4(6)	0.038 2(6)	−0.001 6(6)	C(33)	0.424 2(8)	0.655 6(7)	0.093 8(9)
C(2)	0.160 4(6)	0.012 0(6)	0.200 6(7)	C(34)	0.349 0(10)	0.667 6(8)	−0.003 1(9)
C(3)	0.208 0(6)	0.058 5(6)	0.322 5(7)	C(35)	0.277 0(9)	0.580 9(9)	−0.031 7(8)
C(4)	0.116 9(6)	0.250 9(6)	0.385 0(6)	C(36)	0.280 0(7)	0.500 6(7)	0.037 5(7)
C(5)	0.328 9(6)	0.204 4(6)	0.393 2(6)	O(W1)	0.301 9(5)	0.138 7(5)	−0.238 7(6)
C(6)	0.424 2(6)	0.156 8(6)	0.317 6(6)	O(W2)	0.569 3(6)	0.355 0(5)	0.525 2(5)
C(7)	0.439 6(6)	0.272 1(6)	0.317 6(6)	O(W3)	0.586 9(0)	0.161 9(0)	0.616 4(0)
C(8)	0.420 0(6)	0.078 3(6)	0.112 8(6)	O(W4)	0.295 0(8)	0.050 3(7)	−0.448 1(7)
C(9)	0.338 1(6)	−0.004 3(6)	0.114 0(6)	O(W5)	0.388 9(7)	0.116 0(7)	−0.331 7(8)
C(11)	0.063 4(6)	0.173 5(6)	−0.187 0(6)				

Table 7 (*continued*)

