Exchange in Mixtures of Cadmium with Bis(benzimidazoles)

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Mixtures of cadmium salts and benzimidazoles have been examined by ^1H, ^{13}C and ^{113}Cd NMR spectroscopy in dimethyl sulfoxide and in dimethyl sulfoxide–chloroform mixtures. Evidence of exchange processes both for cadmium entities and for ligand entities was obtained. Structure–shift relationships for ^{113}Cd NMR signals were examined, but were found not to apply. The exchange was slowed in the mixed solvent and on cooling, permitting individual components to be identified (the cadmium entities with stoichiometry CdL_3, CdL_2, CdL, and solvated Cd, identified from the cadmium NMR spectra, and ligand-containing species CdL_2 from proton spectra). Structural hypotheses relating to complexes are made and the role of these species in the observable exchange processes is explored.

The mechanism of exchange of ligands of series **I** in cadmium chloride mixtures was examined[1] by ^1H NMR spectroscopy previously, using the spectrum of the aromatic rings as probe. In mixtures containing an excess of cadmium chloride, exchange of ligand L^1 was found to occur only after dissociation of the complex; equation (1) followed by (2) was suggested as a

$$[CdL]^{2+} \overset{k_d}{\rightleftharpoons} L + Cd^{2+} \quad (1)$$

$$L \rightleftharpoons L^* \quad (2)$$

possible route, where the asterisk in (2) is a label to show that a prototropic change has taken place, as indicated in Scheme 1.

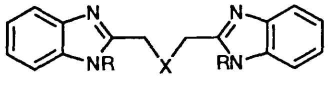
In the presence of an excess of ligand the mechanism was associative at the concentrations used, and equation (3) was

$$L^* + [CdL]^{2+} \rightleftharpoons [CdL^*]^{2+} + L \quad (3)$$

proposed. It was also shown that the tertiary and secondary nitrogens of the benzimidazole structure effectively exchanged, in or immediately following the rate-determining step. The exchange was recognised in the NMR spectrum by the appearance of a single ABCD spectrum at low temperatures coalescing at room temperature to give an apparently symmetrical benzimidazole ligand with an AA′BB′ spectrum: the minimum detail required for this exchange is illustrated in Scheme 1. It was postulated that the exchange observable had to result from attack by a secondary NH, replacing a tertiary N in the cadmium co-ordination sphere, followed by NH exchange between the secondary and tertiary N as in equation (2). A further process of lower energy was postulated to involve attack by tertiary nitrogen. In this study we have looked in more detail at the NH exchange (using ^1H NMR spectroscopy, at ratios of [L]:[Cd] above and below unity); we have also looked at proton, carbon and cadmium spectra for several systems. The kinetic behaviour of one ligand L^2 was appropriate for elucidation of more details of the exchange at lower temperatures, confirming that in low-temperature processes it must employ the tertiary N both as attacking agent and as displaced group. Ligand L^2 in other work[2] was found (in its alkylated form L^3) to be selective for cadmium over zinc and copper. The new evidence is assessed in this paper in relation to the exchange mechanism proposed earlier.[1]

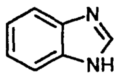
Previous workers have used ^{113}Cd NMR spectroscopy as a probe to characterise the metallic binding sites in metalloproteins, because of the extreme shift sensitivity of this nucleus to changes in co-ordinating features of the ligand. Several reviews of ^{113}Cd NMR research are available.[3–5] Where the

Scheme 1 Illustration of A $\rightleftharpoons$ D, B $\rightleftharpoons$ C, with effective $2^yN \rightleftharpoons 3^yN$. The resulting spectrum is AA′BB′ in the fast-exchange limit, and ABCD in the slow-exchange limit (observed for L^1)



