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Azacryptand host for lead: NMR and structural studies

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Abstract

A near spherical octaamine cryptand forms a thermodynamically and kinetically stable lead complex, suggesting a role as a potential scavenger of this cation; X-ray crystallographic structure determination reveals an irregular site for the Pb^{2+} cation, with four short and four long Pb–N contacts.

Key words· Crystal structures; NMR study; Lead complexes; Amine cryptand complexes; Azacryptand complexes

There is increasing concern that the continuing industrial use of lead on a worldwide scale occasions substantial annual release of this toxin into the environment. It is thus inevitable that, through the food chain, humans are increasingly exposed to and contaminated with lead. Many lead compounds are easily absorbed but only slowly eliminated, so the eventual fate of ingested lead is to bind irreversibly to thiol and phosphate groups in enzymes, proteins and membranes, impairing their function [1].

Lead poisoning is currently treated using O,N- or N,S-chelates, although these are to some extent nonideal on account of poor specificity or low-level toxicity. Thus the search for sequestering agents for lead continues. Cryptand systems are particularly attractive candidates for heavy metal cation scavengers on account of the macrobicyclic effect which manifests itself, among other things, in kinetic stability towards decomplexation of the cationic guest.

In previous work with azacryptand ligands [2], we noted that borohydride reduction of $[PbL^1]^{2+}$ generated, not the heavy precipitate of metallic lead normally expected in such a reduction, but merely a transient flash of grey–black colour, decolourising within seconds presumably because of reaction with the reduced cryptand L^2. We were unable to separate the lead cryptate from other water-soluble products, so decided to generate it directly by insertion of the lead cation into the preformed cryptand. The azacryptand, L^2, was earlier synthesised by Lehn and co-workers [3] using high dilution methods, but for our purposes we found it more convenient to use borohydride reduction of the free ligand generated *in situ*** by [2+3] condensation of the triamine tris-2-ethylaminoamine, tren, with glyoxal.

Results and discussion

When an alcoholic solution of L^2 was treated with Pb^{2+} in the presence of perchlorate, the white powder initially obtained showed IR absorption corresponding to the presence of hydroxo species. The crude product could be purified by recrystallisation from EtOH/MeCN to give crystals of $PbL^2(ClO_4)_2 \cdot H_2O$†† (**1**) in good yield. IR spectra of the recrystallised sample confirmed the integrity of the ligand as well as the presence of uncoordinated perchlorate. FAB-MS likewise confirmed complex formation via observation of strong peaks at $m/z = 577$ and 677, corresponding to $(PbL^2)^+$ and $(PbL^2ClO_4)^+$, respectively.

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**L^2 was prepared by *in situ* reduction of L^1, as follows. To 0.3 cm^3 (2 mmol) tris-2-ethylaminoamine (tren) in 100 cm^3 MeOH was added 0.16 g (3 mmol) glyoxal, and the mixture was refluxed for 30 min. Excess $NaBH_4$ was added as a solid in successive small quantities at reflux. The mixture was stirred overnight at room temperature and worked up in the normal way [4, 5] to yield L^1 as a colourless oil. Purity was confirmed via intensity of the mass spectral peak at $m/z = 370$ and via ^1H NMR spectra.

††$PbL^2(ClO_4)_2 \cdot H_2O$ (**1**) and $CdL^2(ClO_4)_2 \cdot 2H_2O$ (**2**). To 0.1 mmol of L^2 in 5 cm^3 MeOH was added 0 1 mmol $M(ClO_4)_2 \cdot 6H_2O$ in 1:1 MeCN/EtOH solvent mixture. An initial curdy white precipitate was filtered off and the partly crystalline final product could be recrystallised from EtOH/MeCN to give the desired cryptate in 50–60% yield. FAB-MS: $(PbL^2)^+$, $m/z = 577$; $PbL^2ClO_4{}^+$, $m/z = 677$; (CdL^{2+}), $m/z = 483$; $CdL^2ClO_4{}^+$, $m/z = 583$. *Anal.* Calc. for **1**: N, 14.1; C, 27.2; H, 5.6 Found: N, 13.4; C, 26 6, H. 5.0%. Calc for **2**· N, 15.6; C, 30.1; H, 6.5. Found: N, 15.3; C, 30 4; H, 6.2%.

