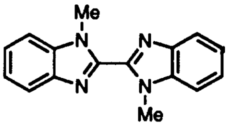
Synthesis and solution complexation behaviour of dimeric zinc-selective bis(benzimidazole) derivatives

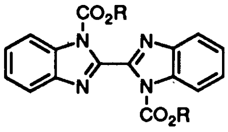
George B. Bates,[a] **David Parker**[a,*] **and Peter A. Tasker**[b]

[a] *Department of Chemistry, University of Durham, South Road, Durham, UK DH1 3LE*
[b] *Zeneca Specialties, Hexagon House, Blackley, Manchester, UK M9 8ZS*

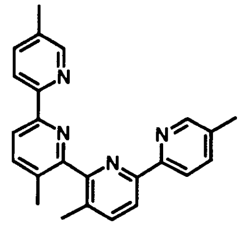
The synthesis of 1,1′-bis(4-*tert*-butylbenzyl)-2,2′-bis(benzimidazole)-4,4′-dicarboxylic acid and its *N*-substituted analogues is reported. Complexation of the ligand by divalent Zn, Cu, Ni, Pb and Cd ions has been studied in methanolic solution by ^{1}H NMR, FT-IR and electrospray mass spectrometry. The ligand forms a dimeric neutral M_2L_2 complex selectively with zinc, favoured by the two rigid tetrahedral binding sites created by the cooperative ligation of two orthogonally disposed ligands. Overall binding affinities follow the sequence Zn > Cd ≈ Ni > Pb > Cu and solution speciation has been defined by ESMS showing non-selective formation of, for example, ML, MLH, M_2L_2X species with all ions but zinc, where the M_2L_2 species was predominant.



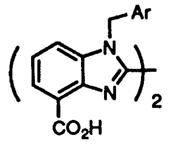
1



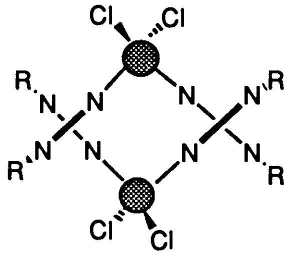
2



3



4 a) Ar = *p*-Bu^t-Ph
b) Ar = Ph
c) Ar = *p*-$C_{12}H_{25}$-Ph



Scheme 1 (View down the 2,2′ bond)

The coordination chemistry of zinc is important both in biological chemistry, where zinc–protease enzymes are very common and for which synthetic models are actively being sought,[1] and in separation chemistry where lipophilic ligands that bind zinc selectively are sought for solvent extraction processes.[2] In the latter case, this poses a significant challenge to modern complexation chemistry if the interferent ions are relatively close neighbours of zinc in the periodic table, *i.e.*, Cu^{2+}, Ni^{2+} and the ferric ion. Indeed the normal order of stability for complex formation (*e.g.*, for amino-carboxylate complexes) is $Zn^{2+} < Cu^{2+} > Ni^{2+}$ (Irving–Williams series).[3] Given the similarity in size of these ions (0.57, 0.55 and 0.60 Å, respectively, are the effective ionic radii for their tetracoordinate complexes),[4] a simple method of distinguishing them is based on their different geometric requirements. Copper(II), and to a lesser extent (depending on the ligand field) nickel(II), prefer a square-planar geometry whereas zinc prefers a tetrahedral coordination site.[5] Selectivity for zinc coordination may be achieved, therefore, by designing conformationally restricted ligands with appropriate donor atoms that engender a well defined tetrahedral binding site and are unable to adopt a square-planar geometry.

There are various strategies for creating such a geometrically well defined binding site. Appropriately functionalised bulky phenanthrolines, related to neocuproine,[6] have been used for example, in the synthesis of catenands where a tetrahedral copper(I) ion in an ML_2 complex involving two orthogonal phenanthrolines templates the ligand synthesis.[7] Attempts have also been made to prepare mononucleating tetradentate ligands based on monofunctionalised 1,5,9-triazacyclododecane ligands,[8,9] but these studies have been thwarted by the tendency of the selected ligands to allow pentacoordination at the metal, either because of inappropriate ligand design or a lack of conformational rigidity.

It has been noted recently that various *N*-substituted bis(benzimidazole) ligands, *e.g.*, **1** and **2**, form well defined dinuclear complexes with zinc chloride, $L_2Zn_2Cl_4$.[10] In these complexes, two mutually perpendicular coordination planes are defined when the dihedral angle between the benzimidazole moieties is close to 90°. This creates two tetrahedral binding sites, (Scheme 1). Such behaviour is reminiscent of the complexes formed by 'quaterpyridines', such as **3**, where there are two orthogonal bipyridyl groups.[11] Indeed these ligands were the prototypes of the various helicating ligands, reported more recently.[12] Incorporation of an anionic donor in both of the '4'-positions of the aryl rings, *e.g.*, **4** allows six-ring chelate formation with the proximate nitrogens, and hence the possibility of formation of *charge-neutral* L_2Zn_2 complexes, as shown in Fig. 1. Complex lipophilicity may be controlled by variation of the N(1) substituents, and selectivity for small and tetrahedrally coordinating ions is favoured by a combination of the six-ring chelates (favouring small ions)[13] and the ligand's preferred binding conformation, imposed by minimising steric interactions between the N(1) substituents.

With this background in mind, the synthesis of the 4,4′-dicarboxybis(benzimidazole) ligand, **4**, has been undertaken[14] and studies of its complexation behaviour, in solution, initiated with the aid of NMR, IR and electrospray mass spectrometric techniques.

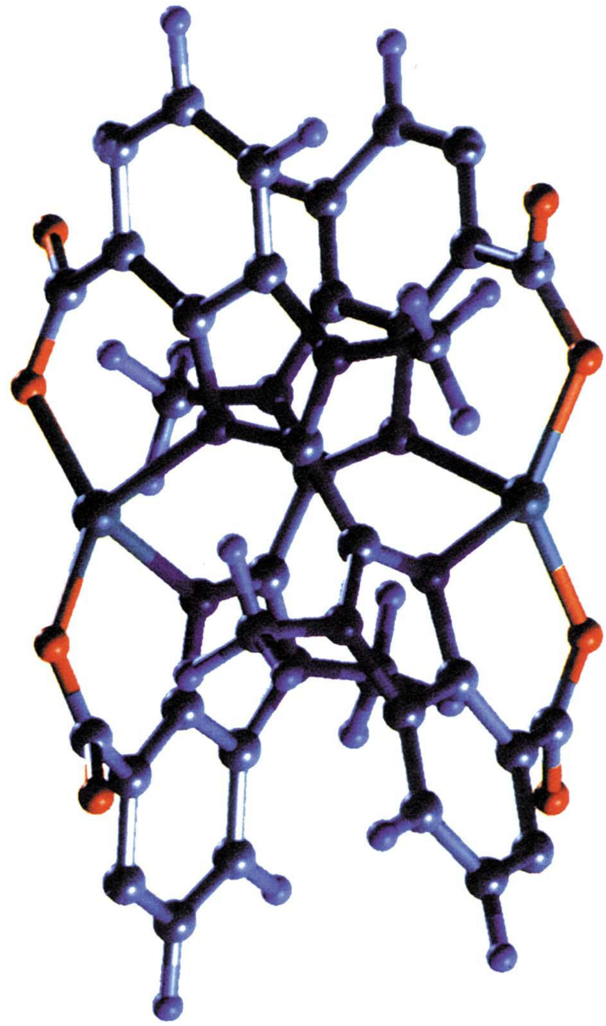
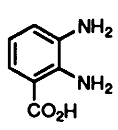
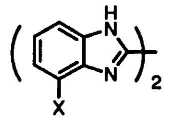


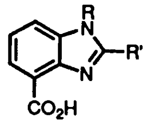
Fig. 1 Model of the putative Zn_2L_2 complex with ligand **4** (an NMe substituent rather than a benzyl group) is shown for clarity



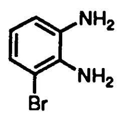
5



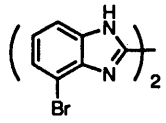
6 a) $X = CO_2H$
b) $X = H$



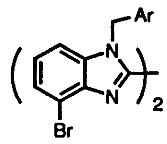
a) $R = H, R' = CCl_3$
b) $R = p\text{-}Bu^t\text{-}Bn, R' = H$



