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Implications for Mercury Toxicity from the Structure of An Oxacalix[3]arene–HgCl₂ Complex?

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***t*-Butyloxacalix[3]arene**tris(diethylacetamide), known to mimic the cellular sodium ion selectivity filter, has been shown to bind HgCl₂. The dimeric complex crystallises in the triclinic space group *P*1 with $a = 17.3019(6)$ Å, $b = 18.7821(4)$ Å, $c = 19.9025(5)$ Å, $\alpha = 67.3010(10)^\circ$, $\beta = 77.664(2)^\circ$; $\gamma = 77.238(2)^\circ$ and $D_c = 1.370$ g cm⁻³ for $Z = 4$. Refinement based on 37,818 observed reflections gave a final *R* value of 0.0483. Implications for routes of mercury uptake are discussed.

Keywords: Macrocycles; Calixarene; Crystallography; Mercury; Toxicology

Recently we have shown that an oxacalix[3]arene derivative (**1**, Fig. 1) binds sodium cations in such a way as to imply a mechanism for *in vivo* Na⁺ selectivity [1]. Given the similarity in ionic radii between Hg²⁺ and Na⁺, we wished to see if mercury could also be complexed by this ligand. Mercury is a potent neurotoxin and impairment of ion channel activity is an important mechanism by which neurotoxicity occurs. In its most hazardous form the metal enters organisms in the form of organomercurials which then pass through cell membranes [2]. Studies have shown that inorganic mercury has similar toxicological effects and that interference by Hg²⁺ has a marked effect on certain Ca²⁺-dependent Na⁺ channels [3]. In addition, both methylmercury and Hg²⁺ decrease Na⁺, K⁺ and Ca²⁺ currents in many cells lines, presumably by blocking the transmembrane ion channels, however, the details of the mechanisms have yet to be determined [4].

The importance of cation– π interactions in biological recognition has been highlighted by

Dougherty [5] though they appear to play little part in the most accurately mapped selectivity filter to date, that of the *Streptomyces lividans* K⁺-channel [6]. The relevance of metal– π interactions to cellular sodium transport has yet to be determined despite the recent elucidation of the structure of the voltage-gated sodium channel from the electric eel, *Electrophorus electricus* [7]. We have shown that Na⁺ interacts with aromatic residues of **1** and expect that similar interactions occur in natural sodium channels rich in aromatic residues. Assuming the charge on the cation is less important than its size and ability to interact with aromatic moieties then mercury, a soft acid, should be attracted to the oxacalix[3]arene's aromatic "funnel" and subsequently be encapsulated by the macrocycle. To test the importance of mercury– π interactions in our model for the Na⁺ selectivity filter we have prepared and structurally characterised a complex of **1** with Hg²⁺.

A solution of **1** (9 mg, 0.01 mmol) in methanol (5 cm³) was added to a solution of HgCl₂ (8 mg, 0.03 mol) in methanol (5 cm³) and refluxed for 1 h. The chloride salt was chosen to best reflect the *in vivo* environment in which chloride is ubiquitous. The poor solubility of **1** in water necessitated the use of methanol and is consistent with our previous reaction conditions [1]. Colourless crystals of (HgCl₂·**1**)₂, suitable for X-ray diffraction studies, grew after several days at room temperature. X-ray single crystal intensity data were measured by a Nonius Kappa CCD diffractometer and data analysis carried out by DENZO-SMN [8]. The structure was

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Hg - Cl _(terminal)	2.318	2.295
Hg - Cl _(bridging)	2.331	2.329
Hg \cdots Cl _(bridging)	3.136	3.130
Hg \cdots Hg	4.077	4.066
Hg - O _(amide)	2.549	
Hg - O _(ether)	2.705	
Hg - Ar _(centroid) ^c	3.875	

^aAverage values (this work); details of individual distances with esd values are given in supplementary information ^bFrom ref. 11 ^cDistance to nearest aromatic centroid

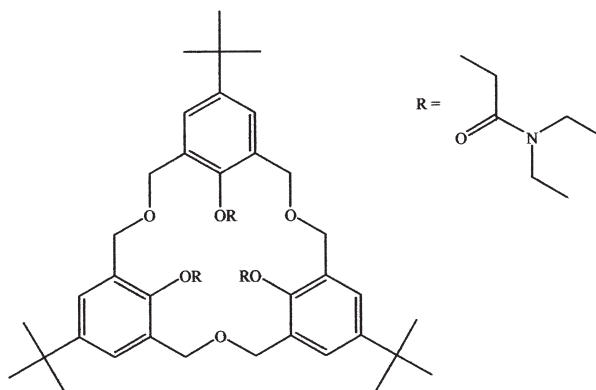


FIGURE 1 Oxacalix[3]arene 1.

solved using direct methods (SHELXS-97 [9]) and refined using SHELXL-97 [9] to give a value of 0.0483 for R_1 based on 37,818 reflections.† Details of the crystal data and a summary of the data collection are given in Table I.