I

	X	R
L^1	SCH_2CH_2S	H
L^2	OCH_2CH_2O	H
L^3	OCH_2CH_2O	C_6H_{13}



L^4

cadmium is static on the NMR time-scale, structure–shift relationships have been established[6] for simple ligands, which have been valuable in interpreting shifts for cadmium in protein sites. In some cases, resonances are broadened by chemical exchange to such an extent that they become impossible to detect under the usual sampling conditions, while in others rapid chemical exchange gives an averaged signal the shift of which is not readily interpreted in terms of a specific co-ordinating arrangement. The difficulties due to rapid exchange can be prevented if solid-state spectra are examined,[7] or if the system is cooled sufficiently to slow the reaction.[8] We have also found that a mixed solvent slows the cadmium exchange considerably. Solid-state spectra have been found valuable elsewhere in assessing chemical shift anisotropy of cadmium.[9]

Experimental

Materials were obtained as previously described.[1,2] The NMR spectra were obtained on a Bruker WM300WB instrument at 66.6 (^{113}Cd), 300 (^1H) and 75 MHz (^{13}C). Shift-correlation experiments were run with $Cd(NO_3)_2$ plus ligand in deuteriated dimethyl sulfoxide. A typical cadmium room-temperature experiment required *ca.* 100 000 scans to accumulate data, since resonances were wide. Experiments at lower temperatures, where signals were sharper, could be completed with 5800 scans.

Table 1 Chemical shifts and linewidths from ^{113}Cd NMR spectrum[a]

$[L^1]$/mol dm^{-3}	δ^b	$\omega_{\frac{1}{2}}$/Hz^c
0.300	82.3	1250
0.200	65.8	1620
0.130	49.4	2240
0.100	38.0	1250
0.067	28.8	1200
0.025	16.8	810
0.020	16.6	510
0.017	16.1	490

[a] All samples contained 0.100 mol dm^{-3} $Cd(NO_3)_2$ in $(CD_3)_2SO$ at 300 K, relative to molar aqueous $Cd(NO_3)_2$ as reference. [b] ± 2%. [c] ± 5%.

Table 2 Effect on ^{113}Cd signal of adding benzimidazole*

$[L^4]$/mol dm^{-3}	$[AgNO_3]$/ mol dm^{-3}	δ	$\omega_{\frac{1}{2}}$/Hz
0.4	0.0	94	440
0.6	0.0	111	480
0.6	0.1	96	480

* Details of NMR spectra as in Table 1. $[Cd(NO_3)_2] = 0.1$ mol dm^{-3}.

Table 3 Effect of $AgNO_3$ on ^{113}Cd NMR linewidth and shift for ligands L^1 and L^2[a]

$[Cd^{2+}]$/ mol dm^{-3}*	$[Ag^+]$/ mol dm^{-3}	$[L^2]$/ mol dm^{-3}	$[L^1]$/ mol dm^{-3}	δ	$\omega_{\frac{1}{2}}$/Hz
0.100	0.100	0.000	0.025	10	15
0.100	0.000	0.000	0.025	17	810
0.020	0.020	0.010	0.000	14	10
0.100	0.000	0.050	0.000	16	1080
1.000	0.000	0.000	0.000	0	10

* NMR spectra obtained as for Table 1. Note extreme narrowness of linewidths when the ligand is complexed to silver and unavailable for co-ordination to Cd.

All signals were referenced to $Cd(NO_3)_2$ in water (1 mol dm^{-3}) assigned at 0 ppm unless otherwise stated. Resonances were also sharper when examined at higher temperatures.

NMR Exchange Processes with NH.—The NH proton of the benzimidazoles was not usually observed at room temperatures, but when samples were cooled, a broad resonance emerged at *ca.* δ 13.3 in most systems, clearly in exchange with the signal for residual water in the system (usually about δ 3.7). The separation of the two signals (*ca.* 2800 Hz) made it possible to determine rates in the slow-exchange region at low temperatures. The signals were treated as part of a two-site exchange (unequal populations, uncoupled sites). The spectra were drawn on a compressed scale (*ca.* 250 Hz per cm) to facilitate examination and fitting of spectra. The populations of the two sites were determined by integration. The temperature dependence of the signals was determined and the appropriate shifts were used in simulations, which used programs from the SERC NMR Program Library as previously.[1] Compound L^1 was used with $CdCl_2$ as salt. Low-temperature spectra were obtained in deuteriochloroform–$(CD_3)_2SO$ (1:1) and always contained additional water. Spectra used for the kinetic simulations were all obtained with an excess of $CdCl_2$ so it was assumed all ligand was complexed and the observed NH signal pertained to the complex only.