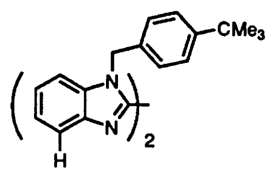
8



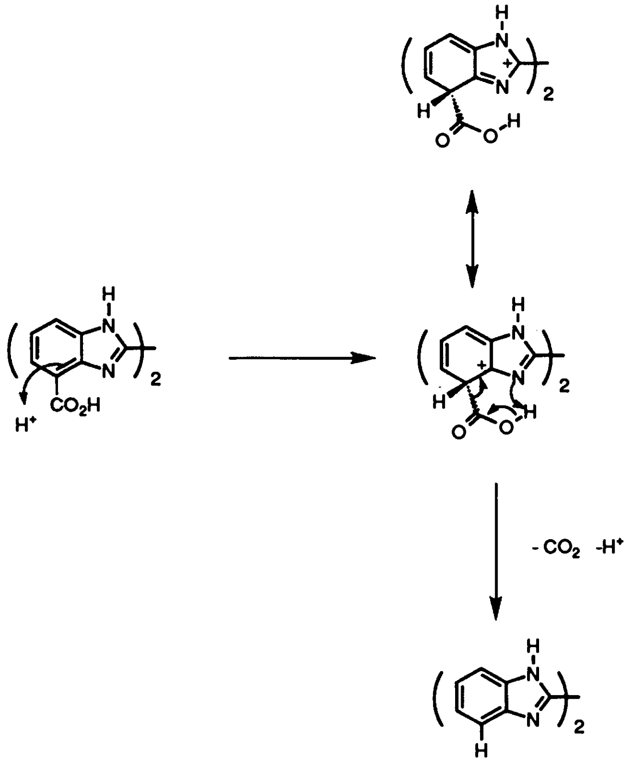
9



10 a) $Ar = p\text{-}Bu^t\text{-}Ph$
b) $Ar = Ph$
c) $Ar = p\text{-}C_{12}H_{25}\text{-}Ph$



11



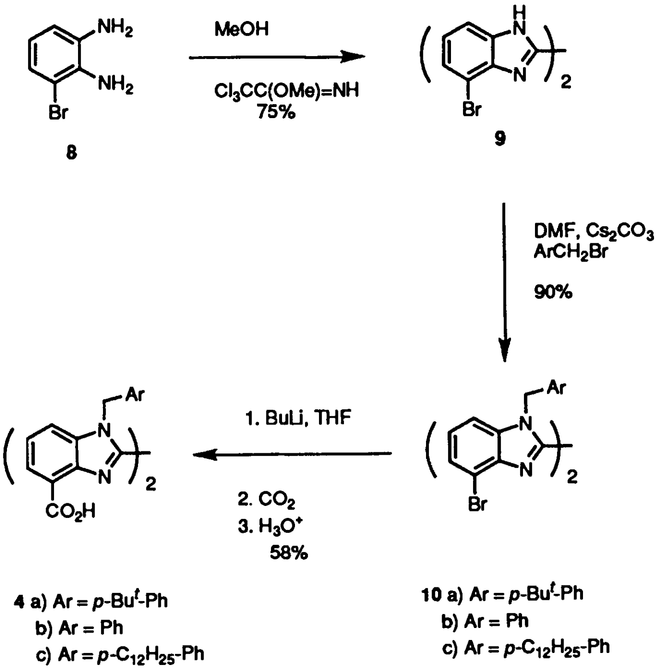
Scheme 2

Ligand synthesis

Initial attempts to synthesise ligand **4** focused on the coupling of 2,3-diaminobenzoic acid, **5**,[15] with oxamide in ethylene glycol at 150 °C. This route did produce the desired product in moderate yield (30%) but it was contaminated by the two decarboxylation products arising from an acid-catalysed pathway (Scheme 2). Attempts to modify this route—either by carrying out the reaction in the presence of potassium carbonate, performing it at a lower temperature (120, 100 or 80 °C), or activating the reaction by microwave irradiation (410 W microwave oven)—failed to inhibit the concomitant decarboxylation. An alternative, higher yielding strategy was therefore sought.

1,2-Diaminobenzene is known to react with methyl trichloroacetimidate, $Cl_3CC(NH)OMe$, to produce the parent bis(benzimidazole).[16] When this reaction was attempted at various temperatures (20–80 °C) in alcoholic solvents either with the mono- or the di-protonated salt of the diamine **5**, no bis(benzimidazole) related products were obtained. However, by working in methanol at 20 °C, the trichloromethyl-substituted product **7a** was obtained (59%). This was alkylated following reaction with *p-tert*-butyl benzyl bromide in DMF, in the presence of potassium carbonate, to give the *N*-benzyl product, **7b**, which underwent loss of the CCl_3 group during the reaction. This compound serves as a mononucleating analogue of the desired product **4**.

Other coupling agents, such as trichloroacetonitrile[16] and 1-nitro-2,2-bis(methylthio)ethene[17] also failed to couple the amino acid **5**. At this stage use of **5** as the direct precursor to **4** was abandoned. Instead, the attempted coupling reaction of the bromo-analogue, 2,3-diaminobromobenzene,[18] **8**, was studied. In this case (Scheme 3), coupling occurred at 20 °C in methanol to yield the desired bis(benzimidazole), **9**, in 75% yield using methyl trichloroacetimidate. The bulky bromo substituent at C-4 also controls the regioselectivity of *N*-alkylation. Reaction of **9** in DMF at 80 °C in the presence of Cs_2CO_3 with a variety of benzyl bromide derivatives afforded the N1 substituted products selectively (**10a**, **10b** and **10c**). Nuclear Overhauser difference ^1H NMR spectroscopy revealed that the NCH_2 protons were close in space only to H7 of the benzimidazole (8% enhancement of the H7 signal following irradiation of NCH_2). Lithiation of the aryl halide (BuLi, THF) at −78 °C followed by reaction with CO_2 afforded the desired ligands, **4a**, **4b** or **4c**, typically in 60–70% yield. Thus the target ligand could be prepared in 40% overall yield from the known diaminobenzene derivative,[18] **8** (Scheme 3). The long chain derivative **4c**, prepared as a mixture of constitutionally isomeric branched hydrocarbons, offered the possibility of enhanced solubility in the non-polar solvents (*e.g.*, kerosenes) used in solvent extraction processes.



Scheme 3

Solution complexation behaviour

In order to allow valid correlations to be made, NMR, IR and electrospray MS studies were carried out in methanolic solution (for NMR and IR, a 25% CD_3OD–$CDCl_3$ mixture was used). Complexation of anhydrous metal triflate salts (M = Ni, Cu, Zn, Cd, Pb) was monitored by ^1H NMR spectroscopy at 293 K. In principle various equilibria may be set up in solution involving differently protonated mononuclear or dinuclear complex species, eqns. (1) to (5). The equilibrium in eqn. (5) is distinguished by its concentration dependence, while that in eqn. (3) should be apparent at low M/L ratios.

$$\mathrm{M + L \overset{K_1}{\rightleftharpoons} ML} \qquad (1)$$

$$\mathrm{ML + H \rightleftharpoons MLH} \qquad (2)$$

$$\mathrm{M + 2L \rightleftharpoons ML_2} \qquad (3)$$

$$\mathrm{ML_2 + M \rightleftharpoons 2ML} \qquad (4)$$

$$\mathrm{2ML \overset{K_2}{\rightleftharpoons} M_2L_2} \qquad (5)$$

Table 1 NMR-derived binding constants for complex formation with the bis(benzimidazole)diacid **4a** (293 K, 25% CD_3OD–$CDCl_3$)

Metal	*K*
Zn[a]	$>10^5$
Ni	1.1×10^4
Pb	3.4×10^3
Cd[b]	$10^4 < K > 10^5$
Cu	3×10^2

[a] The value for *K* given is the product of K_1 and K_2 at least [eqns. (1) and (5)]. [b] Complex equilibria involving CdL, Cd_2L_2, Cd_3L_3 and species involving triflate ligation were each observed in electrospray MS.

