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Some penta- and hexa-dentate Macrocyclic Schiff Base Complexes of the Toxic Metals

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Lead, cadmium and mercury are notorious for their toxic effects, and this aspect of their behaviour has been well documented [1, 2]. The toxic effects are often associated with the displacement of calcium from its natural ligands. The ionic radius for Ca^{++} is 0.99 Å and those for Pb^{++}, Cd^{++} and Hg^{++} are 1.21, 0.97 and 1.10 Å respectively [3], and thus would allow for isomorphous replacement. Current treatment of chronic lead poisoning centres on the propensity for lead to replace calcium [1]. Calcium disodium edta is injected intravenously with subsequent excretion of lead disodium edta; after the bulk of the lead has been removed *D*-penicillamine is added to further reduce the lead burden. There have recently been suggestions that the selectivity of appropriate synthetic macrocycles could be exploited to remove heavy metals from the body [4, 5].

Hexadentate macrocyclic Schiff base complexes of calcium, (I)·$Ca(NCS)_2$, may be synthesised using template procedures, from $Ca(NCS)_2$, 1,11-diamino-3,6,9-trioxaundecane and the corresponding pyridine diketone or dialdehyde [6]. Treatment of the calcium complexes with lead(II) thiocyanate in ethanol gives the corresponding lead(II) complexes, (I)·$Pb(NCS)_2$, a facile transmetallation having occurred [7]. The lead containing macrocycles may also be directly synthesised, using template procedures, and shown to be identical with the product isolated in the transmetallation reaction.

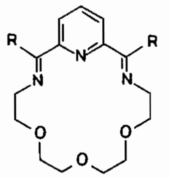
Ia, R = H
Ib, R = CH_3

TABLE I.

Complex	$^{\nu}$N–C(NCS) cm^{-1}	Known structural type
(Ia)·$Ca(NCS)_2$	2065	both –N–bonded (ref. 14)
(Ib)·$Ca(NCS)_2$	2050	
(Ia)·$Pb(NCS)_2$	2085, 2065	one –N, one –S (ref. 10)
(Ib)·$Pb(NCS)_2$	2080, 2020	both –N–bonded (ref. 11)
(Ia)·$Cd(NCS)_2$	2080	
(Ib)·$Cd(NCS)_2$	2075, 2045	
(Ia)·$Hg(NCS)_2$	2100	
(Ib)·$Hg(NCS)_2$	2100	
(IIa)·$Mg(NCS)_2$	2080	[a]
(IIb)·$Mg(NCS)_2$	2080	[a]
(IIa)·$Cd(NCS)_2$	2080, 2050sh	
(IIb)·$Cd(NCS)_2$	2045	both –N–bonded (ref. 12)
(IIa)·$Hg(NCS)_2$	2105	
(IIb)·$Hg(NCS)_2$	2105	
(III)·$[Pb(NCS)_2]_2$	2080, 2010	–S and –N–bonded (ref. 15)

[a] The C–N stretches in both $Ca(NCS)_2$ and $Mg(NCS)_2$ complexes of the related cyclic polyether benzo-15-crown-5 lie in the region 2080–2100 cm^{-1}. The crystal structures of these complexes shown that –N–bonding has occurred. [D. G. Parsons and J. N. Wingfield, *Inorg. Chim. Acta, 18,* 263 (1976); J. D. Owen, *J. Chem. Soc. Dalton,* 1416 (1978)]. This suggests that –N– bonding has occurred in the above magnesium complexes, and draws attention to the difficulty of absolute assignment of thiocyanate bonding modes in such complexes.

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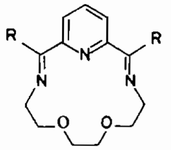
The IR spectra of the complexes are used to monitor the progress of the transmetallation reactions, and to investigate the mode of thiocyanate bonding in the complexes, through the position of the thiocyanate C–N stretching frequency. S- and N-bonded thiocyanates are reported [8] to have frequencies in the ranges 2120–2080 and 2080–2040 cm^{-1} respectively, however caution must be exercised before absolute assignments are made [6]. The C–N frequencies and known structural features for the macrocyclic complexes, prepared by template procedures are given in the Table I. It can be seen that there is a considerable shift in frequency on going from the calcium complexes to the toxic metal complexes of (I) and this change can be used to furnish evidence that transmetallation has occurred.