Results and Discussion

It was necessary to review the available information on the structures of cadmium complexes in dimethyl sulfoxide (dmso) and to evaluate published cadmium NMR data before considering the various observable processes. Ahrland and co-workers[10–13] have studied the nature of cadmium complexes in dmso, reporting on the formation constants for cadmium halide species. More than one stereochemistry for the cadmium species present was proposed. An octahedrally co-ordinated Cd–dmso solvate was formed, but the species $[CdL_4]^{2-}$ ($L = Cl^-$, Br^-, I^- or SCN^-) were all tetrahedral. A recent crystal structure of a mixed dmso–methanol solvate of cadmium chloride shows Cd bridged by chloride ions forming a polymeric chain, with octahedral co-ordination of the cadmium completed by one dmso and one methanol molecule co-ordinating to each Cd. The cadmium bromide double solvate has a related polymeric chain structure.[14] The NMR shifts of the ^{113}Cd nucleus cover a wide range and are useful in assessing donor-atom type and co-ordination. Summers and co-workers[5,6] obtained slow-exchange spectra for compounds containing N-donor chelate ligands in $(CD_3)_2SO$ and D_2O solutions, together with the weakly binding nitrate or perchlorate, and derived a structure–shift relationship [equation (4)] to calculate shifts obtained in

$$\delta = 75A + 51B + 31C \qquad (4)$$

$(CD_3)_2SO$ solution and referenced to 1.0 mol dm^{-3} $Cd(NO_3)_2$ in $(CD_3)_2SO$, where A, B and C are the number of primary, secondary and tertiary (or pyridine) N-donor atoms respectively. This shift relationship was shown not to hold for complexes in fast exchange. An additional term D was later added for the number of benzimidazoles co-ordinated [equation (5)], the value for the cadmium shift per benzimidazole being 42 ppm.

$$\delta_{calc} = 75A + 51B + 31C + 42D \qquad (5)$$

Cadmium NMR Spectra.—Our initial results for room-temperature ^{113}Cd spectra of the $Cd(NO_3)_2$ mixtures of ligand L^1 in dimethyl sulfoxide did not conform to the relationship (5), presumably because of unfavourable exchange rates. Usually a single broad signal was observed, at all [Cd]:[L] ratios. The observed shifts and linewidths are shown in Table 1. Note the maximum line-width and a smooth change in the shift variation occur near the 1:1 ratio. However, even at high or low cadmium to ligand ratios the signals were all broad, suggesting rapid equilibration between a range of specific cadmium sites. For a 1:1 complex of ligand L^1 in our studies equation (5) would give a calculated shift δ_{calc} 84 assuming that only the two benzimidazole tertiary N per ligand were bound, while the actual shift at the ratio [Cd]:[L] = 1:1 (Table 1) is $\delta_{obs} \approx 38$. However, the linewidths of our data made it probable that fast exchange was affecting the results. Since the thioether is also a potential donor, and a model for the side-chain donor of methionine, we compared the effects of ligands L^1 and L^2 (where S is replaced by O). Also silver was added to complex preferentially with the benzimidazole nitrogens of L^1 and L^2, in the hope of interpreting the residual cadmium signals in terms of other donors present. In most cases unfortunately there was fast exchange (shown by the large linewidth) which complicated the interpretation. The results are in Tables 2 and 3.