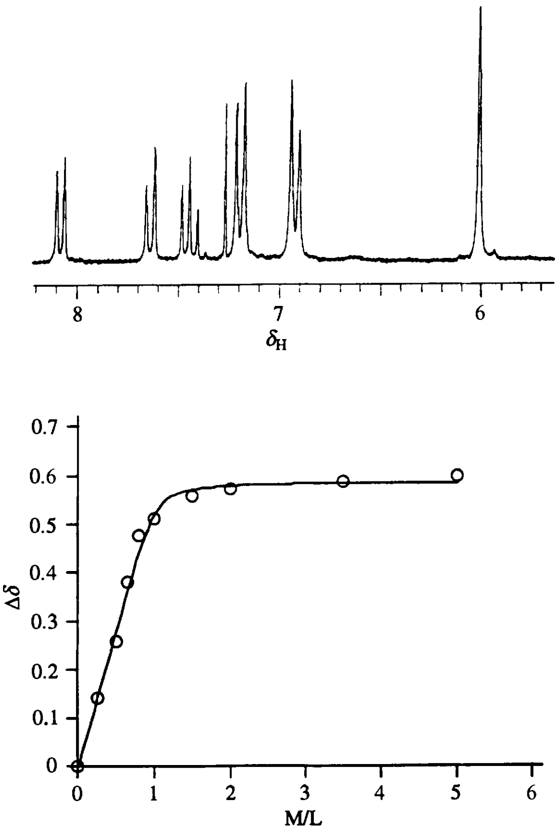


Fig. 2 Proton NMR titration curve monitoring complexation of **4a** by $Pb(CF_3SO_3)_2$ (293 K, 200 MHz; 25% CD_3OD–$CDCl_3$), examining the shift of the methylene protons as a function of added lead concentration. The upper spectrum is the limiting spectrum obtained at a Pb:L ration of 5:1.

Incremental addition of lead triflate to a methanol solution of **4a** (2×10^{-2} mol dm^{-3}) led to a shift to lower frequency in the methylene NCH_2Ar protons. Free and bound species were in fast exchange on the NMR timescale (200 MHz; 293 K), so that a single resonance only was observed. Analysis of the titration curve (Fig. 2), indicated that a complex of 1:1 stoichiometry was formed and the form of the curve at low M/L ratios suggested that ML_2 species were not involved significantly. An equilibrium constant of 3.4×10^3 was estimated following a non-linear least-squares analysis of the $\Delta\delta_H$ *versus* M/L variation.[19]

Notwithstanding the slight paramagnetically induced line-broadening, similar experiments were also undertaken with nickel and copper. Addition of nickel triflate again gave a shift in the resonance of the NCH_2Ar protons and 1:1 complex formation was observed [eqn. (1)], with log $K_{ML} = 1.1 \times 10^4$. For copper, the plots of $\Delta\delta_H$ *versus* M/L, in the range M/L = 0.05–0.5, showed positive deviations from the theoretical curve for 1:1 complex formation consistent with intermediate CuL_2 formation, *en route* to formation of the ML complex. The 1:1

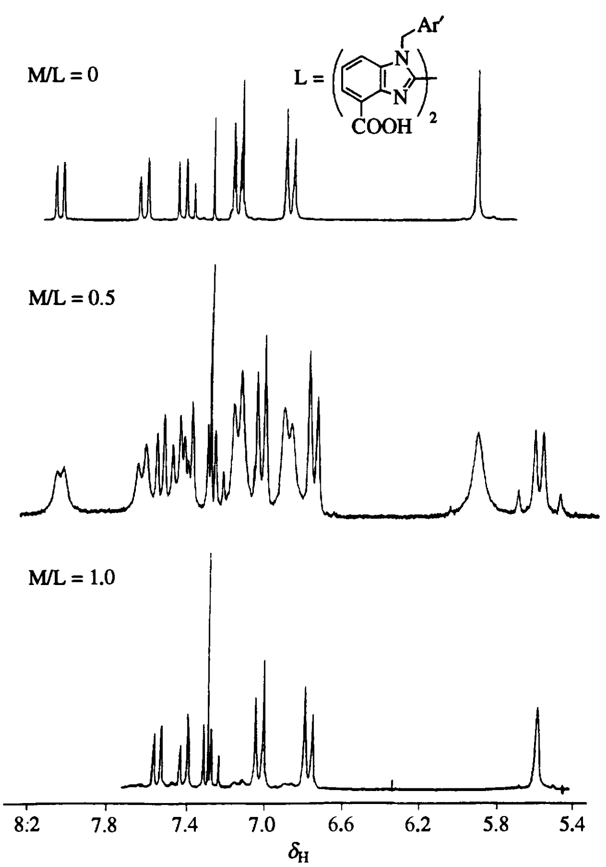


Fig. 3 Proton NMR spectra following addition of 0.25 (top) 0.5 and 1.0 equiv. of $Zn(CF_3SO_3)_2$ to a solution (25% $CD_3OD–CDCl_3$) of **4a** (293 K; 200 MHz)

complex that formed was relatively weak, log K_{ML} = 300 (Table 1).

When zinc triflate was added to **4a** in $CD_3OD–CDCl_3$ (25:75), a very different set of spectra were observed (Fig. 3). At M/L ratios of less than unity, separate resonances were observed for the free ligand and for a bound species consistent with slow-exchange on the NMR timescale (*i.e.*, log $K > 5$). Indeed at M/L = 0.5, 50% of the signals were due to the exchange-broadened ligand ($\omega_{\frac{1}{2}}$ = 13 Hz for NCH_2Ar; 200 MHz; 293 K) and the remaining sharper signals were due to a complex of 1:1 overall stoichiometry. At an M/L ratio of 1, only signals due to the bound complex were discerned and no change in the spectrum was observed at higher M/L ratios. Such behaviour is consistent with intermediate formation of a weak ML complex [eqn. (1)], followed by dimerisation to give a neutral M_2L_2 complex [eqn. (5)] with $K_2 > K_1$.[20]

The ^1H NMR titration of cadmium triflate with **4a** was characterised by more complicated behaviour. At low M/L ratios (< 0.5), signals were discerned due to the free ligand (shifted from their position in the unbound ligand) together with certain very broad resonances due to a cadmium complex species (Fig. 4). Further addition of $Cd(CF_3SO_3)_2$ caused considerable line-broadening to all of the ligand resonances which sharpened somewhat beyond an M/L ratio of 1.5. However at an M/L ratio of 5, signals due to a major complex species in slow exchange with at least one different species could be defined. The resonances due to the minor species were considerably exchange broadened. The ^1H NMR spectrum of the major species (*ca.* 70% of the total signal) at high M/L ratios was similar in form to that observed with zinc. Stepwise dilution of this sample with the deuteriated NMR solvents gave less and less of the major species and more of the exchange-broadened species, consistent with the formation of a dimeric complex at higher concentration. Assuming that the equilibria in eqns. (1) and (5) are operative, and knowing the relative proportions of the two species (^1H NMR integration) and the total concentration of ligand used, then the association constant for formation of the Cd_2L_2 species (from CdL; L = **4a**) was estimated to be 400 (± 150) dm^3 mol^{-1}.

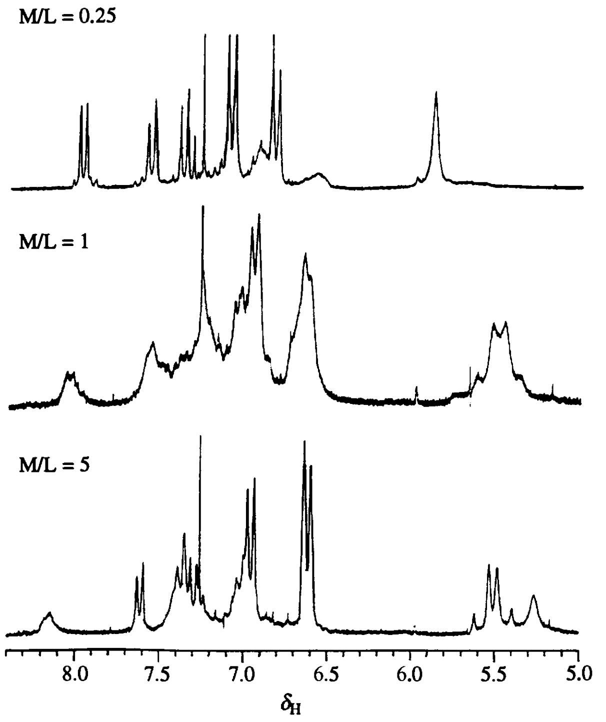


Fig. 4 Proton NMR spectra obtained (293 K; 200 MHz; 25% $CD_3OD–CDCl_3$) following incremental addition of anhydrous $Cd(CF_3SO_3)_2$ to **4a**

The binding of zinc triflate by the bidentate ligand **7b** was also examined. This ligand may be regarded as the monomeric analogue of **4a**, and hence may be expected to form ML_2 but not M_2L_2 complexes. It was observed that the free and bound ligand species were in fast exchange on the NMR timescale, and monitoring the shift of the methylene protons as a function of added zinc gave rise to a binding isotherm (293 K; 25% $CD_3OD–CDCl_3$) in which the limiting chemical shift ($\Delta\delta_H$ = 0.21) was duly observed at a M:L stoichiometry of 1:2. The bis(benzamidazole), **11**, lacking any carboxy groups was also studied by ^1H NMR spectroscopy, examining the binding of zinc triflate in the same solvent system. In this case, very weak binding was observed and not even information regarding the stoichiometry of complexation could be gained, highlighting the importance of the carboxy group in complex formation with **4a**.

