

Conformationally Biased Tri- and Di-basic 1,3,5-Triazacyclohexyl Ligands

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The biased ligand *cis-cis*-2,4,6-trimethyl-1,3,5-triaminocyclohexane is weakly basic and may be converted into di- and tri-basic complexing agents bearing hydroxyphenyl, carboxylate or phosphinate groups; an unusual tricyclic bis-aminal intermediate hydrolyses in acidic media to yield a stable bicyclic amidine *via* an intramolecular hydride transfer mechanism.

Non-planar ligands that are pre-disposed to bind metal ions potentially not only may form particularly thermodynamically stable complexes, but also may bind the metal ion more rapidly than related ligands which lack such a conformational bias. Examples of such systems are often macrocyclic, such as the series of L_3X_3 ligands based on 1,4,7-triazacyclononane.^{1,2} In seeking alternative triamino ligands we were attracted by the possible range and versatility of complexing agents derived from a facially coordinating, conformationally biased 1,3,5-triaminocyclohexyl sub-unit. The parent compound *cis-cis*-1,3,5-triaminocyclohexane **1** is, *e.g.* well-known to form ML_2 complexes with Ni^{2+} and Co^{2+} ,^{3,4} and more recently a variety of complexes derived from 1,3,5-triamino-1,3,5-trideoxy-*cis*-inositol **2**, has been defined.^{5,6} Given that in their metal

complexes, such facially coordinating ligands will engender three six-membered chelate rings upon complexation, it might be expected that they will bind preferentially to, and form more stable complexes with, small metal cations.⁷ Complexing agents that give 6-ring chelates prefer to bind to metals with coordination numbers of 4 to 6, with short preferred M–N bond lengths and relatively large N–M–N bond angles. The related ligand *cis-cis*-2,4,6-trimethyl-1,3,5-triaminocyclohexane **3** has therefore been chosen as a ligand framework that merits attention. In the two limiting chair conformers, either the three methyl groups adopt equatorial positions, allowing the axial amino groups to hydrogen-bond intramolecularly (to alleviate lone-pair repulsion), or the amino groups are disposed in equatorial positions giving rise to unfavourable steric repulsion between 1,3-synaxial methyl groups, Scheme 1.

Reduction of trinitromesitylene⁸ **4** with $NaBH_4$ in the presence of $Cu(OAc)_2$ in aqueous ethanol gave the triamine **5** (m.p. 103 °C) in 80% yield. Catalytic hydrogenation (20 °C, 3 atm. H_2 , 6 d) over a Rh/Pd-C catalyst (Rh: Pd 100:1) in aqueous sulfuric acid (0.3 mol dm^{-3}) led to formation of a mixture of the *cis-cis* triammonium salt of **3** and the *cis-trans* diastereoisomer (4:1, 82% overall) from which the desired *cis-cis* isomer was isolated as the sulfate salt by crystallisation from $H_2O-EtOH-CH_2Cl_2$. The crystal structure of the salt confirms the configuration of the salt and shows the protonated amino groups in equatorial positions, as expected in order to minimise coulombic repulsion (Fig. 2).[‡] Reaction of **3** with PhCHO in ethanol followed by addition of $NaBH_4$ yielded the *N,N',N''*-tribenzyl derivative **6**, for which a preliminary X-ray structural analysis (of the neutral amine)[‡] confirmed that the methyl groups occupied equatorial sites. The successive protonation constants for **3** were determined (Table 1) and indicated that the ligand is less basic than the unbiased analogue **6** and the related