Since the ligand used by Summers *et al.*[6] to establish the shift value [as shown in equation (5)] for benzimidazole was a tripod, and might have special characteristics of a 'pocket', free benzimidazole itself L^4 was used in our study. Table 2 summarises the results. In the mixture of composition [L]:[Cd] = 6:1 ($L = L^4$) the observed shift is only δ 111, suggesting incomplete co-ordination. On addition of an equimolar quantity of $AgNO_3$ (which is extremely likely to form a 2L:Ag complex and so remove 2L per Ag, returning the [L]:[Cd] ratio to 4:1), the cadmium shift returns to δ 96 showing that silver is preferentially co-ordinated by the ligand. In earlier studies of the Cd^{II}–imidazole system by Munakata *et al.*[8] where $Cd(ClO_4)_2$ solutions in ethanol were examined at −90 °C, the mole ratio of imidazole (Him) to cadmium was varied from 0 to 6, since stability constants for stepwise co-ordination of imidazole to Cd ($K_1 = 631, K_2 = 126, K_3 = 33.5, K_4 = 13.5$ dm^3 mol^{-1}) showed a progressive drop. In that solvent a separate signal for each complex present could be seen at any particular ratio, with Cd(Him)$_n$ qualitatively seen to be less thermodynamically stable than Cd(Him)$_{n-1}$; at the 6:1 mole ratio the five-co-ordinate complex is the major component of the mixture, with a small proportion of the six-co-ordinate complex. The deshielding efficiency decreases continuously as increasing numbers of imidazole molecules are bound to cadmium (from δ 52 to 30 going from $n = 1$ to 6). Our results for co-ordination of benzimidazole in dmso are consistent with formation of a series of benzimidazole complexes, undergoing rapid exchange of Cd between several sites, but it does not appear that a full complement of 6N donors is observed. It is also clear that silver will displace cadmium from these ligands.

Nature of Cadmium Species in Solution.—Any interpretation of the room-temperature cadmium NMR data in Table 1 is necessarily speculative. However the shift variation and linewidth reversal indicated that there were at least three 'exchanging sites' in equilibrium. It was postulated that these were: a fully complexed species at high ligand concentration, at the composition [Cd]:[L] = 1:1, a 1:1 species, and a signal(s) corresponding to Cd with no co-ordinated benzimidazole nitrogen; the last of these sometimes will correspond to solvated Cd(NO$_3$)$_2$. Three separate cadmium signals were in fact observed for mixtures of Cd with ligand L^2, with [L]:[Cd] ratios up to 2:1, in support of this initial postulate; at the higher ratio [L]:[Cd] = 4:1, a fourth cadmium could be identified, as described below. Judging from linewidths, some of these signals belonged to sites which were composite, consisting of rapidly exchanging entities.

To enable cadmium studies to be undertaken at low temperature, a mixture of CDCl$_3$ and (CD$_3$)$_2$SO was used, which remained liquid down to 230 K in most instances. The effect of this solvent change on the spectra of cadmium mixtures with ligands L^2 or L^3 is an upfield shift from δ 0 to approximately −13. The shifts are referenced to 0.24 mol dm^{-3} Cd(NO$_3$)$_2$ in CDCl$_3$–(CD$_3$)$_2$SO. The most notable difference on going from (CD$_3$)$_2$SO to (CD$_3$)$_2$SO–CDCl$_3$ would appear to be the slowing down of the cadmium-exchange process. The mixed solvent thus provided the opportunity to study systems in a state of slow exchange, which expanded the study dramatically.

Low-temperature Cadmium NMR Spectra in the Presence of Ligand L^2 *in Mixed Solvent.*—At low temperatures, four cadmium signals were found, corresponding in shift to species with 6N (at the composition ratio 3L:Cd), 4N (2L:Cd), 2N (L:Cd) and one with O donors. However, only the signal corresponding to the 4N species was sharp and narrow, indicative of slow exchange, while the other signals, especially that for the 'free' Cd, were broad, suggesting intramolecular or intra-site exchanges, not yet frozen out. Mixtures with a ratio [L]:[Cd] = 1:1 or less gave signals at shifts (linewidths in brackets) of δ 17 (270), 64 (167) and 152 (33 Hz); at the ratio [L]:[Cd] = 2:1 only the signals at δ 64 and 152 were seen, corresponding to the N$_2$ and N$_4$ sites, and at the ratio [L]:[Cd] = 4:1 only signals at δ 152 (30) and 215 (120 Hz), corresponding to the N$_4$ and N$_6$ sites. Fig. 1 shows representative spectra taken at 230 K and different initial ratios of ligand L^2 to cadmium salt. The shift separations between the O, N$_2$, N$_4$ and N$_6$ sites are 47, 88 and 63 ppm respectively. The species giving the narrow signal at δ 152 corresponds to an N$_4$ site. The greater shift separation between the middle two species than for the other pairs may indicate a structural change in the series, *e.g.* between octahedral and tetrahedral geometries round the Cd, or the occurrence of bridged oligomers. Thus a structure–shift relationship was not attempted. The formula [CdL$_n$]$^{2+}$ should not be taken to have a structural implication. The spectra also have mechanistic implications. The spectra give definite evidence that the cadmium sites with N$_2$ and N$_4$ co-ordination are connected by exchange. The reaction shown in equation (6) is suggested to occur in solutions of excess of