Electrospray mass spectroscopic studies

The advantages of using an atmospheric pressure inlet source, coupled with the intrinsic 'softness' of the ionisation method has led to a growing awareness of the utility of this technique in accurately assessing the solution speciation of ions (*i.e.*, solvation)[21] and their ligand complexes.[22] Using a 1.5×10^{-4} molar solution of the ligand in 25% $CHCl_3–MeOH$, and of the appropriate anhydrous metal triflate, ESMS spectra were recorded at various sample concentrations between 10^{-4} and 10^{-5} mol dm^{-3}. In addition to an ML species, the major peaks observed (source temperature 60 °C; cone voltage 25 V) for **4a** in the presence of one equivalent of zinc triflate were due to a Zn_2L_2 species, with good agreement between observed and calculated isotope patterns for the signals centred at *m*/*z* 1356 (Fig. 5). At higher cone voltages (*e.g.*, 64 V and an 80 °C source temperature), fragmentation of this species (benzylic cleavage) gave an intense daughter cluster of peaks centred at *m*/*z* 1210 (Zn_2L_2 – CH_2-p-Bu^t-Ph). The peaks which were observed at

Table 2 Major species observed by electrospray mass spectrometry[a] in complexation of ligand **4a** by metal trifluoromethanesulfonates

Complex	Observed species	Observed mass	Calculated mass[b,d]
[Zn-**4a**]	Zn_2L_2	1354, 1355, *1356*, 1357	1354, 1355, *1356*, 1357
	$\begin{bmatrix}\mathrm{ZnL}\\ \mathrm{ZnLH}\end{bmatrix}$	*677.1*, 678.1, 679.2, 680.2	*676.2*, 677.2, 678.2, 680.2
[Cd-**4a**]	$\begin{bmatrix}\mathrm{CdL}\\ \mathrm{CdLH}\end{bmatrix}$	*724.6*, 725.9, 727.1, 728.1	724.2, 725.2, *726.2*, 727.2
	Cd_2L_2	1448.6, *1450.3*, 1451.4, 1452.5	1449.4, *1450.4*, 1451.4, 1452.4
	Cd_2L_2X	*1599.5*, 1600.6, 1601.5	1598.3, *1599.3*, 1600.3, 1601.3
	$Cd_2L_2X_2$ (weak)	1748.6, *1749.7*, 1750.7, 1751.7	1747.3, *1748.2*, 1749.3, 1750.3
	CdLX (weak)	*874.7*, 875.8	873.1, 874.1, *875.1*
[Pb-**4a**][e]	PbL	819.3, *820.5*, 821.8	818.3, 819.3, *820.3*, 821.3
	PbLX (weak)	969.5, *970.9*, 972.0	969.2, *970.2*, 971.2
	Pb_2L_2 (v. weak)	1638.1, 1639.2, *1640.2*, 1641.3	1638.5, 1639.5, *1640.5*, 1641.5
[Cu-**4a**][c]	CuLH	*676.2*, 677.3, 678.3	*676.2*, 677.2, 678.2
	Cu_2L_2	1351.1, *1352.4*, 1353.3, 1354.5	1350.4, 1351.4, *1352.4*, 1353.4
[Ni-**4a**]	NiL	670.6, *671.8*, 672.7, 673.6	*670.2*, 671.2, 672.2, 673.2
	NiLH		*671.2*, 672.2, 673.2, 674.2
	Ni_2L_2	*1341.5*, 1342.5, 1343.4, 1344.2	1340.4, 1341.4, *1342.4*, 1343.4
[Fe^{III}-**4a**]	FeL	667.7, *668.8*	*668.2*, 669.2

[a] 30 V cone voltage, 5 V skimmer voltage, 60 °C source temperature, sample concentration = 1.5×10^{-4} mol dm^{-3} in 30% $CHCl_3$–MeOH solution. [b] Error on observed mass was typically (± 0.4 D); good agreement was obtained between observed and calculated isotope patterns for species with good signal/noise; only the four major peaks are reported for a given pattern and the strongest peak is italicised. [c] Very weak spectra were observed, with several other species present. [d] L^{2-} has a mass of 612; $CF_3SO_3^-$(X) = 149. [e] On standing, a PbL(OH), complex centred at 838, was the major species.

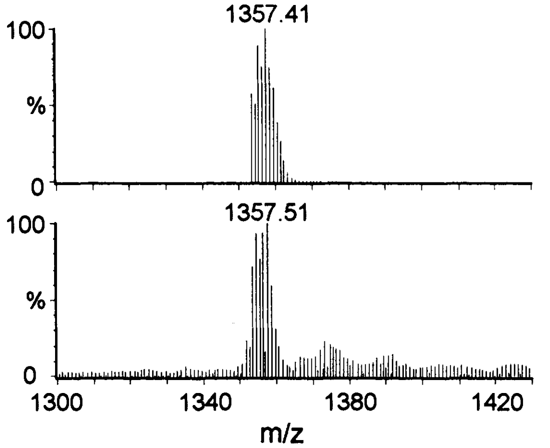


Fig. 5 Dimeric M_2L_2-derived species observed in the ESMS spectrum of an equimolar mixture of **4a** and $Zn(CF_3SO_3)_2$ (30% $CHCl_3$–MeOH; 25 V cone voltage). The upper spectrum shows the calculated isotope pattern.

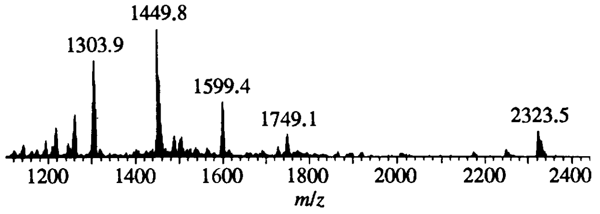


Fig. 6 Variety of bound species observed in the electrospray mass spectrum of an equimolar mixture of $Cd(CF_3SO_3)_2$ and **4a** (30% $CHCl_3$–MeOH)

m/*z* 677, 678 and 680 were in a relative ratio that was consistent with the presence of both ZnL and ZnLH. A further set of peaks at mass 695, 696 and 698 were attributed to $ZnL(OH_2)$. Dilution of the sample by a factor of five had little effect on the observed relative intensities of the ZnL and Zn_2L_2 species.

This behaviour provides clear evidence for the favoured formation of a charge-neutral $[Zn_2(\mathbf{4a})_2]$ complex, and a similar pattern of behaviour was observed in zinc complexation with the related ligand **4b**. Parallel experiments with equimolar quantities of **4a** and $Cd(CF_3SO_3)_2$ revealed more complex behaviour with several dinuclear and even trinuclear species observed (Fig. 6). Notwithstanding the low nucleophilicity of the triflate anion in methanol solution, species due to Cd_2L_2X, $Cd_2L_2X_2$, Cd_3L_3X and CdLX were observed, in addition to CdL, CdLH and Cd_2L_2 (L = **4a**). Higher solution concentrations or high Cd/**4a** ratios led to higher intensities of the oligomeric species at the expense of the mononuclear complex species (Table 2). Anion ligation was also observed in the nickel complex species. In this case, the major species observed was due to a 1 : 1 complex (NiL and NiLH), and peaks due to Ni_2L_2, Ni_2L_2X, $Ni_2L_2X_2$ and $Ni_2L_2X_3$ were significantly weaker. For copper, only CuL and CuLH species could be discerned, and the spectra obtained were rather weak. With lead, the most intense signal was also due to the 1 : 1 adduct PbL, and a much weaker signal due to a 'dimer'. An aged (wet) sample revealed peaks due to PbL(OH) and Pb_2L_2(OH) at 1658 and 1660. In the presence of ferric chloride, only an ML species was observed, with no evidence for MLH or M_2L_2 complexes.