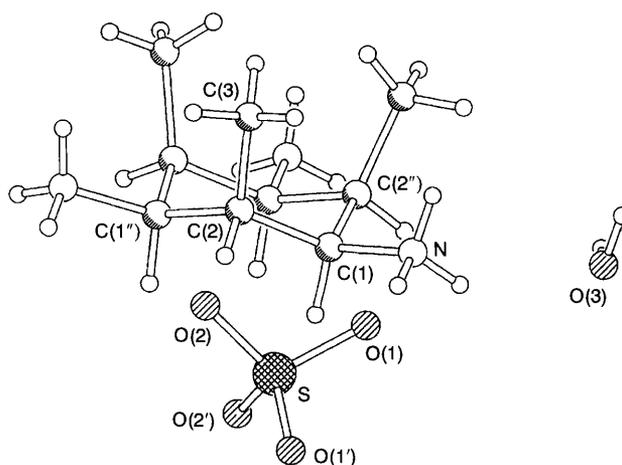
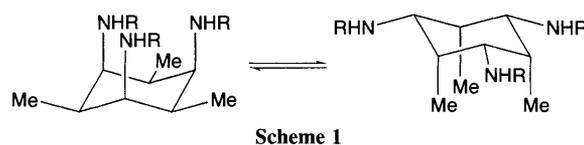
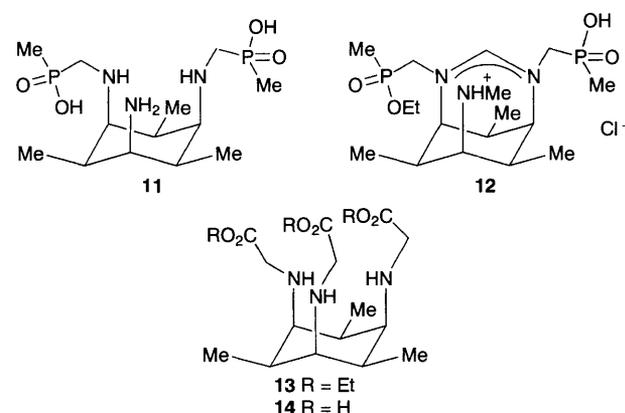
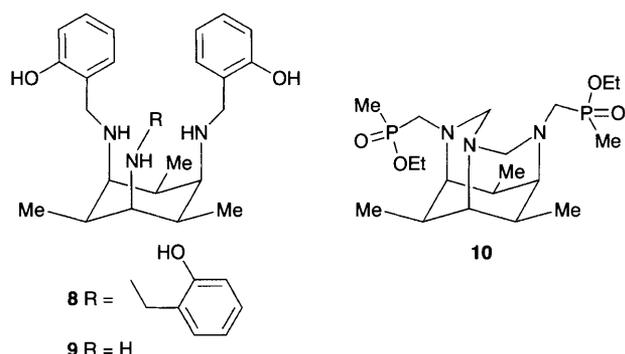
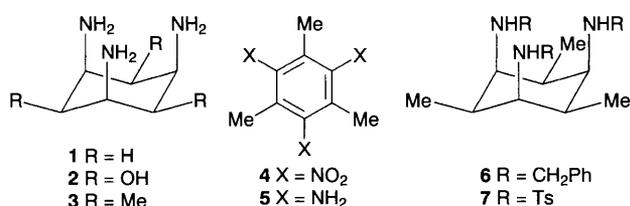


Fig. 1 Structure of the trication $[H_3 \cdot 3]^{3+}$ in the crystal

triol **7**. The reduced affinity of **3** for protons suggests strongly that in all of the protonated forms (LH^+ , LH_2^{2+} , LH_3^{3+}) the amino groups occupy equatorial sites and relief of steric compression between proximate methyl groups occurs only on formation of the unprotonated amine **3**. The amine **3** (notwithstanding its reduced basicity) rapidly formed a paramagnetic pale orange six-coordinate ML_2 complex on addition of CoCl_2 in water $[\text{Co}(\cdot\text{3})_2]^{2+}$: λ_{max} 345, 494 nm, $\epsilon = 41 \text{ dm}^3 \text{ mol}^{-1} \text{ cm}^{-1}$.⁹ This complex slowly oxidised to the corresponding diamagnetic Co(III) complex in aqueous solution, over a period of several hours, but with very little change in the visible absorption spectrum. Reaction of **3** with toluenesulfonyl chloride (Et_3N , THF) gave the tritosylamide **7**. Attempts to alkylate **7** (DMF, Cs_2CO_3 , 60 °C, MeI or $\text{BrCH}_2\text{CO}_2\text{Et}$; NaH, THF, 65 °C, MeI) failed to give the desired *N*-substituted products and steric inhibition of reaction may also account for the failure of **6** to undergo a standard phosphinoxymethylation reaction¹⁰ [$(\text{CH}_2\text{O})_n$, MeP(OEt)_2 , THF, 60 °C, 72 h].