The reaction of 2,6-diacetyl pyridine, or 2,6-diformyl pyridine with 1,11-diamino-3,6,9-trioxaundecane in ethanol in the presence of cadmium, or mercury(II), thiocyanates yielded the complexes (I)·$Cd(NCS)_2$ and (I)·$Hg(NCS)_2$ [9]. The IR spectra indicate S-bonded thiocyanate in the mercury complexes but are more ambiguous for the cadmium complexes where with (Ia) the band lies in the borderline region, and with (Ib) two bands are observed. By analogy with the corresponding lead complexes this can be interpreted as evidence for the presence of both N and S-bonded thiocyanates for the (Ib) complex [10], and for N-bonded thiocyanate for the (Ia) complex [11]. The cadmium complex of the related pentadentate macrocycle (IIb) is reported to contain N-bonded thiocyanate [12] and the band appears in the more normal range at 2045 cm^{-1}.

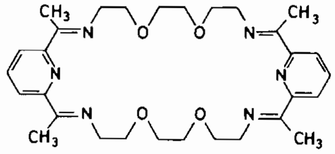
Transmetallation reactions in ethanol to prepare the cadmium and mercury complexes from (I)·$Ca(NCS)_2$ have been carried out (Ia)·$Cd(NCS)_2$ and (I)·$Hg(NCS)_2$ have been obtained and identified by IR but the reaction between (Ib)·$Ca(NCS)_2$ and cadmium thiocyanate led only to recovery of starting materials, even after prolonged refluxing. When the toxic metal complexes are refluxed with excess calcium thiocyanate the toxic metal complex is recovered indicating that the reverse reaction is slow, if it occurs at all, and suggesting that binding is stronger between the macrocycles and toxic metals.

There is a fine control by the metal cation present in the synthesis of multidentate Schiff Base macrocycles [6, 13]. Complexes of (I) can be synthesised using Ca^{++}, Sr^{++}, Ba^{++}, Pb^{++}, Cd^{++} and Hg^{++}, but not Mg^{++}, whereas for the pentadentate macrocycles, (II), cations of radius greater than 0.95 Å (*e.g.* Ca^{++}) do not facilitate synthesis. If large cations such as Ag^{+} (1.15 Å) and Pb^{++} (1.20 Å) are used in attempts to produce (II) double macrocycles of type (III) are prepared [7, 13]. The reaction of cadmium thiocyanate with the pyridine precursors and 1,8-diamino-3,6-dioxaoctane gave the complexes (II)·$Cd(NCS)_2$. The complex (IIb)·$Cd(NCS)_2$ has been prepared previously by metathesis from (IIb)·$CdBr_2$, H_2O and shown to be isostructural with the corresponding manganese complex [12]. A similar template reaction using mercury(II) thiocyanate gave products analysing as (II)·$Hg(NCS)_2$ [9] but, by analogy with the Ag^{+} and Pb^{++} reactions, it is more probable that these are double macrocyclic complexes of the type (III), $2Hg(NCS)_2$. No suitable crystals for X-ray analysis have yet been obtained for these compounds. No transmetallation reactions have been successful starting from (II), $Mg(NCS)_2$. This is perhaps not unexpected for Pb^{++} and Hg^{++} where a ring expansion reaction would have to occur to give the favoured double ring products.



IIa, R = H

IIb, R = CH_3



III

It is evident that toxic metal complexes of hexadentate Schiff base macrocycles can be synthesised by both template and calcium exchange procedures, whereas for the pentadentate complexes the template procedure is most effective. It is therefore plausible to suggest that physiologically acceptable macrocycles based on the type reported here could be exploited in the removal of metals from the body. The hexadentate ligand could be introduced as its calcium complex which would undergo exchange with the toxic metal to give a removal metal complex leaving calcium behind.

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