Solution FTIR studies

The infrared stretching frequency of the protonated ligand, **4a**, in 25% $CHCl_3$–methanol solution occurred at 1734 cm^{-1}. In the 1 : 1 complex with zinc, generated *in situ* following admixture of equimolar (*ca.* 8×10^{-3} mol dm^{-3}) quantities of the ligand and zinc triflate, a single sharp carbonyl stretch was observed at 1636 cm^{-1}. This is consistent with the presence of a metal-bound carboxylate in the major solution Zn_2L_2 complex. In the corresponding lead complex, examined under similar conditions, the carbonyl stretch occurred at 1657 cm^{-1}

Table 3 Infrared stretching frequencies for complexes of **4a** (0.8×10^{-2} mol dm^{-3} in CaF_2 cells, 25% MeOH–$CHCl_3$ solution, 293 K)

Species	ν_{CO}/cm^{-1}
4a	1734 (CO_2H)
'ZnL'	1636 (bound carboxylate)
'PbL'	1657 (free carboxylate)
'CdL'	1637 and 1650
'NiL'	1634
'CuL'	1630 (very broad)

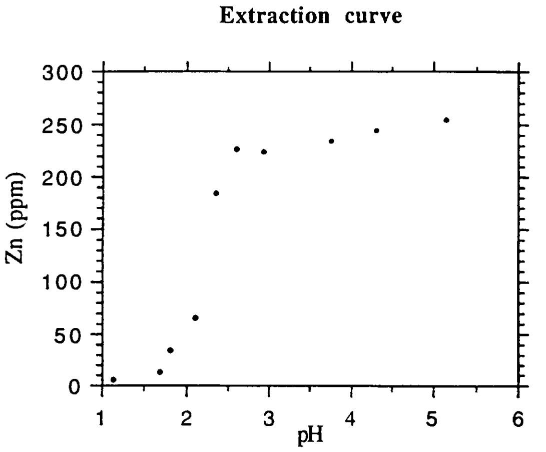


Fig. 7 pH dependence of zinc extraction from an aqueous hydrochloric acid phase into dichloromethane

(Table 3), while for cadmium two stretches were observed at 1637 and 1650 cm^{-1}, consistent with a free carboxylate stretch in the former case and a mixture of free and cadmium-bound carboxylates in the latter. With added nickel, only a single stretch at 1634 cm^{-1} was measured indicative of carboxylate ligation to the metal, while with copper a rather broad band was observed at 1630 cm^{-1} suggestive of carboxylate binding.

Conclusions

Taken together, these experimental studies of the nature and structure of the metal complex species of ligand **4a** in solution allow some definite conclusions to be drawn. The ligand forms a well defined 2:2 charge neutral complex with zinc, with an overall stability constant of greater than 10^5 in which each metal is tetrahedrally bound by N3 and a carboxylate oxygen of two orthogonally disposed ligands (Scheme 1). The copper(II) ion forms a much weaker complex, and there is evidence for intermediate CuL_2 formation *en route* to an ill defined copper(II) 'CuL' complex. Such behaviour is expected for a ligand which is *unable* to present a well defined square planar array of donor atoms in either an ML_2 and more particularly in ML or M_2L_2 complexes. Tetrahedral coordination geometry is somewhat more common for Ni^{II} complexes, and nickel appears to form a relatively stable complex of 1:1 overall stoichiometry according to the NMR studies. The ESMS work indicates that it is quite likely that in solution a mixture of ML, MLH, M_2L_2 and even M_2L_2X complexes is in equilibrium, in each of which the carboxylate is bound (IR work). The situation with lead is more straightforward: a weak complex of 1:1 overall stoichiometry was observed by NMR ($\log K \approx 3 \times 10^3$), and the observation of PbL(OH) and to a lesser extent $Pb_2L_2(OH)$ species in the ESMS study correlates well with the absence of carboxylate binding inferred from the IR results. Clearly lead is binding to the nitrogen of the benzimidazole moiety, but the acuteness of the chelate site angle engendered by cooperative binding of N3 and the carboxylate oxygen to the large Pb^{2+} ion renders this binding less energetically favourable compared with ligation of an innocent hydroxy group, derived from the low percentage of water present in the solvent. The more favourable interaction between a six-ring chelate and small metal ions (*e.g.*, Zn^{II} and Ni^{II}) compared with a larger ion, such as Pb^{2+}, is now well defined in coordination chemistry.[13]

The situation with cadmium binding is the most complicated. Both NMR and ESMS studies revealed that there was a mixture of monomeric, *e.g.*, CdL and dimeric, *e.g.*, Cd_2L_2 species in equilibrium. The additional ESMS observation of CdLX and $Cd_2L_2X(X_2)$ species, is consistent with the occurrence of both free and metal-bound carboxylates in the IR study. Evidently the relatively large Cd^{2+} ion is able to adopt a tetrahedral geometry, as required for M_2L_2 formation, but this type of coordination is far from ideal because of the unfavourable strain energy induced in forming a six-ring chelate with a relatively large cation (effective ionic radii are: Cd^{2+}, 0.78 Å; Zn^{2+}, 0.60 Å and Pb^{2+}, 0.98 Å in tetracoordinate complexes[4]). Binding by the relatively poor triflate anionic donor therefore becomes competitive.

The ligand **4a** (and the derivatives **4b** and **4c**), prefers to bind to the tetrahedral zinc(II) ion and the observed order of overall complex stability (Zn > Cd ≈ Ni > Pb > Cu) does reflect the combination of the steric requirements imposed by the ligand and the intrinsic metal ion selectivity resulting from a chelating N,O donor set which favours binding to small cations. The availability of lipophilic derivatives of **4** (*e.g.*, **4c**) through alkylation at N1, has allowed the synthesis of a lipophilic zinc-selective ligand that offers promise in the selective solvent extraction of zinc ions. A preliminary examination of the ability of **4c** to transport zinc ions into an organic phase (CH_2Cl_2) from an acidic aqueous phase has been undertaken. The pH at which the ligand was found to be 50% efficient in extracting zinc was 2.3 (Fig. 7). Given that such ligands need to extract zinc from an acidic (pH 2) aqueous phase into a kerosene organic phase in order to be commercially viable, then a carboxylate donor may not be optimal, and more acidic anionic donors may be preferred.

Experimental

All reactions were carried out in apparatus that had been oven-dried and cooled under argon. All solvents were dried from an appropiate drying agent and water was purified from the Purite system.

Alumina refers to Merck Alumina activity II–III that had been soaked in ethyl acetate for at least 24 h prior to use. Silica refers to Merck silica gel F60 (230–400 mesh). Preparative TLC was carried out using either Merck 5726 Alumina PLC 150 F_{254} (type T) pre-coated 1.55 mm plates or Merck Silica PLC 60 F_{254} pre-coated 2 mm plates. Analytical and preparative HPLC were performed on a Varian Vista 5500 or Star 5065 instrument fitted with a reversed-phase column (Dynamax).

^1H and ^{13}C NMR spectra were obtained with a Bruker AC 250 operating at 250.13 and 62.90 MHz, respectively, a Varian Gemini 200 operating at 200 and 50 MHz, respectively, a Varian XL 200 operating at 200 MHz, or a Varian VXR 400S operating at 400 MHz. All chemical shifts are given in ppm relative to tetramethylsilane or the residual solvent resonance and coupling constants are given in Hz.

Mass spectra were recorded on a VG 7070E, operating in FAB, EI$^+$ or DCI ionisation modes as stated. Electrospray mass specta were recorded using a VG Platform (Fisons instruments) operating in ES$^+$ mode or were performed by the EPSRC mass spectroscopy service at Swansea. Accurate mass spectroscopy was performed by the EPSRC mass spectroscopy service.

Infrared spectra were recorded on a Perkin-Elmer 1600 FT-IR spectrometer as thin films or KBr discs as stated. Ultraviolet spectra were recorded on a UVIKON 930 spectrometer.

CHN analysis was performed using an Exeter Analyical Inc CE440 elemental analyser. Metal concentations in aqueous solution were determined by atomic absorption spectroscopy using a Perkin-Elmer 5000 atomic absorption spectrophotometer.

Melting points were determined on a Gallenkamp melting point apparatus and are uncorrected.

NMR titrations

A stock solution of the ligand and the required metal triflate (five times more concentrated than the ligand) were made up in the NMR solvent system used (25% $CDCl_3$–CD_3OD). Using the ligand solution (0.4 cm^3), the appropriate amount of metal triflate solution was added and where necessary extra solvent was added so that each NMR sample was made up to a final volume of 0.8 cm^3. The metal/ligand ratio was varied from 0 to 5.

The shift of one of the resonances of the ligand (usually the methylene resonance) was recorded as a function of M/L ratio. Using a curve-fitting program operating in Kaleidagraph, the equilibrium constant K_1 was determined, where appropriate.

Electrospray mass spectrometry complexation analysis

Stock solutions of the ligand (10 cm^3; 0.3 mmol dm^{-3}) in wet methanol containing about 1–5% water and 40% chloroform and the metal triflates (10 cm^3; 1.5 mmol dm^{-3}) in methanol were made up. To a sample of the ligand solution (1 cm^3) the appropriate amount of metal triflate solution (of the order of 0.2 cm^3) was added to make a 1 : 1 metal/ligand ratio. Using 10 μl of the test solution, mass spectra were obtained on a VG platform (II) electrospray mass spectrometer (cone voltage 30 V; sample temperature 60 °C) with positive ionisation.