$$[\mathrm{CdL}]^{2+} + \mathrm{L} \rightleftharpoons [\mathrm{CdL}_2]^{2+} \qquad (6)$$

ligand L^2 as a possible route. This throws additional light on equation (3) suggested from the exchange of ligand L^1 with cadmium chloride mixtures, which was originally written [1] as an I$_A$ mechanism [equation (3)]. The present result shows the formation of an intermediate associative complex through which reaction (3) proceeds, suggesting an A mechanism [equation (6)] certainly for the cadmium nitrate–ligand L^2 system. The special nature of the N$_4$ site cannot be understood in terms of these equations without more structural verification. Similarly, the cadmium sites with N$_4$ and N$_6$ co-ordination are seen from the cadmium NMR spectra to be connected by an

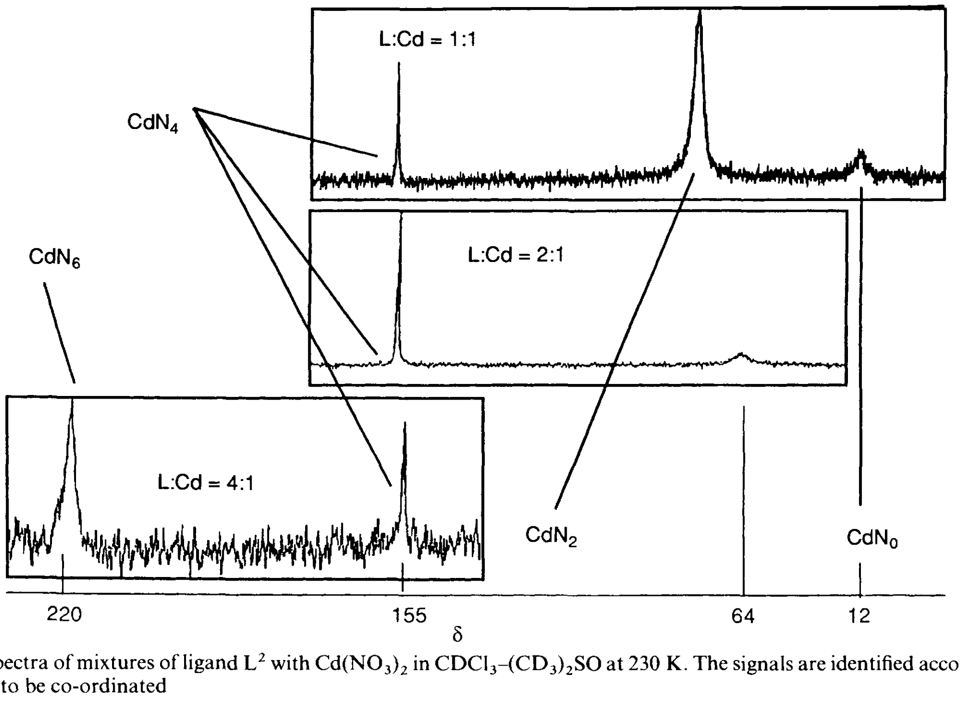


Fig. 1 The ^{113}Cd spectra of mixtures of ligand L^2 with Cd(NO$_3$)$_2$ in CDCl$_3$–(CD$_3$)$_2$SO at 230 K. The signals are identified according to the number of N atoms believed to be co-ordinated

exchange process, for which the additional A mechanism in equation (7) is proposed.