Atom	x	y	z	Atom	x	y	z
(*d*) $[H_3O][CoL^1]\cdot 4H_2O$							
Co	$\frac{2}{3}$	$\frac{1}{3}$	0.446 19(7)	C(12)	0.263 1(2)	0.013 1(2)	0.218 6(4)
P(1)	0.426 44(6)	0.178 87(6)	0.380 51(8)	C(13)	0.218 4(3)	−0.056 1(3)	0.097 0(4)
O(1)	0.523 4(2)	0.282 4(2)	0.326 9(2)	C(14)	0.285 1(3)	−0.051 0(3)	−0.019 3(4)
O(2)	0.336 1(2)	0.186 6(2)	0.454 0(2)	C(15)	0.393 4(3)	0.020 8(3)	−0.014 2(4)
N(1)	0.567 5(2)	0.208 5(2)	0.604 5(3)	C(16)	0.437 5(2)	0.088 9(3)	0.108 0(4)
C(2)	0.525 4(2)	0.253 3(2)	0.720 0(3)	O(100)	0.185 4(2)	0.262 2(2)	0.637 4(3)
C(3)	0.640 5(2)	0.174 8(2)	0.671 0(3)	O(200)	0	0	0.693 7(5)
C(4)	0.481 6(2)	0.121 7(2)	0.513 8(3)	O(300)	$\frac{2}{3}$	$\frac{1}{3}$	0.054 4(6)
C(11)	0.372 0(2)	0.086 0(2)	0.224 6(3)				
(*e*) $[H_3O][NiL^1]\cdot 4H_2O$							
Ni	$\frac{2}{3}$	$\frac{1}{3}$	0.454 07(10)	C(3)	0.640 35(32)	0.174 33(31)	0.666 66(47)
P(1)	0.429 04(8)	0.183 47(8)	0.379 52(13)	C(4)	0.481 90(31)	0.123 59(30)	0.510 59(47)
O(1)	0.527 55(21)	0.287 28(20)	0.331 28(31)	C(11)	0.375 42(33)	0.091 76(33)	0.225 72(48)
O(2)	0.338 01(21)	0.191 05(23)	0.450 04(34)	C(12)	0.266 05(36)	0.018 61(37)	0.217 22(56)
O(W1)	0.189 34(27)	0.030 17(25)	0.636 22(42)	C(13)	0.223 55(44)	−0.048 58(42)	0.097 82(70)
O(W2)	0	0	0.687 65(90)	C(14)	0.289 54(56)	−0.043 85(44)	−0.014 19(64)
O(W3)	$\frac{2}{3}$	$\frac{1}{3}$	0.052 88(87)	C(15)	0.397 07(53)	0.027 01(46)	−0.008 67(63)
N(1)	0.567 41(24)	0.209 40(26)	0.601 01(38)	C(16)	0.440 22(39)	0.094 24(41)	0.111 73(59)
C(2)	0.524 95(32)	0.253 69(33)	0.714 23(48)				
(*f*) $[H_3O][ZnL^1]\cdot 4H_2O$							
Zn	$\frac{2}{3}$	$\frac{1}{3}$	0.440 54(3)	C(12)	0.263 1(1)	0.013 3(1)	0.218 7(2)
P(1)	0.426 57(3)	0.179 25(3)	0.380 13(5)	C(13)	0.219 6(2)	−0.055 6(2)	0.096 7(2)
O(1)	0.524 06(9)	0.282 99(9)	0.326 7(1)	C(14)	0.286 2(2)	−0.050 0(2)	−0.019 6(2)
O(2)	0.336 31(9)	0.187 8(1)	0.452 7(1)	C(15)	0.395 1(2)	0.022 7(2)	−0.013 7(2)
N(1)	0.566 4(1)	0.207 4(1)	0.605 2(1)	C(16)	0.438 9(1)	0.090 5(2)	0.107 8(2)
C(2)	0.525 0(1)	0.253 1(1)	0.719 4(2)	O(100)	0.186 8(1)	0.027 9(1)	0.637 1(2)
C(3)	0.640 2(1)	0.174 4(1)	0.670 0(2)	O(200)	0	0	0.693 6(3)
C(4)	0.480 6(1)	0.121 4(1)	0.514 4(2)	O(300)	$\frac{2}{3}$	$\frac{1}{3}$	0.053 7(4)
C(11)	0.372 6(1)	0.087 1(1)	0.225 0(2)				
(*g*) $[H_3O][CuL^1]\cdot 4H_2O$							
Cu	$\frac{1}{3}$	$\frac{2}{3}$	0.450 48(10)	C(12)	0.734 1(4)	0.752 5(4)	0.217 3(6)
P(1)	0.571 65(8)	0.754 81(9)	0.379 11(14)	C(13)	0.778 4(4)	0.728 8(5)	0.099 3(4)
O(1)	0.474 16(23)	0.760 31(23)	0.328 6(3)	C(14)	0.711 8(5)	0.667 4(5)	−0.013 0(6)
O(2)	0.661 68(22)	0.853 43(23)	0.450 1(4)	C(15)	0.603 3(5)	0.629 7(5)	−0.008 0(6)
N(1)	0.433 09(23)	0.642 91(24)	0.602 6(4)	C(16)	0.561 0(4)	0.635 3(4)	0.111 5(6)
C(2)	0.475 0(3)	0.729 5(3)	0.715 8(5)	O(W1)	$\frac{1}{3}$	$\frac{2}{3}$	0.056 6(9)
C(3)	0.360 4(3)	0.535 1(3)	0.667 2(5)	O(W2)	1	1	0.689 8(10)
C(4)	0.519 0(3)	0.642 7(3)	0.511 9(5)	O(W3)	0.808 0(3)	0.838 9(3)	0.636 9(4)
C(11)	0.625 0(3)	0.716 1(3)	0.225 2(5)				

$[CoL^1]\cdot 5H_2O$. This complex was prepared as above except that hydrogen peroxide (100%, 5 cm^3) was added to the pink aqueous solution of the cobalt(II) complex. After standing in air at 20 °C for 2 weeks, dark blue crystals had formed which were filtered off and dried in air (yield 35%) (Found: C, 43.6; H, 6.00; N, 5.50. $C_{27}H_{33}CoN_3O_6P_3\cdot 5H_2O$ requires C, 43.9; H, 5.80; N, 5.70%); δ_P(CD_3OD) 58.7; δ_C(CD_3OD) 134.17 (d, PC, ^1J = 138), 132.7 (d, *m*-C, ^3J = 14), 132.3 (s, *p*-C), 128.11 (d, *o*-C, ^2J = 12), 65.90 (d, NCH_2P, ^1J = 85 Hz), 65.05 (s, CH_2N) and 61.55 (s, CH_2N); δ_H(CD_3OD) 8.33 (6 H, dd, *o*-H), 7.71 (3 H, td, *p*-H), 7.55 (6 H, td, *m*-H), 4.36 (3 H, ddd, CHN), 4.10 (3 H, ddd, CHN 'equatorial'), 3.85 (3 H, dd, NCHP), 3.55 (3 H, dd, CH'N 'axial') and 3.34–3.21 (6 H, dd + dd, NCH'P + NCH' 'axial'); λ_{max}(water) 565 nm.