Infrared studies of complexation

1,1′-Bis(4-*tert*-butylbenzyl)-2,2′-bisbenzimidazole-4,4′-dicarboxylic acid (5 mg, 0.0081 mmol) was dissolved in a mixed solvent system (1 cm^3, 25% CH_3OH–75% $CHCl_3$) and the appropiate amount of metal triflate (0.00814 mmol) added to obtain a 1 : 1 metal/ligand ratio. IR measurements were recorded for samples in a CaF_2 solution cell (internal gap of 0.1 mm) with a Perkin-Elmer 1600 FTIR spectrometer.

Bisbenzimidazole extraction tests

(*a*) Zinc pH extraction study. 1,1′-Bis(4-dodecylbenzyl)-2,2′-bisbenzimidazole-4,4′-dicarboxylic acid (1.28 g, 1.524 mmol) was dissolved in Analar dichloromethane (15 cm^3). Zinc chloride (1.863 g, 7.622 mmol) dissolved in aqueous sulfuric acid (15 cm^3; 0.05 mol dm^{-3}; pH 1) was added. The binary phase mixture was stirred vigorously for 15 min and then allowed to separate. The pH of the top aqueous layer was measured (Corning semi-micro pH combination electrode and Molspin program). Aliquots (0.2 cm^3) of the aqueous and organic layer were removed. The pH of the mixture was adjusted by addition of sodium hydroxide solution (4.5 mol dm^{-3}; 0.1–0.3 cm^3) and the mixture stirred vigorously. The procedure of aliquot removal and pH adjustment was repeated to obtain 12 organic and aqueous samples in the pH range 0.71–5.15.

The aqueous samples were diluted with water (to 10 cm^3) and the zinc content determined by atomic absorption spectroscopy. The organic samples were diluted with chloroform (5 cm^3) and either decanted or filtered through a cotton wool plug to remove any residual water. The organic solution was mixed vigorously with hydrochloric acid (10 cm^3; 1 mol dm^{-3}). The aqueous layer was carefully separated and the zinc content determined by atomic absorption spectroscopy.

Compounds **5** and **8** were prepared according to minor variations of literature methods.[15–18]

2-Trichloromethylbenzimidazole-4-carboxylic acid (7a)

Methyl 2,2,2-trichloroacetimidate (0.29 g, 1.64 mmol) dissolved in methanol (2 cm^3) was added to freshly sublimed 2,3-diaminobenzoic acid (0.5 g, 3.29 mmol) in dry methanol (5 cm^3). The reaction was stirred at room temperature in the dark for 24 h with nitrogen gas passing through the mixture. Water (20 cm^3) was added and the light yellow precipitate collected by filtration, 0.27 g (59%). Recrystallisation from hydrochloric acid (0.1 mol dm^{-3}) gave a light yellow solid mp 201–202 °C; δ_H[$(CD_3)_2SO$] 7.45 (1 H, t, Ar H 6), 7.98 (2 H, m, Ar H 5 and H 7); *m*/*z* (DCI NH_3) 283 (M^+ + 1), 281, 279, 245 (M^+ − Cl); ν_{max}(KBr)/cm^{-1} 3391 (NH), 3084 (OH), 1694 (CO), 843, 822 (CCl) (Found: C, 38.81; H, 1.93; N, 9.74%. $C_9H_5Cl_3N_2O_2$ requires: C, 38.66; H, 1.80; N, 10.06%).

1-(4-*tert*-Butylbenzyl)benzimidazole-4-carboxylic acid (7b)

To a mixture of 2-trichloromethylbenzimidazole-4-carboxylic acid (0.182 g, 0.578 mmol) and caesium carbonate (0.414 g, 1.27 mmol) in dry DMF (1.5 cm^3) was added 4-*tert*-butylbenzyl bromide (0.127 cm^3, 0.693 mmol). The mixture was heated (80 °C) under an argon atmosphere for 35 h. On cooling, DMF was removed and the solid was washed with water (20 cm^3). Recrystallisation from chloroform gave the product as a white solid, 100 mg (58%); mp 198 °C; δ_H(75% $CDCl_3$–25% CD_3OD) 1.27 (9 H, s, CH_3), 5.44 (2 H, s, CH_2), 7.39 (4 H, s, benzyl Ar), 7.63 (1 H, t, H6), 8.05 (1 H, d, H7), 8.20 (1 H, d, H5), 9.48 (1 H, s, H2); δ_C(CD_3OD) 31.64 (CH_3), 35.41 (CH_2), 68.3 (C2), 118.6, 120.7, 126.5, 127.6, 129.5, 131.0, 133.2, 148.8, 152.8, 154.3, 165.3 (COOH); *m*/*z* (DCI, NH_3) (M^+ + 1) 309, (M^+ − Ar) 163; ν_{max}(KBr)/cm^{-1} 3425 (OH), 3100, 2961, 1706 (COOH), 1289 [Found: 309.1603 (M^+ + 1). Calc. for $(C_{19}H_{20}N_2O_2 + H)^+$: 309.1603].

4,4′-Dibromo-2,2′-bis(1*H*-benzimidazole) (9)

To a stirred solution of 3-bromo-1,2-diaminobenzene (2.98 g, 15.9 mmol) in dry methanol (25 cm^3), methyl-2,2,2-trichloroacetimidate (0.95 cm^3, 7.67 mmol) was added followed by concentrated hydrochloric acid (0.02 cm^3). After 3 h fine mesh potassium carbonate (0.5 g) was added, followed by another addition (1 g) 3 h later. After 18 h water (80 cm^3) was added and the yellow precipitate collected by filtration and dried under vacuum. The crude product was purified by boiling the mixture in methanol to remove soluble impurities. After cooling to room temperature the mixture was filtered and dried under vacuum to give a yellow solid, 2.32 g (75%); mp > 350 °C; δ_H($CDCl_3$–0.5% TFA) 7.55 (2 H, t, H6), 7.83 (2 H, d, H7), 7.89 (2 H, d, H5); δ_C($CDCl_3$–0.5% TFA) 107.8 (CBr), 115.0, 131.0, 133.0, 133.2 (C–C), 133.8, 134.0; *m*/*z* (DCI, NH_3) 391 (M^+ + 1), 393 (M^+ + 1), 395 (M^+ + 1); ν_{max}(KBr)/cm^{-1} 1395, 1341, 778, 741, 732 (Found: C, 42.54; H, 2.01; N, 14.17. $C_{14}H_8Br_2N_4$ requires: C, 42.89; H, 2.06; N, 14.29%).

1,1′-Bis(4-*tert*-butylbenzyl)-4,4′-dibromo-2,2′-bis(benzimidazole) (10a)

Dimethylformamide (50 cm^3) was added to a mixture of 4,4′-dibromo-2,2′-bis(1*H*-benzimidazole) (2.97 g, 7.58 mmol) and caesium carbonate (5.43 g, 16.7 mmol) and the mixture was stirred at room temperature under a nitrogen atmosphere for 15 min. 4-*tert*-Butylbenzyl bromide (3.78 g, 16.7 mmol) was added and the temperature raised to 80 °C for 18 h. On cooling, methanol (70 cm^3) was added and the precipitate collected by filtration, washed with water (40 cm^3) and dried to give an off-white solid. Recrystallisation from methanol gave a white solid, 4.7 g (90%); mp 316–317 °C; δ_H($CDCl_3$–0.5% TFA) 1.21 (18 H, s, CH_3), 5.53 (4 H, s, CH_2), 7.10 (4 H, d, H10), 7.27 (4 H, d, H11), 7.67 (4 H, m, H6 and H7), 7.96 (2 H, dd, H5); δ_C($CDCl_3$–0.5% TFA) 30.82 (CH_3), 34.74 (C), 51.38 (CH_2), 109.8, 112.4, 126.8, 127.2, 127.8, 130.1, 133.8, 134.1, 134.3, 154.2; *m*/*z* (DCI, NH_3) 687 (M^+ + 1), 685 (M^+ + 1), 683 (M^+ + 1), 607 (M − Br^+ + 2), 605 (M − Br^+ + 2), 537 [M − $CH_2C_6H_4C(CH_3)_3{}^+$ + 2], 527 (M − $2Br^+$ + 3), 459 [M − Br − $CH_2C_6H_4C(CH_3)_3{}^+$ + 3]; ν_{max}(KBr)/cm^{-1} 2964, 1410, 1334, 744 (Found: C, 63.38;

H, 5.26; N, 8.19. $C_{36}H_{36}Br_2N_4$ requires C, 63.17; H, 5.30; N, 8.18%).