$$[CdL_2]^{2+} + L \rightleftharpoons [CdL_3]^{2+} \qquad (7)$$

^{1}H NMR Spectra of Ligand L^2 *in the Presence of* $Cd(NO_3)_2$ *in Mixed Solvent.*—Examination of the low-temperature ^{1}H NMR spectra gave further information. The presence of more than one cadmium complex was confirmed for the ligand L^2 from detailed ^{1}H NMR studies of appropriate mixtures. In the spectra of mixtures of L^2 with cadmium nitrate at room temperature the signals were not sharp, and so not at the fast-exchange limit; on cooling to 270 K, broad signals, which we assigned from the mass balance and shift as the aryl CH_2O protons of the 2:1 L:Cd complex discovered in the ^{113}Cd studies, began to decoalesce in the aryl CH_2O region from the average signal (a broad singlet). These new signals froze to a pair of sharp doublets indicating the presence of just one AB system, with J_{AB} = 15.9 Hz, typical of a *gem* coupling, in the 2:1 complex. At this temperature, however, only broad resonances for the aromatic protons were seen; fine structure (sharp doublets and triplets) was observed for one component in the aromatic region when the temperature was lowered to 240 K while at 233 K even the NH signal was split into one sharp and one wider resonance; examples are shown in Figs. 2 and 3. The significant information is that sharp signals are found for the 2:1 complex, with clear coupling, while the residual species give wide signals with no fine structure. Fig. 2 shows the emergence of the sharp signals in a 2:1 mixture of ligand L^2 and cadmium salt. Results for mixtures with ratios of L^2 to Cd of 0.75:1, 1:1, 1.3:1 and 2:1 indicated an increase in the concentration of the aromatic species with the sharp signals from 1/10 of the total ligand signal, through 1/7, 1/6 to 1/2. The mass balance requires the presence of residual ligand species and residual cadmium species in each mixture.

Implications from the Aromatic Spectra.—We have evidence from variable-temperature spectra that the AA'BB' system seen at room temperature splits to give one static ABCD and one mobile system, where the signals have no fine structure (shown in Fig. 2). One clear triplet (B or C) is resolved upfield from the rest of the spectra, and one broad aromatic signal is resolved downfield of the other aromatic signals. From the intensities of these two signals, and the appearance of the other overlapping signals, it can be deduced that the residual aromatic signals for this mobile system consist of three broad signals in the ratio 1:1:2, which must also represent a system with four chemically distinct aromatic protons rather than two (EFGH, not AA'BB'). This must result from exchange between at least two such sites, labelled here IJKL and MNOP, and this exchange must preserve the chemical distinction between the four aromatic protons of each site; this requires that the attacking or leaving groups of the benzimidazoles at a cadmium centre must be the tertiary nitrogens in each case as shown in Scheme 2. The ligand can never be unco-ordinated in this process, since the fast tertiary–secondary nitrogen switch [equation (2) and Scheme 1] would effectively symmetrise the aromatic signals. Thus we have evidence for the occurrence of several ligand-containing species, the static 2:1 which gives the ABCD spectrum and the time-averaged mixture EFGH arising from exchange of (at least) two L sites, with IJKL and MNOP aromatic systems. These deductions are valid whether the cadmium complexes are octahedral or tetrahedral, and whether monomer or bridged oligomer. A reasonable postulate is that the 2:1 complex is tetrahedrally co-ordinated with 4N, while the rapidly exchanging mix contains a 1:1 chelate, and possibly a 3:1 chelate, which might be octahedral at Cd. This would be consistent with the anomalous shift separations observed in the cadmium NMR spectra where the N_4 chelate was concerned.