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An X-ray diffraction structure analysis carried out* on **1** showed (Fig. 1) that the lead cation is unsymmetrically sited within the cryptand, making contacts of around 2.6–2.7 Å to four of the *sec*-amine nitrogen donors, and longer contacts, >2.8 Å to the bridgehead and the other two *sec*-amine nitrogens. The asymmetry among the *sec*-amine nitrogens suggests that the Pb lone pair is stereochemically active. Taking the lone pair as a pseudo-coordination site and assuming it to be directed midway between the two long imine distances (to N22 and N31), the coordination can be regarded either as nine-coordinate (if all N–Pb contacts are included) or five-coordinate [7] with reasonably good trigonal bipyramidal geometry (if the >2.8 Å contacts are ignored). In the latter case the Pb–N bond lengths are longer than in macrocyclic complexes by around 0.1–0.2 Å (for Pb–sp^{2}N) or <0.1 Å (for Pb–sp^{3}N) [8, 9], but shorter by >0.2 Å than the Pb–sp^{3}N distances in the only other cryptate [PbL^3]$^{2+}$ (L^3 = crypt (2,2,2)) to be structurally characterised [10]. In this N,O cryptate, indeed, both Pb–N and Pb–O distances are reported to 'exceed the sum of van der Waals radii'. This compares with the present cryptate **1** which, in addition to four longish Pb–N contacts of the order of those in [PbL^3]$^{2+}$, contains also four much shorter bonds with lengths typical of macrocyclic [8, 9] or chelate [11] ligands.

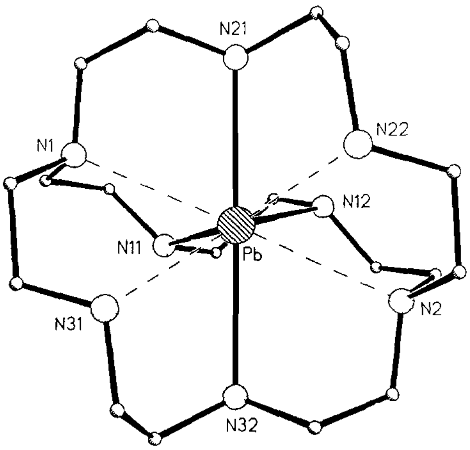
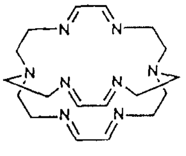


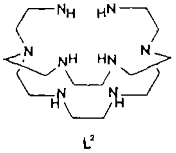
Fig. 1. Perspective view of the [PbL^2]$^{2+}$ cation Selected interatomic distances (Å) and angles (°) Pb–N11 2 675(11); Pb–N12 2.686(13); Pb–N21 2 685(12); Pb–N32 2.737(13); Pb–N1 (2 83(1); Pb–N2 2.87(1); Pb–N22 2.81(1); Pb–N31 2 83(1); N11–Pb–N12 66.6(3); N21–Pb–N32 176.7(4).

The cryptand **1** is more spherical than others we have characterised; the analogous hexaimine cryptand L^1 has an N$_{br}$–N$_{br}$ distance 0.4 Å longer (in the mono-cobalt(II) complex) [12] or 0.7 Å longer (in the di-copper(I) complex) [13] than the 5.707 Å observed here. The shorter length may be in response to the greater width demanded by the larger Pb^{2+} cation. The two-fold axis is non-crystallographic, and there are no H bond contacts to counterion or solvate.

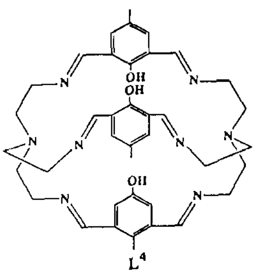
To judge by the combination of inner- and outer-sphere Pb–N distances, the Pb^{2+} guest is quite strongly held within its cryptand host, certainly more strongly than within L^3 [10], if not so strongly as within L^4 [14], which however has not so far been obtained as the free ligand host. However, for many purposes the value of a sequestering agent depends on the kinetics of complexation and decomplexation. The well-known 'macrocyclic' and 'macrobicyclic' effects depend to a significant extent on slow decomplexation of the cation from the multidentate assembly. NMR spectra can provide information on the rate of exchange of cations between ligand and solvent environments.



L^1



L^2



L^4

Accordingly, we carried out a ^{1}H NMR study (Table 1) on the lead cryptate **1** and its cadmium analogue [CdL^2](ClO$_4$)$_2$ (**2**) (see footnote†† on p. 5).