1,1′-Bis(4-*tert*-butylbenzyl)-2,2′-bis(benzimidazole)-4,4′-dicarboxylic acid (4a)

To a cold (−78 °C) slurry of 1,1′-bis(4-*tert*-butylbenzyl)-4,4′-dibromo-2,2′-bis(benzimidazole) (1 g, 1.46 mmol) in dry THF ($30\ cm^3$) was added BuLi ($2.64\ cm^3$, 3.22 mmol) under a nitrogen atmosphere. After 1 h, dry CO_2 was bubbled through the mixture for 20 min which was allowed to warm to room temperature. Water was added ($30\ cm^3$) and the solution was acidified to pH 1 (HCl). The mixture was extracted with chloroform ($3 \times 20\ cm^3$), dried ($MgSO_4$), filtered and concentrated to give a light yellow solid. After recrystallization from methanol the residue was taken up in chloroform ($30\ cm^3$) and adsorbed onto silica. The starting material was recovered by washing the silica (2% MeOH–98% CH_2Cl_2, $3 \times 20\ cm^3$) and the product was then abstracted from the silica (40% MeOH–60% CH_2Cl_2, $3 \times 30\ cm^3$). The product eluate was filtered and the solution evaporated under reduced pressure. The resulting solid was stirred with hydrochloric acid (0.01 mol dm^{-3}, $40\ cm^3$) at 40 °C for 10 h, filtered, washed with water and dried under vacuum (25 °C, 0.1 mmHg); 0.52 g (58%); mp 290 °C; δ_H($CDCl_3$) 1.26 (18 H, s, CH_3), 6.06 (4 H, s, CH_2), 7.01 (4 H, d, *ortho*-H), 7.30 (4 H, d, *meta*-H), 7.52 (2 H, t, H6), 7.68 (2 H, d, H7), 8.20 (2 H, d, H5); δ_C($CDCl_3$) 31.19 (CH_3), 34.55 (C), 49.40 (CH_2), 116.4, 120.1, 125.6, 125.9, 126.1, 127.3, 131.5, 135.5, 140.7, 141.4, 151.5, 165.2 (CO_2H); *m*/*z* (DCI, NH_3) 615 ($M^+ + 1$), 469 [$M^+ - CH_2C_6H_4C(CH_3)_3 + 2$]; ν_{max}(KBr)/cm^{-1} 3211 (OH), 2955 (CHs), 1740 (C=O), 1392, 1346, 755 (Found: C, 73.04; H, 6.29; N, 8.93. $C_{38}H_{38}N_4O_4{\cdot}0.5H_2O$ requires C, 73.17; H, 6.30; N, 8.98%).

1,1′-Dibenzyl-4,4′-dibromo-2,2′-bis(benzimidazole) (10b)

DMF ($9\ cm^3$) was added to a mixture of 4,4′-dibromo-2,2′-bis(1*H*-benzimidazole) (0.5 g, 1.28 mmol) and caesium carbonate (0.915 g, 2.81 mmol) and the mixture was stirred at room temperature under an argon atmosphere for 10 min. Benzyl bromide ($0.333\ cm^3$, 2.80 mmol) was rapidly added and the mixture heated at 80 °C for 18 h. After cooling, methanol ($40\ cm^3$) was added and the resultant precipitate was collected by filtration, washed with water and dried under vacuum to give a white solid, 0.55 g (75%) which was recrystallised from chloroform, mp > 250 °C; δ_H($CDCl_3$–0.5% TFA) 5.53 (4 H, s, CH_2), 6.74 (4 H, d, *ortho*-H), 7.08 (4 H, t, *meta*-H), 7.18 (2 H, t, *para*-H), 7.38 (4 H, d + d, H5 + H7), 7.73 (2 H, t, H6); δ_C($CDCl_3$–TFA) 50.36 (CH_2), 111.2, 111.9, 126.8 (*ortho*-C), 128.8, 129.3, 129.4 (*meta*-C), 130.4, 132.3, 134.4, 135.8, 136.6; *m*/*z* (EI^+) 572 (M^+), 481 ($M^+ - CH_2C_6H_5$), 401 ($M^+ - Br - CH_2C_6H_5$); ν_{max}(KBr)/cm^{-1} 1413, 1335, 747, 715, 696 (Found: C, 56.90; H, 3.49; N, 9.25. $C_{28}H_{20}Br_2N_4{\cdot}H_2O$ requires: C, 56.97; H, 3.78; N, 9.49%).

1,1′-Dibenzyl-2,2′-bis(benzimidazole)-4,4′-carboxylic acid (4b)

To a cold slurry (−78 °C) of 1,1′-dibenzyl-4,4′-dibromo-2,2′-bisbenzimidazole (0.179 g, 0.313 mmol) in dry THF ($10\ cm^3$) butyllithium (1.18 mol dm^{-3}; $0.58\ cm^3$, 0.69 mmol) was added. The mixture was stirred under an argon atmosphere for 3 h. Dry carbon dioxide was bubbled through the mixture for 10 min and the mixture was allowed to warm to room temperature. Water ($30\ cm^3$) was added and the solution acidified to pH 1 (HCl). The mixture was extracted with chloroform (3 × 20 ml) and concentrated to give an off-white solid. Purification by column chromatography on silica (eluent 3% CH_3OH–97% CH_2Cl_2 to 50% CH_3OH–50% CH_2Cl_2) gave a white solid. This was stirred with dilute hydrochloric acid (0.05 mol dm^{-3}, $40\ cm^3$) for 12 h at room temperature and vacuum dried to give the product as a white solid, 27 mg (17%), mp > 250 °C; δ_H($CDCl_3$) 6.09 (4 H, s, CH_2), 7.05 (4 H, m, *ortho*-H), 7.29 (6 H, m, *meta*- and *para*-H), 7.54 (2 H, t, H6), 7.67 (2 H, dd, H7), 8.23 (2 H, dd, H5); δ_C($CDCl_3$) 49.69 (CH_2), 116.2, 120.2, 125.8, 126.0 (*ortho*-C), 127.5, 128.5, 129.3 (*meta*-C), 134.6, 135.6, 140.8, 141.4, 165.1 (COOH); *m*/*z* (DCI, NH_3) 503 ($M^+ + 1$), 459 ($M^+ - COOH + 2$), 415 ($M^+ - 2COOH + 3$), 369 ($M^+ - CH_2Ph - COOH + 3$), 325 ($M^+ + CH_2Ph - 2COOH + 4$); ν_{max}(KBr)/cm^{-1} 3447 (OH), 1736 (C=O), 1407, 1396, 724 (Found: C, 71.4; H, 4.61; N, 11.1. $C_{30}H_{22}N_4O_4$ requires C, 71.7; H, 4.39; N, 11.2%).

1,1′-Bis-(4-dodecylbenzyl)-4,4′-dibromo-2,2′-bis(benzimidazole) (10c)

Dimethylformamide ($20\ cm^3$) was added to a mixture of 4,4′-dibromo-2,2′-bis-(1*H*-benzimidazole) (1 g, 2.55 mmol) and caesium carbonate (1.8 g, 5.52 mmol) and the mixture stirred at room temperature under argon for 5 min. 4-Dodecylbenzyl bromide (1.9 g, 5.61 mmol) was added and the temperature raised to 80 °C for 36 h. Once cooled, the mixture was poured onto methanol ($100\ cm^3$) and the solid collected by filtration, washed with water ($40\ cm^3$) and dried under vacuum to give a light yellow solid, 1.64 g (71%). Crystallisation from light petroleum (bp 40–60 °C) gave a white solid mp 134–137 °C; δ_H($CDCl_3$) 0.65–1.7 (50 H, br m, $C_{12}H_{25}$), 6.25 (4 H, s, NCH_2), 7.05–7.2 (10 H, m, Ar CHs), 7.38 (2 H, t, H6) 7.50 (2 H, d, H5); *m*/*z* (DCI, NH_3) 910 ($M^+ + 1$), 896 ($M^+ - CH_2 + 1$), 882, 868, 854, 840; ν_{max}(KBr)/cm^{-1} 2980 (CHs), 1420, 1340, 770 (Found: C, 67.48; H, 7.54; N, 6.35. $C_{52}H_{68}Br_2N_4{\cdot}H_2O$ requires C, 67.38; H, 7.54; N, 6.19%).