Biodistribution Studies and Measurement of Partition Coefficients.—The methods used to evaluate the biodistribution of the ^{111}In- and ^{67}Ga-radiolabelled complexes in mice were as reported earlier.[25]

For the measurement of the partition coefficients of the ^{111}In-radiolabelled complexes, the following procedure was used. To a solution of the given macrocyclic ligand (10 µl of a 20 mmol dm^{-3} aqueous solution) was added 100 µCi (3.7×10^6 Bq) of $^{111}InCl_3$ (Amersham) plus 10% of indium chloride in ammonium acetate (0.2 mol dm^{-3}, pH 5) to give a total volume of 100 µl. After 15–30 min at 37 °C the mixture was quenched with a 10-fold excess of diethylenetriamine-*N*,*N*,*N*′,*N*″,*N*″-pentaacetic acid) and the radiolabelled [9]aneN_3 complex was separated by HPLC on a Poros Q/M column with the eluent (2 cm^3 min^{-1}) aqueous ammonium acetate (0.15 mol dm^{-3}, pH 6.8).

Four different mixtures (1 : 1 v/v) were used, comprising (*a*) octanol–water, (*b*) octanol–phosphate-buffered saline (pH 7.3, Dulbeccos-A), (*c*) butanol–water and (*d*) butanol–phosphate-buffered saline (pH 7.3). All solvents were 'saturated with their partner' (*i.e.* allowed to equilibrate for 3 h) before certain volumes for the experiment were dispensed. For each of the above mixtures, three different volume ratios were employed: 0.5 cm^3 + 0.5 cm^3, 0.75 cm^3 + 0.25 cm^3 and 0.25 cm^3 + 0.75 cm^3. To each of these mixtures was added 10 µl of a solution containing the ^{111}In-radiolabelled [9]aneN_3 macrocycle (in 0.15 mol dm^{-3} ammonium acetate, pH 6.8). The solutions were shaken for 1 h, and then centrifuged for 2 min to allow the phases to separate. Duplicate samples (100 µl each) were taken from each phase of each tube and were counted for radioactivity (LKB Compugamma).

The value of the partition coefficient *P* was determined as the ratio of the activity (counts min^{-1}) in the organic to the aqueous phase. Results are shown in Table 4. The large standard deviations (in parentheses) for the log *P* values obtained with the [9]aneN_3 $P(CH_2Ph)$ and PPh complexes in octanol–water occurred because when the volume ratio was varied (1 : 3 to 1 : 1 to 3 : 1) the log *P* values also changed. This effect was not so marked in the butanol–water mixtures.

Acknowledgements

We thank the SERC for support (to R. C. B. C.) and for a CASE award (to E. C. with W. R. Grace Ltd.), the MRC for support (to L. R.), Dr. Dermot O'Hare (Oxford) for the low-temperature ESR measurements, NSERC for continuing support *via* operating grants (to G. F.), and the University of Durham for an equipment grant.

References

1 C. J. Broan, K. J. Jankowski, R. Kataky and D. Parker, *J. Chem. Soc., Chem. Commun.*, 1990, 1738; C. J. Broan, K. J. Jankowski, R. Kataky, A. M. Randall and A. Harrison, *J. Chem. Soc., Chem. Commun.*, 1990, 1739; 1991, 204.

2 D. Parker, *Chem. Soc. Rev.*, 1990, **19**, 271; D. Parker and K. J. Jankowski, in *Advances in Metals in Medicine*, eds. B. A. Murrer and M. J. Abrams, Jai Press, London, 1993, vol. 1, pp. 29–73.

3 K. P. Pulukkody, T. J. Norman, D. Parker, L. Royle and C. J. Broan, *J. Chem. Soc., Perkin Trans. 2*, 1993, 605.

4 J. P. L. Cox, K. J. Jankowski, R. Kataky, D. Parker, N. R. A. Beeley, B. A. Boyce, M. A. W. Eaton, K. Millar, A. T. Millican, A. Harrison and C. A. Walker, *J. Chem. Soc., Chem. Commun.*, 1989, 797; C. J. Broan, J. P. L. Cox, A. S. Craig, R. Kataky, D. Parker, G. Ferguson, A. Harrison and A. M. Randall, *J. Chem. Soc., Perkin Trans. 2*, 1991, 87.

5 E. Cole, C. J. Broan, K. J. Jankowski, D. Parker, K. Pulukkody, B. A. Boyce, N. R. A. Beeley, K. Millar and A. T. Millican, *Synthesis*, 1992, 63.

