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trans- and cis-1,3,5,7-Tetraazadecalin (TAD). A New and Strong Binding Mode in cis-TAD Chelates of Heavy Metal Ions¹

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Abstract. trans- and cis-1,3,5,7-tetraazadecalin (TAD) (2 & 3) were isolated and structurally characterized (VT-NMR). One of the cis-TAD derivatives intended to act as "cores" of new host systems, 2,6-di(hydroxymethyl)-cis-TAD (5), gave heavy metal ion (Cd^{II}, Pb^{II}, etc.) complexes with remarkably high binding constants, as measured by polarography. X-ray analyses of the Cd^{II} (7a) and Pb^{II} (7b) complexes revealed a new, unique binding mode. © 1997 Elsevier Science Ltd.

We have recently put forward a general scheme for new types of host systems built on 1,3,5,7-tetraheterodecalin (THD) core units. The *cis*-THD unit, is of particular interest, since derived podands (1) and macrocycles (1, R---R) are anticipated to possess good ion or molecule inclusion ability, due to its built-in cavity and high electron lone pair concentration. These ideas were implemented firstly in the diacetal tetraoxadecalin (X=O) (TOD) series¹, establishing the validity of the approach to new host design. We present now the interesting diaminal, 1,3,5,7-tetraazadecalin (TAD), system (X = NH).

Aminals are known by now as viable, reasonably stable and usefully reactive systems²⁻⁴, exhibiting stereoelectronic effects⁵. In the 1,3,5,7-tetraazadecalin (TAD) series to date, the tetra-N-nitroso- and tetra-N-nitro-1,3,5,7-TAD derivatives have been prepared^{6a} and very recently^{6b}, some alkyl substituted TAD compounds were reported. The parent tetraazadecalins, however, have been neither isolated nor characterized. We report now the isolation and characterization of *trans*- and *cis*-1,3,5,7-tetraazadecalin (TAD), i.e. X=NH, and the first *cis*-TAD derivatives with "host" character and with unusual complexation behaviour (Scheme 1)[†]. The starting

Scheme 1. The reaction of the diastereomeric 1,2,3,4-tetraaminobutanes (TAB) with aldehydes.

materials are *erythro*- or *threo*-1,2,3,4-tetraaminobutane (TAB)⁶, which provide stereospecifically the respective diaminal TAD systems. Full NMR analysis confirmed the rigid *trans*-TAD isomer (2), while *cis*-TAD (3) occurs as two conformationally interconverting chair-chair forms, "*N-inside*" (3i) and "*N-outside*" (3o), the equilibrium of which (in MeOH) was studied by NMR techniques: direct measurement at 299 K, gave $\Delta G^0_{299}=1.0 \text{ Kcal mol}^{-1}$ (K₂₉₉=0.18, i.e., 85% "*N-inside*") and a variable temperature ¹H NMR study corroborated this result.

A variant of the synthetic procedure (Scheme 1), using formaldehyde in excess, gave 1,7;3,5-dimethylenecis-TAD (4), the smallest TAD cage, which was also obtained from cis-1,3,5,7-TAD (3) with two formaldehyde equivalents. The reaction of 3 with glycolaldehyde (dimer) provided the desired 2,6-di(hydroxymethyl)-cis-1,3,5,7-TAD (5) (Scheme 1) and already at the podand level 5 exhibited, by any standards⁷, remarkable heavy metal ion e.g., Cd^{II}, Pb^{II} binding affinity, as measured by both normal (NPP) and differential (DPP) pulse polarography (Table 1).

Table 1. Association constants, and stoichiometric ligand (L) to metal ratios for 5 by NPP and DPP pulse polarography at 25.0 ± 0.2 C.*.

Ion (M)	Solvent	Complex ML _n	log K	Ion (M)	Solvent	Complex ML _n	log K
(M)	MeOH	ML ₂	NPP: 14.9±0.4	Pb ^{II}	MeOH	ML	NPP: >10
Cdū	Water ^b	ML	DPP: 14.6±0.3 NPP: 2.9±0.1 DPP: 3.27±0.02		Water b	ML	NPP: 6.8±0.3 DPP: 7.0±0.3

a) Lingane's method⁸ for reversible processes was used, save for Pb^{II} in methanol (see text). The DPP method was used because of the low concentrations. b) at pH=7

Significantly, Pb^{II} showed strong binding (for an ML complex, with a dissociation lower than 0.02% at 0.002 M concentration) and complete selectivity in mixtures with Cd^{II} and other ions. Large equilibrium constants were measured in methanol for the complexes of 5 with both Cd^{II} and Pb^{II}. Lingane's method⁸ failed in these conditions with Pb^{II} and only an evaluation of the lowest limit of the stability constant of 5 in methanol (log K>10) could be made. It was however, possible to determine the ligand to metal ratio: two reversible half-wave potentials were measured on the same polarogram (Figure 1), attributed to Pb^{II} (-0.280V) and to the [5*Pb]^{II}