1,1′-Bis-(4-dodecylbenzyl)-2,2′-bis(benzimidazole)-4,4′-dicarboxylic acid (4c)

To a cooled solution (−78 °C) of 1,1′-bis(4-dodecylbenzyl)-4,4′-dibromo-2,2′-bis(benzimidazole) (0.8 g, 0.88 mmol) in dry THF ($20\ cm^3$) was added butyllithium (1.18 mol dm^{-3}; $1.80\ cm^3$, 2.11 mmol). After 18 min of stirring under an argon atmosphere, dry carbon dioxide was bubbled through the solution for 10 min. After warming to room temperature, water ($15\ cm^3$) was added and the acidity adjusted to pH 1. The mixture was extracted with diethyl ether ($3 \times 15\ cm^3$), dried ($MgSO_4$) and concentrated to give a yellow solid. Crystallisation from light petroleum (bp 40–60 °C) gave the product as a light yellow solid, 0.5 g (68%); mp 198–203 °C; δ_H($CDCl_3$) 0.4–1.6 (50 H, m, $C_{12}H_{25}$), 6.04 (4 H, s, CH_2), 6.99 (4 H, d, *ortho*-H), 7.19 (4 H, d, *meta*-H), 7.52 (2 H, t, H6), 7.68 (2 H, d, H7), 8.21 (2 H, d, H5); *m*/*z* (DCI, NH_3) 839 ($M^+ + 1$), 825 ($M^+ - CH_2 + 2$), 811, 795; ν_{max}(KBr)/cm^{-1} 3182 (OH), 2956, 2928, 2867 (CH), 1736 (C=O), 1403, 1361, 758 (Found: C, 77.33; H, 8.42; N, 6.66. $C_{54}H_{70}N_4O_4$ requires C, 77.29; H, 8.41; N, 6.68%).

1,1′-Di(4-*tert*-butylbenzyl)-2,2′-bis(benzimidazole) (11)

4-*tert*-Butylbenzyl bromide ($1.36\ cm^3$, 7.4 mmol) was added to a slurry of 2,2′-bis(1*H*-benzimidazole) (0.395 g, 1.69 mmol) and caesium carbonate (1.21 g, 3.71 mmol) in DMF ($30\ cm^3$). The mixture was heated (80 °C) under nitrogen and the course of the reaction followed by TLC on silica [1% MeOH–99% CH_2Cl_2; R_f(product) = 0.83]. After 24 h more 4-*tert*-butylbenzyl bromide ($0.681\ cm^3$, 3.71 mmol) was added and the mixture was heated for a further 6 h. Reduced pressure distillation of DMF left a green-yellow solid. The solid was taken up into chloroform ($40\ cm^3$), filtered and concentrated. Purification by column chromatography on silica (CH_2Cl_2) gave a yellow solid, 194 mg (22%), δ_H($CDCl_3$) 1.33 (18 H, s, CH_3), 5.31 (4 H, br s, CH_2), 6.52–6.7 (4 H, m), 6.82 (2 H, t), 7.01 (2 H, t), 7.13 (2 H, m), 7.28–7.38 (6 H, m); δ_C($CDCl_3$) 31.35 (CH_3), 34.68 (ArC), 45.66 (NCH_2), 104.7, 113.7, 122.5, 125.5, 125.7, 126.5, 126.8, 131.6, 133.5, 139.1, 149.9; *m*/*z* (DCI NH_3) 528 ($M^+ + 1$), 527 (M^+), 381 ($M^+ - CH_2ArBu^t$), 235 ($M^+ - 2 \times CH_2ArBu^t$); ν_{max}(KBr)/cm^{-1} 2962, 1472 (C=N), 738 (Found: C, 82.32; H, 7.24; N, 10.16. $C_{34}H_{34}N_4$ requires: C, 82.09; H, 7.27; N, 10.64%).

Acknowledgements

We thank EPSRC for support under the CASE scheme, the BBSRC for an equipment grant (B0223) and the EPSRC mass spectrometry service for accurate mass determinations.

References

1 I. Bertini, C. Luchinat, W. Maret and M. Zeppezauer, eds., *Zinc Enzymes*, Brikhauser, Boston, 1986; T. Koike, S. Kajitani, I. Nakamura, E. Kimura and M. Shiro, *J. Am. Chem. Soc.*, 1995, **117**, 1210.

2 *'Hydrometallurgy—Fundamentals, Technology and Innovations'*, eds. J. B. Hiskey and G. W. Warren, Soc. Min. Metall. Expl., Littleton, Colorado 1993.

3 H. M. N. H. Irving and R. J. P. Williams, *J. Chem. Soc.*, 1953, 3192.

4 R. D. Shannon, *Acta Crystallogr., Sect. A*, 1976, **32**, 751.

5 *The Biological Chemistry of the Elements*, J. J. R. Frausto da Silva and R. J. P. Williams, Clarendon Press, Oxford, 1991, pp. 24–45.

6 B. G. Stephens, H. L. Felkel Jr. and W. M. Spinelli, *Anal. Chem.*, 1974, **46**, 692; G. Dessy and V. Fares, *Cryst. Struct. Commun.*, 1979, **8**, 507.

7 C. O. Dietrich Buchecker, J.-P. Sauvage and J.-M. Kern, *J. Am. Chem. Soc.*, 1984, **106**, 3043; C. O. Dietrich Buchecker and J.-P. Sauvage, *Chem. Rev.*, 1987, **87**, 795.

8 E. Kimura, I. Nakamura, T. Koike, M. Shionaya, Y. Kodama, T. Ikeda and M. Shiro, *J. Am. Chem. Soc.*, 1994, **116**, 4764.

9 N. W. Alcock, A. C. Benniston and P. Moore, *J. Chem. Soc., Chem. Commun.*, 1991, 706; T. Koike, E. Kimura, I. Nakamura, Y. Hashimoto and M. Shiro, *J. Am. Chem. Soc.*, 1992, **114**, 7338.

10 D. Barnes, A. Bashall, G. B. Bates, L. F. Burgess, D. C. Cupertino, R. F. Dalton, T. J. Denning, R. Docherty, M. McPartlin, D. Parker, I. J. Scowen, P. A. Tasker and D. Thorp, submitted for publication in *Angew. Chem., Int. Ed. Engl.* and unpublished work.

11 J.-M. Lehn, J.-P. Sauvage, J. Simon, R. Ziessel, C. Piccinni Leopardi, G. Germain, J.-P. Declercq and M. Van Meerssche, *Nouv. J. Chim.*, 1983, **7**, 413.

12 J.-M. Lehn, A. Rigault, J. Siegel, J. Harrowfield, B. Chevrier and D. Moras, *Proc. Natl. Acad. Sci. USA*, 1987, **87**, 2565; A. F. Williams, C. Piguet and G. Bernardinelli, *Angew. Chem., Int. Ed. Engl.*, 1990, **29**, 1140.

13 R. D. Hancock and A. E. Martell, *Chem. Rev.*, 1989, **89**, 1875.

14 Molecular modelling studies suggested that carboxy groups in the 4 and 4′ positions can chelate with N(3) to a small tetrahedrally coordinating cation in a '2 + 2' M_2L_2 complex.

15 J. B. Jones and K. E. Taylor, *Can. J. Chem.*, 1977, **55**, 1653.

16 G. Holan, E. L. Samuel, B. C. Ennis and R. W. Hinde, *J. Chem. Soc. C*, 1967, 20.

17 H. Schaefer and K. Gewald, *Z. Chem.*, 1976, **16**, 272.

18 T. Neilson, H. C. S. Wood and A. G. Wylie, *J. Chem. Soc.*, 1962, 371.

19 L. Collie, J. E. Denness, D. Parker, F. O'Carroll and C. Tachon, *J. Chem. Soc., Perkin Trans. 2*, 1993, 1747.

20 Given that the *N*,*O*-bound 1 : 1 complex of zinc with **4a** is likely to be weaker than with copper(II), it is likely that K_2 has a value of at least 10^3 (*cf.*, 400 for Cd^{II}), consistent with positive cooperativity in binding.

21 G. R. Agnes and G. Horlick, *Appl. Spectrosc.*, 1994, **48**, 655; J. M. Curtis, P. J. Derrick, A. Schnell, E. Constantin, R. T. Gallagher and J. R. Chapman, *Org. Mass. Spectrom.*, 1992, **27**, 1176.

22 F. Bitsch, C. O. Dietrich-Buchecker, A. K. Khemiss, J.-P. Sauvage and A. Van Dorsselaer, *J. Am. Chem. Soc.*, 1991, **113**, 4023; E. Leize, A. Van Dorsselaer, R. Kramer and J.-M. Lehn, *J. Chem. Soc., Chem. Commun.*, 1993, 990.

Paper 5/07035J
Received *25th October* 1995
Accepted *8th January* 1996