The condensation of **3** with paraformaldehyde in the presence of MeP(OEt)_2 (THF, 60 °C, 4 Å sieves) gave the unusual tricyclic bis-aminal **10** in 60% yield, as a mixture of the *RR/SS* and *RS/SR* diastereoisomers (specifying chirality at P).§ Acid hydrolysis of **10** (6 mol dm^{-3} HCl, 110 °C, 18 h) yielded in addition to the expected amino-acid **11** (an L_3X_2 ligand),¹¹ the unusual bicyclic amidine **12** (m/z 380 positive ion ESMS, 378 negative ESMS; δ_{C} (pD 0.5) 154.3 and δ_{H} 8.20 for NCHN). This may have been formed by a rearrangement involving intramolecular hydride transfer (Fig. 3). The key step must involve migration of hydride from the aminal bridge to the proximate iminium ion, thereby generating the unique *N*-Me group.

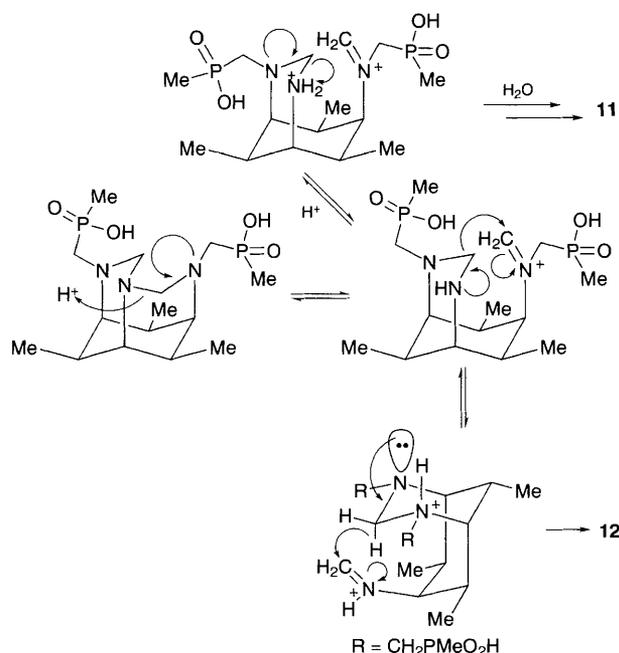


Fig. 2 Suggested mechanism for acid hydrolysis of the tricyclic aminal **10**, forming the bicyclic amidine **12** and the L_3X_2 ligand **11**

Table 1 Protonation equilibria for **3** and related triamines (293 K)

Ligand	pK_1	pK_2	pK_3
3 ^a	7.83	6.73	5.15
1 ^b	10.17	8.66	7.17
2 ^c	8.90	7.40	5.95

^a 0.1 mol dm^{-3} NMe_4NO_3 , values (± 0.02) were obtained by standard potentiometric methods followed by 'SUPERQUAD' data analysis. ^b 0.1 mol dm^{-3} KCl, reference 4. ^c 0.1 mol dm^{-3} KNO_3 , reference 5.