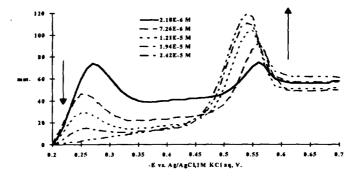


Figure 1. DPP polarographic determination of ligand to metal ratio in the complexation of Pb^{II} and 6 by titration. Pb^{II} concentration was 2.54E-5 M in methanol and the supporting electrolyte, 0.5M NaClO₄. Pulse width 50 ms.

complex (-0.550V). The 1:1 ligand to metal ratio in [5*Pb]^{II}.(NO₃)₂ was unequivocally proven also by mass-spectrometry of the isolated complex.

We were very intrigued by the question of the nature and geometry of coordination in these complexes: do they have "double ethanolamine" character, as in 6 (which has the C_2 symmetry suggested by its NMR spectrum), or would a stronger (as in 7), 5-amino-1,3-diazane type coordination be possible. The latter was found to be the case for both above complexes, the structures of which (7a,b) could be substantiated by single crystal X-ray diffraction analysis (Figure 2).

$$\begin{bmatrix}
0 & 0 & 0 \\
HN & HN & 0 \\
N & NH & 0
\end{bmatrix} \cdot 2HX$$

$$\begin{bmatrix}
H & 0 & H \\
H & NH & 0
\end{bmatrix} \cdot 2X^{-1}$$

$$6 \qquad a. \quad Cd \qquad Br \\
b. Pb \qquad NQ$$

We see in both the anticipated, *unique* feature of coordination to three out of the four nitrogens in the tetraazadecalin ligand, supplemented by one (nearest) hydroxy group and the two bromides. In solution, however, to explain the symmetry indicated by the NMR spectra, an internally fluctuating ligation between the metal ion and the two equivalent parts of the ligand 5 within 7 has to be invoked. 7 has four five-membered rings in the chelate system, in accord with Hancock's conclusion that, correlating the geometry of the chelate ring with the metal ion size, five-membered rings will do best with large metal ions.

There is a highly interesting stereoelectronic aspect of the mode of complexation in 7. The shorter (stronger) M---N5 bond is easily understood: the axial proton on N7 indicates that a typical anomeric effect⁵ operates, with N7 as donor and N5 as acceptor (with increased electron density). The similar and relatively weaker coordination of N1 and N3 to the metal is due to the absence of negative hyperconjugation (the protons on both N1 and N3 are equatorial).

Significant implications for ligand design, chirality and specific metal complexation for biomedical and environmental applications¹⁰ are being currently examined.

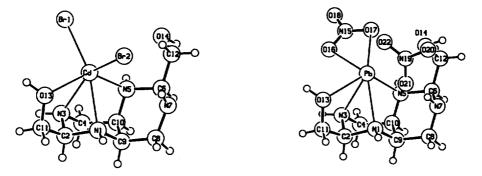


Figure 2. ORTEP drawings of the 2,6-dihydroxymethyl-cis-TAD complexes [5.Cd]¹¹.Br₂ (7a) and [5.Pb]¹¹.(NO₃)₂ (7b).

Footnotes

[†]New compounds were fully characterized by spectrometric methods (ir, nmr, ms), X-ray or elemental analysis and chemical correlation. All data will be provided in a full paper or, meanwhile, on request from the authors.
[‡]Crystal data (atomic coordinates, bond lengths and angles, torsion angles and thermal parameters have been deposited at the Cambridge Crystallographic Data Center): 7a - C₈H₁₈N₄O₂CdBr₂, formula weight 474.46, monoclinic, space group $P2_1/n$, a = 7.699(1), b = 14.529(3), c = 12.299(8) Å, $β = 100.29(3)^\circ$, V = 1353.6(9) Å³, Z = 4, $D_{calc} = 2.328$ g.cm⁻³, F(000) = 912, μ(MoKα) = 75.1 cm⁻¹, 2771 unique reflections, R=0.035 for 2365 observations above intensity threshold of 2σ, R=0.047 for 2771 unique data; at convergence, S = 0.80 and |Δρ| ≤ 0.68 e.Å³. 7b - C₈H₁₈N₆O₈Pb, formula weight 533.47, orthorombic, space group $Pna2_1$, a = 16.310(4), b = 7.473(1), c = 12.245(7) Å, V = 1492.5(9) Å³, Z = 4, $D_{calc} = 2.374$ g.cm⁻³, F(000) = 1016, μ(MoKα) = 113.6 cm⁻¹, 1583 unique reflections, R=0.037 for 1278 observations above intensity threshold of 2σ, R=0.048 for 1583 unique data; at convergence, S = 0.91 and |Δρ| ≤ 1.20 e.Å³.

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