The structure (Fig. 2) shows sheets of oxacalixarenes in a herringbone pattern with intercalated HgCl_2 dimers. This structural motif is also seen for 1:2DMF in which organic solvent, rather than a chelated metal, intercalates between layers of macrocycles oriented in opposing directions [10]. The coordination environment around each mercury atom consists of two Hg–Cl bonds, one weak Hg \cdots Cl interaction and two interactions with the

lower rim substituents of an oxacalix[3]arene (ether and carbonyl oxygens from the same diethylacetamide moiety). The latter arise through one of the pendent amides adopting an orientation *exo* to the macrocyclic cavity, breaking the pseudo- C_3 symmetry of the oxacalix[3]arene. The result is a distorted square based pyramidal geometry around each mercury atom. One of the two symmetry independent dimers is shown in Fig. 3 and important mercury interactions are given in Table II. The Hg–Cl bond distances in the HgCl_2 dimer are in excellent agreement with those generated by quasirelativistic computational methods for Hg_2Cl_4 with C_{2h} symmetry [11] and are reminiscent of the

†The structure was initially solved in the space group $P-1$, however, gross disorder of both unique molecules was present and a model requiring two alternative positions for all atoms was required. The disorder was absent from a $P1$ solution in which each asymmetric unit contained four unique HgCl_2 –oxacalix[3]arene moieties. Despite the fact that $P1$ refinement gave the better convergence, a further attempt was made to refine the structure in the much more common $P-1$ space group. All atoms in the $P1$ solution were translated, giving a pseudo inversion centre on the origin, to generate a $P-1$ model but the disorder was still present. Non-unique molecules in $P-1$ were deleted and the structure re-refined with two independent molecules. An extremely poor refinement resulted with substantial residual electron density, particularly around the Hg atoms. It was concluded that $P1$ (which gave an unordered solution) was indeed the correct space group. The complex supramolecular assembly in this case may have contributed to the lowering of the crystal symmetry. The large number of parameters in the final refinement required the use of loose ISOR restraints (0.01 target variation) in order to control refinement and the high absolute structure parameter was due to the crystal being a racemic twin.

TABLE I Crystal data and structure refinement for (1·HgCl₂)₂

Formula	C ₅₄ H ₈₁ Cl ₂ HgN ₃ O ₉
Molecular weight	1187.71
T (K)	100(2)
Wavelength (Å)	0.71070
Space group	P1
<i>Cell constants</i>	
<i>a</i> (Å)	17.3019(6)
<i>b</i> (Å)	18.7821(4)
<i>c</i> (Å)	19.9025(5)
α (°)	67.3010(10)
β (°)	77.664(2)
γ (°)	77.238(2)
<i>V</i> (Å ³)	5759.7(3)
Molecules/unit cell	4
<i>D_c</i> (g cm ⁻³)	1.370
Absorption coefficient (mm ⁻¹)	2.818
<i>F</i> (000)	2448
Crystal size (mm)	0.10 × 0.10 × 0.08
θ range (°)	1.31–25.00
Index ranges	–20 ≤ <i>h</i> ≤ 20 –22 ≤ <i>k</i> ≤ 22 –23 ≤ <i>l</i> ≤ 23
Reflections collected	37,818
Independent reflections	37,818 [<i>R</i> (int) = 0.063]
Data/restraints/parameters	37,818/1599/2481
Goodness-of-fit on <i>F</i> ²	1.012
Final <i>R</i> indices [<i>I</i> > 2σ(<i>I</i>)]	<i>R</i> ₁ = 0.0483, <i>wR</i> ₂ = 0.0915
<i>R</i> indices (all data)	<i>R</i> ₁ = 0.0795, <i>wR</i> ₂ = 0.1049
Absolute structure parameter	0.483(8)
Largest diff. peak and hole (eÅ ⁻³)	0.896 and –1.103

metal environment in temazepam·HgCl₂ [12] and adenine *N*-oxide·HgCl₂ [13].