The synthesis of L_3X_3 ligands based on **3** may be achieved either by a reductive condensation reaction or, because of steric inhibition of dialkylation at N, by direct alkylation of **3**. Reaction of **3** with salicylaldehyde in EtOH followed by reduction of the yellow tris-imine intermediate with NaBH_4 (EtOH, 40 °C), gave the hexadentate ligand **8**.^{6,12} The pentadentate analogue **9** has also been isolated: addition of 2.2 equiv. of NaBH_4 to the isolated tris-imine in boiling EtOH followed by mild acid hydrolysis gave a mixture of **8** and **9** which was separated by preparative reverse-phase HPLC.

Direct alkylation of **3** ($\text{BrCH}_2\text{CO}_2\text{Et}$, Cs_2CO_3 , DMF, 60 °C) gave the triester **13**, in 83% yield after purification by chromatography on alumina. Acid hydrolysis (6 mol dm^{-3} HCl, 110 °C, 18 h) quantitatively yielded the amino-acid **14**. This hexadentate ligand forms neutral ML complexes with a variety of small tripositive metal ions (e.g. Al^{3+} , Ga^{3+} , Fe^{3+} , In^{3+}), as shown by electrospray mass spectrometry following admixture of equimolar amounts of the ligand **14** and the appropriate metal salt in a water-acetonitrile (pH 4.5) mixed solvent system. For example, the aluminium complex was characterised as the monocationic $[\text{AlLH}]$ complex in positive ion ESMS ($m/z = 370$), and as the chloride adduct ($m/z = 404, 406$) in negative ion mode. The ^1H NMR spectrum of the aluminium complex (pD = 3.7), showed resonances consistent with overall C_3 symmetry [δ_{H} (D_2O): 3.61 (s, 6 H, CH_2CO), 3.52 (br d, 3 H, CHN), 2.74 (dq, 3 H, CHMe), 1.18 (d, 9 H, CH_3)], in contrast to the behaviour of the related gallium complex for which proton NMR revealed a lack of C_3 symmetry for the complex in solution.

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Footnotes

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‡ Crystal data for $[\text{H}_3\text{3}]^{3+}$: $(\text{C}_9\text{H}_{24}\text{N}_3)_2(\text{SO}_4)_3 \cdot 6\text{H}_2\text{O}$, $M = 744.90$, trigonal, $T = 150 \text{ K}$, $a = 14.482(7)$, $c = 28.44(2) \text{ \AA}$, $U = 5165(6) \text{ \AA}^3$ (from 18 reflections with $12 < \theta < 13^\circ$), space group $R\bar{3}c$ (No. 167), $Z = 6$, $D_c = 1.44 \text{ g cm}^{-3}$, $F(000) = 2412$, graphite-monochromated Mo-K α radiation, $\lambda = 0.71073 \text{ \AA}$, $\mu = 2.95 \text{ cm}^{-1}$, crystal size $0.2 \times 0.2 \times 0.5 \text{ mm}$, Rigaku AFC6S diffractometer, ω -scan, $2\theta \leq 45^\circ$, 1292 data collected (757 unique, $R_{\text{int}} = 0.038$), direct methods structure solution (SHELXS-86), with full-matrix least-squares refinement (SHELXL-93, non-H atoms anisotropic, H isotropic, 109 variables) against F^2 of all data with 2-term Chebyshev weights, $wR(F^2) = 0.098$, for 664 data with $I > 2\sigma(I)$, $R(F) = 0.037$, $\Delta\rho_{\text{max}} = 0.29 \text{ e \AA}^{-3}$. Atomic coordinates, bond lengths and angles, and thermal parameters have been deposited at the Cambridge Crystallographic Data Centre. See Information for Authors, Issue No. 1.

The structure of **6** has not been fully refined due to disorder in the lattice, but is sufficiently good to distinguish between the axial or equatorial preference of the *N*-benzyl group.

§ New compounds and complexes gave mass spectroscopic and NMR (^1H , ^{13}C , ^1H) data in accord with the proposed structures. The constitution of **10**, **11** and **12** in particular was established with the aid of 2-D NMR methods (^1H - ^1H , ^1H - ^{13}C COSY).

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