The spectrum of **1** is fluxional and close to coalescence at 298 K in the 400 MHz CD$_3$CN or D$_2$O spectrum. By 343 K it is fully mobile, with H$_{a,b}$ methylene protons appearing as an unsplit singlet close to 3.0 ppm and H$_{c,d}$ and H$_{e,f}$ as triplets centred on 2.87 and 2.63 ppm. The NH resonance, which is removed by D$_2$O shake, takes the form of a broad signal with a poorly resolved structure close to 2.4 ppm. One feature noticeable on all three methylene signals (and possibly also on the NH resonance) is the presence of poorly resolved satellite peaks in the wings of each band, attributable to coupling, $^3J(^1\text{H}-^{207}\text{Pb})$ with the $I = 1/2$ ^{207}Pb isotope, present at 22% in natural abundance. These satellites, corresponding to ^{207}Pb–^{1}H coupling of the order of 15–25 Hz, show up more clearly in the D$_2$O-shaken

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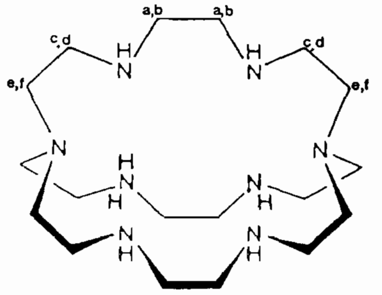
*Crystal data· [PbL^2](ClO$_4$)$_2$·H$_2$O, C$_{18}$H$_{42}$Cl$_2$N$_8$O$_9$Pb, colourless block, 0 6×0 35×0.25 mm, orthorhombic, $a = 21\ 369(4)$, $b = 9.403(2)$, $c = 14.358(3)$ Å, $U = 2885(1)$ Å^3, $\mu = 6.13$ mm^{-1}, space group $Pna2_1$, $Z = 4$, $F(000) = 1576$. Data collected at 183 K on a Nicolet R3m diffractometer using Mo Kα radiation. Using 1.8° ω scans at 4.88° min^{-1}, 2650 unique reflections were collected ($4 < 2\theta < 50°$) and 3280 with $F > 6\sigma(F)$ were used in the refinement The structure was solved by direct methods and least-squares refinement converged with $R = 0.032$, $R_w = 0\ 040$. Hydrogen atoms were inserted at calculated positions using a riding model with a common, fixed isotropic thermal parameter except for those on the water solvate molecule which were not included. All programs used in data reduction, solution and refinement are contained in the SHELXTL-PC package [6]. See 'Supplementary material'.

TABLE 1. ^1H NMR spectra of the lead and cadmium cryptates[g]



	T (K)	ν (MHz)	H_a	H_b	H_c[m]	H_d[n]	H_e[m]	H_f[n]	(N)H
$PbL^2(ClO_4)_2$	343	400	3.00s[h,k] [12H]		2.87tr[h,k] [12H]		2.63tr[h,k] [12H]		2 39br,s [6H]
(D_2O shake)	223	400	3.12d [6H]	⟵ ≈2.78d[i]	≈[2.7–2.8]m [24H]		⟶ ≈2.70[i]	2.39d [6H]	
$CdL^2(ClO_4)_2$	295	400	2.74d[l]	2.46d[l]	2.82tr[l]	2.54m[l,o]	2.64tr[j,l]	2.29d[j,l]	2.12br,s

[g] CD_3CN solution, shifts in ppm from TMS; s = singlet, d = doublet, tr = triplet, m = multiplet, br = broad. [h] ^1H–^{207}Pb coupling ≈20 Hz. [i] Inferred from NOE, COSY experiments [j] Assignment decided by decoupling experiment (2.3 ppm irradiation). [k] Fluxional: axial, equatorial protons undifferentiated. [l] These signals too overlapped for accurate integration [m] Axial protons. [n] Equatorial protons. [o] Contains $^{111,113}Cd$ couplings.

spectrum, which unfortunately rules out observation of the NH signal.