6 T. B. Karpishin, T. P. P. Stack and K. N. Raymond, *J. Am. Chem. Soc.*, 1993, **115**, 182.

7 E. Cole, D. Parker, G. Ferguson, J. F. Gallagher and B. Kaitner, *J. Chem. Soc., Chem. Commun.*, 1991, 1473.

8 K. Weighardt, U. Bossek, P. Chaudhuri, H. Herrmann, B. C. Menke and J. Weiss, *Inorg. Chem.*, 1982, **21**, 4308.

9 P. Comba, A. M. Sargeson, L. M. Engelhardt, J. M. Harrowfield, A. H. White, E. Horn and M. R. Snow, *Inorg. Chem.*, 1985, **25**, 2325.

10 R. Hoffmann, J. M. Howell and A. R. Rossi, *J. Am. Chem. Soc.*, 1976, **98**, 2484.

11 E. I. Stiefel, R. Eisenberg, R. C. Rosenberg and H. B. Gray, *J. Am. Chem. Soc.*, 1966, **88**, 2956.

12 J. A. Bertrand, J. A. Kelly and E. G. Vassien, *J. Am. Chem. Soc.*, 1969, **91**, 2394; G. A. Zakrzewski, C. A. Ghilardi and E. C. Lingafelter, *J. Am. Chem. Soc.*, 1971, **93**, 4411.

13 H. Al-Sagher, I. Fallis, L. J. Farrugia and R. D. Peacock, *J. Chem. Soc., Chem. Commun.*, 1993, 1499.

14 A. S. Craig, I. M. Helps, H. Adams, N. Bailey, M. Williams and G. Ferguson, *Polyhedron*, 1989, **8**, 2481.

15 R. C. Matthews, D. Parker, G. Ferguson, J. F. Gallagher and B. Kaitner, *Polyhedron*, 1991, **10**, 1951.

16 M. J. van der Merwe, J. C. A. Boeyens and R. D. Hancock, *Inorg. Chem.*, 1983, **22**, 3489.

17 M. I. Kabachnik, M. Y. Antipin, B. K. Scherbakov, A. P. Baranov, Y. T. Struchkov, T. Y. Medved and Y. M. Polikarpov, *Koord. Khim.*, 1988, **14**, 299; M. Y. Antipin, A. P. Baranov, M. I. Kabachnik, T. Y. Medved, Y. M. Polikarpov, Y. M. Struchkov and B. K. Scherbakov, *Izv. Akad. Nauk. SSSR, Ser. Khim.*, 1986, 31.

18 D. L. Cullen and E. C. Lingafelter, *Inorg. Chem.*, 1970, **9**, 1858; 1971, **10**, 1264.

19 B. Hathaway, J. Mullane, M. Duggan, A. Murphy, C. Power and B. Walsh, *Coord. Chem. Rev.*, 1981, **36**, 267.

20 R. I. Sheldon, A. J. Jircitano, M. A. Beno, J. M. Williams and K. B. Mertes, *J. Am. Chem. Soc.*, 1983, **105**, 3028.

21 A. Bevilacqua, R. I. Gelb, W. B. Hebard and L. J. Zompa, *Inorg. Chem.*, 1987, **26**, 2699.

22 A. Harrison, C. A. Walker, K. A. Pereira, D. Parker, L. Royle, K. Pulukkody and T. J. Norman, *Magn. Reson. Imaging*, 1993, **11**, 761; S. Aimé, M. Botta, K. Senanayake, D. Parker, J. A. K. Howard, G. Williams and A. Batsanov, *Inorg. Chem.*, in the press.

23 A. S. Craig, D. Parker, H. Adams and N. Bailey, *J. Chem. Soc., Chem. Commun.*, 1989, 1792.

24 D. Parker, *Chem. Rev.*, 1991, **91**, 1441.

25 A. Harrison, C. A. Walker, K. A. Pereira, D. Parker, L. Royle, R. C. Matthews and A. S. Craig, *Nuc. Med. Commun.*, 1992, **13**, 667.

26 M. J. Welch and S. Moerlein, *Inorg. Chem. Biol. Med.*, 1980, **7**, 121.

27 E. J. Gabe, Y. Le Page, J.-P. Charland, F. L. Lee and P. S. White, *J. Appl. Crystallogr.*, 1989, **22**, 384.

28 P. V. Betteridge, C. K. Prout and D. J. Watkin, CRYSTALS, University of Oxford, 1984.

29 TEXSAN, Molecular Structures Corporation, Houston, TX, 1992.

Received 7th February 1994; *Paper* 4/00729H