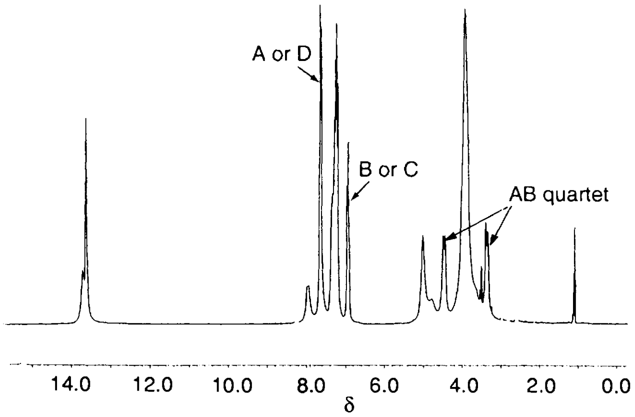


Fig. 2 Proton NMR spectra of a 2:1 mixture of L^2 and $Cd(NO_3)_2$ at 230 K, showing from right to left of the aromatic region, a triplet (B or C, intensity 1), doublet and triplet (intensity 2) superposed on a wide signal (intensity 2), doublet (A or D, intensity 1) superposed on wide line (intensity 1) and lastly a wide line (intensity 1)

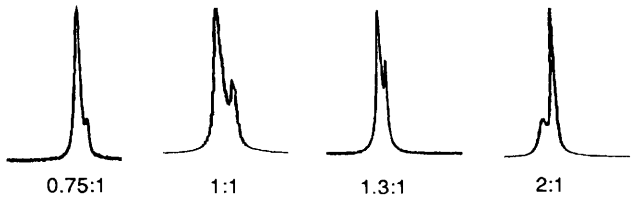
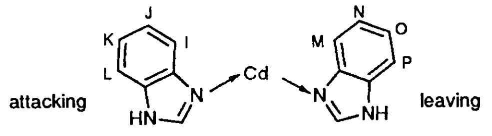


Fig. 3 Expansion of NH signals from the low-temperature ^{1}H NMR spectrum for the L:Cd ratios indicated, L = L^2

The postulated 2:1 complex at its slow-exchange limit must have both ligands equivalent, consistent with a tetrahedral configuration, since there is only one aromatic system (the A and D protons appear as two-line spectra, with the *ortho* coupling constant in the expected range, while the B and C protons are apparent triplets as expected from the two *ortho* couplings to which each is subject). The methylene protons next to the aromatic ring appear as one AB quartet, and hence sets of methylenes are equivalent within one ligand, and between the two purported ligands, yet the two protons of each methylene are distinct. This suggests a rigid, very symmetrical complex, perhaps polymeric and helical. Alternative structures for the mobile sites might include polymeric structures with bridging ligands switching between cadmium species.

Carbon NMR Spectra of Ligand L^2 *in the Presence of* $Cd(NO_3)_2$ *in Mixed Solvent.*—The carbon NMR spectra were then examined in the hope of further elucidation of the ligand-containing species. At room temperature there were only six signals, corresponding to three distinct aromatic carbons, on one ring, and one unique carbon on the imidazole ring, plus one for each aliphatic carbon. This indicates symmetrisation as proposed by Rushton and co-workers.[1] On cooling the three distinct aromatic signals split into pairs (equal intensity), while the unique carbon did not. At still lower temperatures there was evidence of further splitting, but the right temperature range could not be reached with the solvent systems available because



Scheme 2 Illustration of $3^y \rightleftharpoons 3^y$ exchange on Cd. $I \rightleftharpoons M$, $J \rightleftharpoons N$, $K \rightleftharpoons O$, $L \rightleftharpoons P$. The result is an EFGH spectrum in the fast-exchange limit (observed here for L^2), but IJKL + MNOP in the slow-exchange limit. These deductions are valid whether the cadmium complexes are monomers or oligomers, have dangling ligands, and whether Cd is octahedral or tetrahedral, or has an intermediate geometry

Table 4 Rate constants for the NH $\longleftrightarrow$ H_2O exchange[a]

T/K	$[L^1]$/ mol dm^{-3}	[LiCl]/ mol dm^{-3}	k/s^{-1}
298	0.100		—
	0.050[b]		500
	0.050[c]	0.100	360
	0.033[d]		300
280	0.100		—
	0.050		210
	0.050	0.100	182
	0.033		150
270	0.100		—
	0.050		120
	0.050	0.100	120
	0.033		100
260	0.100		—
	0.050		70
	0.050	0.100	80
	0.033		60
250	0.100		—
	0.050		40
	0.050	0.100	50
	0.033		40
240	0.100		—
	0.050		20
	0.050	0.100	30
	0.033		20

[a] All samples contained 0.100 mol dm^{-3} $CdCl_2$. [b] Arrhenius energy for this composition 32.8 kJ mol^{-1} (s.d. 0.16). [c] Arrhenius energy for this composition 25.4 kJ mol^{-1} (s.d. 0.09). [d] Arrhenius energy for this composition 27.3 kJ mol^{-1} (s.d. 0.32).