On cooling to 223 K the spectrum (run as D_2O shake for better resolution) becomes more complex as the methylene signals freeze out, differentiating according to their axial/equatorial nature as well as to their siting in the cryptand. In particular, the 3.1 ppm signal splits into axial and equatorial components and develops a *gem* $^2J(^1H, ^1H)$ coupling of around 10 Hz. The low symmetry revealed by X-ray crystallography means that methylene protons in the three strands are no longer equivalent, and the complexity of the ^1H NMR spectrum suggests that this extends to solution, which makes a full assignment of the spectrum prohibitively difficult, given the high degree of overlapping. Couplings to lead presumably persist, but would be hard to separate from any normal AA′BB′ patterns which could also explain the small side-band flanking components observed. Integration shows that the ≈3.1 ppm doublet corresponds to 6H (i.e. to two equivalent protons in each of the three strands) as does that at 2.39 ppm. The remaining 24 methylene protons present as a complex multiplet in the ≈2.7–2.8 ppm region. A COSY 45 experiment shows that the 3.1 ppm doublet couples to a signal centred on 2.78 ppm and the 2.39 ppm doublet to one centred around 2.70 ppm. NOE confirms these findings in respect to connectivity; enhancements, presumably of *gem* protons, are noted for 2.78 ppm following irradiation at ≈3.1 ppm; for 2.70 ppm following irradiation at 2.39 ppm and vice versa. Some part of the anisotropy which leads to different chemical shifts for each methylene proton may derive from paramagnetic circulation arising from directed bonding of Pb^{2+}, which affects protons in its vicinity, and leaves unaffected others such as the equatorial proton adjacent to the bridgehead, H_f(eq), which the X-ray structure shows to be sited on the outside of the cavity, well away from the coordination site.

The anisotropic circulation may be expected to be different where a different cation is substituted for lead, particularly if there is more ionic bonding. The ^1H NMR spectrum of $[CdL^2](ClO_4)_2$ (**2**) demonstrates the existence of a frozen-out conformation at all accessible temperatures in CD_3CN. The methylene signals, which are better resolved and less heavily overlapped than those of **1**, cover a smaller range (≈0.6 versus ≈0.8 ppm in **1**). A 2.12 ppm signal, removable by D_2O shake, is attributed to NH resonance. As in the lead cryptate **1** and other cryptates of the series [4, 15] there is a doublet at high field clearly separated from the rest of the spectrum. This 2.29 ppm band was irradiated to reveal a negative NOE effect affecting the broad 2.64 ppm triplet. These two signals are also related by their similar broad appearance at 295 K and above, suggesting the onset of conformational mobility in the outer methylene $H_{e,f}$ protons. Decoupling at 2.3 ppm shows that this signal also couples to the triplet at 2.82 as well as the complex signal centred around 2.55 ppm, which means these latter two signals can be assigned to resonance of the $H_{c,d}$ protons. The remaining sharp doublets centred on 2.74 and 2.46 ppm therefore correspond to the central $H_{a,b}$ methylenes.

Given that the spectrum argues for equivalence of the three strands and two ends of the cryptate, it seems likely that some of the smaller splittings observed in the well-resolved methylene signals, especially H_c and

H_d, correspond to ^{111,113}Cd satellites, but the complexity and overlapping pattern make it impossible to decide which.

Conclusions from the ^{1}H NMR study are as follows.

Neither Cd^{2+} nor Pb^{2+} undergo rapid exchange with the solvent environment. In the case of **1** this is demonstrated by the observation of ^{207}Pb couplings even when the methylene signals are fluxional; in the case of **2** it may be inferred from the well-resolved nature of the cryptand spectrum, which rules out any rapid dynamic process, particularly involving those resonances which contain the ^{113}Cd couplings.

The Cd^{2+} ion appears more symmetrically placed within the cryptand than the Pb^{2+} ion, whose more complex NMR spectrum suggests that the unsymmetric solid-state structure (Fig. 1) may persist in solution. The smaller size of Cd^{2+} causes the methylene chain to contract about the cation generating a lower degree of conformational mobility than in the lead analogue. Part of the difference between the spectra may also derive from the absence of any lone pair effect or directed bonding in the Cd^{2+} cryptate.

X-ray crystallographic measurements thus indicate strong complexation of Pb^{2+} within the cryptand, and NMR spectra suggest a high degree of kinetic stability towards decomplexation. Preliminary results from stability constant determination experiments, based on the 300 nm absorption of **1**, show [16] (from the observation of a value of ligand:cation ratio of 1.04 for full 1:1 complexation) that log K_s is well in excess of 6, so that spectroscopic techniques are unsuitable for its determination. An electrochemical determination of the stability constant is planned [16].

In summary, it appears that thermodynamics and kinetics of complexation of both lead and cadmium cations by L^2 justify its consideration as a sequestering agent for both toxins.

Supplementary material

Atomic coordinates, bond lengths and angles, and thermal parameters have been deposited at the Cambridge Crystallographic Data Centre.

Acknowledgements

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