Close inspection reveals that a phenolic ring from neighbouring oxacalix[3]arene interacts with each HgCl₂ fragment. The ring appears to block the sixth coordination site around each metal, however, the Hg···C distances between the carbon *para* to the *t*-butyl group are significantly shorter, suggesting an interaction may be present (Hg···C close contacts range from 3.602 to 3.686 Å). The combined van der Waals radii of Hg²⁺ (1.73 Å) and an aromatic ring (1.70 Å) would seem to indicate that the interactions are outside the range for bonding [14], however, examples of organomercury compounds with Hg···C_(aromatic) distances from 3.483(8) [15] to

TABLE II Comparison between experimental and calculated bond length (Å) for the HgCl₂ dimer

	Experimental*	Calculated†
Hg–Cl _(terminal)	2.318	2.295
Hg–Cl _(bridging)	2.331	2.329
Hg···Cl _(bridging)	3.136	3.130
Hg···Hg	4.077	4.066
Hg–O _(amide)	2.549	
Hg–O _(ether)	2.705	
Hg–Ar _{(centroid)‡}	3.875	

* Average values (this work); details of individual distances with esd values are given in supplementary information. † From Ref. [11]. ‡ Distance to nearest aromatic centroid.

3.64 Å (midpoint of a C–C aromatic bond) [16] have been reported.

It appears that mercury–π interactions have a rôle to play in oxacalix[3]arene chemistry though given their weak nature they may be the result of solid state packing factors. The intercalated Hg₂Cl₄ structure is the more important feature, linking macrocycles together through pendent amide groups and external faces of aromatic rings rather than inducing inclusion within the macrocyclic cavity. Caution must be given to inferences made from solid state structures when considering potential solution behaviour although it is clear that inorganic mercury is not attracted to the π-electron rich funnel of **1**. This observation indicates that Hg²⁺ would not be drawn to *in vivo* ion channels that rely on aromatic moieties as part of their selectivity process.

SUPPLEMENTARY INFORMATION

Details of the crystal structure have been deposited at the Cambridge Crystallographic Data Centre with the reference number CCDC 168653. A thermal ellipsoid plot and mercury close contact details are available as supplementary data.

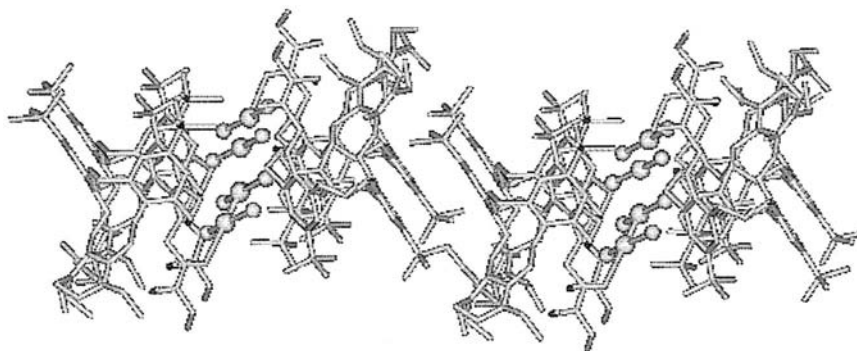


FIGURE 2 Herringbone packing of (1·HgCl₂)₂.

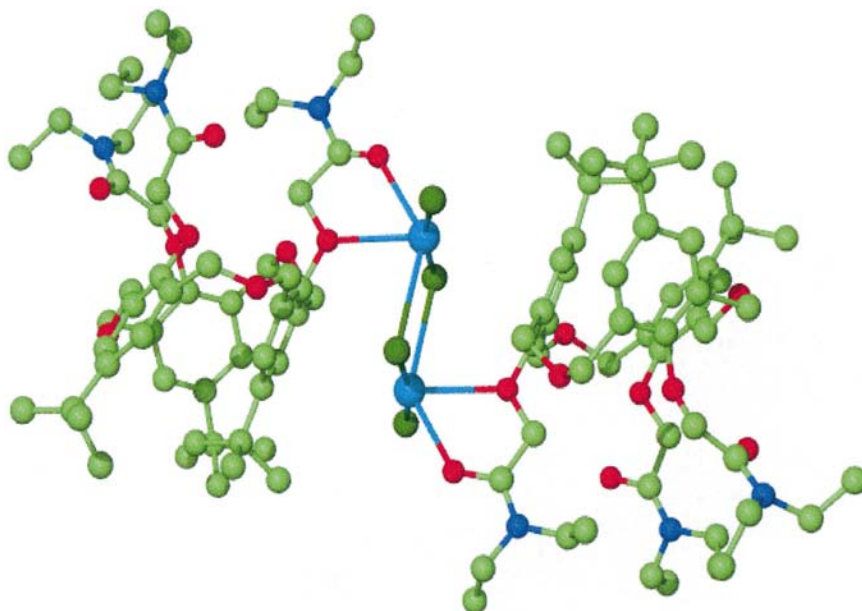


FIGURE 3 One of the symmetry independent dimers in $(1 \cdot \text{HgCl}_2)_2$, hydrogens removed for clarity.

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