Table 5 Summary of processes for which evidence has been obtained

Process	Conditions	Evidence
(1)	[Cd]:[L] $\geqslant$ 1:1	^{1}H ABCD $\longleftrightarrow$ AABB*
(2)	Free L	^{1}H*
(3)	[L]:[Cd] $\geqslant$ 1:1	^{1}H and ^{113}Cd
(3)	[L]:[Cd] $\approx$ 2:1	^{1}H IJKL + MNOP $\longleftrightarrow$ EFGH
(6)	[L]:[Cd] $\approx$ 2:1	^{113}Cd
(7)	[L]:[Cd] $\approx$ 3:1	^{113}Cd
(8)	[Cd]:[L] $\geqslant$ 1:1	^{1}H NH + H_2O $\longleftrightarrow$

* Ref. 1.

of unfavourable solubilities, and no further information could be obtained.

The NH $\longleftrightarrow$ H_2O *Exchange*.—The dissociative pre-equilibrium (1) was postulated previously[1] to account for retardation of the ABCD $\longleftrightarrow$ DCBA exchange by excess of cadmium in the L^1 system with $CdCl_2$. This is consistent with the overall rate of the ligand-exchange process becoming vanishingly small at $[Cd^{2+}] = \infty$ and points to the occurrence of a step such as the forward reaction in (1), before the critical exchange, which must include a step such as (2). The NMR spectra for the exchange reactions of L^1 with an excess of or equimolar $CdCl_2$ show an exchange between the residual water from the solvent and the NH groups of the benzimidazole; since exchange of NH in the free benzimidazole is known to be fast on the time-scale concerned, the slow process observed in the NMR spectra must represent the (overall) exchange of the NH of complexed benzimidazole with water [equation (8)], not

$$Cd(L\ NH^*) + H_2O \longrightarrow Cd(L\ NH) + HOH^* \quad (8)$$

necessarily in a single step. The water signal lies between the two aliphatic signals and its position was verified in similar mixtures of benzimidazole and $CdCl_2$ and also for other bis(benzimidazole) ligands, and for the L^2 with $Cd(NO_3)_2$ or with $AgNO_3$ as salt. A similar exchange is seen in all of these situations. Table 4 shows the rate of proton exchange between NH and H_2O, determined by line-shape analysis. The rate constants are slightly less (by a factor of 3) than for the aromatic symmetrisation (rate constants for which appear in ref. 1), and were obtained for the same spectra, drawn on a different scale to facilitate analysis, and consistent with this step being subsequent to the aromatic symmetrisation. This is consistent with equation (1) as the first step, followed by (2) with water mediating the exchange. Proton transfers in dimethyl sulfoxide solution are often found to have rates below diffusion-controlled limits, indicating that the proton-transfer step is not rate limiting.[15] Under some circumstances the proton may be relayed by an intermediate water molecule. The NH to H_2O exchange seems to be a relay for the NH to complexed N exchange in our system. Interestingly, the crystallographic structures of copper complexes of similar ligands published in ref. 1 showed no evidence for hydrogen bonding at any of the benzimidazole nitrogens, although solvent methanol was found in hydrogen bonding with nitrate ions. The dependence of the rate on the ratio of [L]:[Cd] was similar to that for the aromatic switch, and the activation energies slightly greater in most of the systems studied.

The evidence for the nature of the reactions which have been found to occur in these solutions is summarised in Table 5. The original proposals from ref. 1 shown in equations (1)–(3) can now be amplified with the additional information in (6)–(8). The findings may be helpful in future mechanistic models of protein systems in which zinc or cadmium is bound to several histidine side chains. It is clear that a range of rapid exchange processes may occur with an excess or deficit of metal ions.

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