

Preparations and structures of novel *cis,cis*-1,3,5-triaminocyclohexane based zinc complexes: development of new carbonic anhydrase models with variable superstructures

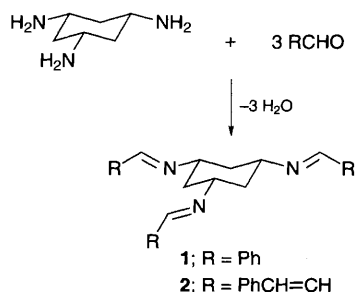
Bryan Greener, Madeleine H. Moore and Paul H. Walton*

Department of Chemistry, University of York, Heslington, York, UK YO1 5DD

Reactions of the ligands *cis,cis*-1,3,5-tri-(*E*)-benzylideneaminocyclohexane and *cis,cis*-1,3,5-tri-(*E,E*)-cinnamylideneaminocyclohexane with zinc salts afford two new metal complexes, the single-crystal X-ray structures of which show unusual, stereochemically rigid superstructures.

Small-molecule model complexes¹ have been used extensively to model the zinc-containing enzyme carbonic anhydrase (CA),² which catalyses the hydration of carbon dioxide at a near diffusion limited rate. These complexes have been valuable in confirming the Lewis acid behaviour of the zinc ion in the enzyme and the coordination modes of substrates in CA. The major problems with such complexes have been dimerisation³ and the irreversible binding of product (bicarbonate) to the metal centre.⁴ Also, most of the models have been limited to modelling the immediate tris-histidine zinc coordination geometry and none have reproduced the high catalytic efficiency of the enzyme. The reasons for this certainly involve the participation of amino acid residues in the active site of the enzyme that are not directly coordinated to the metal centre. Site-directed mutagenesis studies on CA have shown, for example, that histidine 64, which is 7.9 Å away from the zinc centre, is essential for maximum catalytic activity.⁵ We recognise that an effective model for CA must aim to mimic such essential features.

To extend existing model studies⁶ we present here a ligand system which is designed not only to mimic the immediate zinc coordination geometry, but also to incorporate a stereochemically rigid superstructure around the fourth coordination site of zinc. The superstructure can be varied systematically to provide a basis for modelling amino acid residues remote from the zinc centre. Species coordinated to the zinc are encapsulated within the superstructure providing opportunities for modelling the p*K*_a control, substrate selectivity *etc.* observed in CA. The ligand system is easily prepared from the condensation of *cis,cis*-1,3,5-triaminocyclohexane⁷ (tach) with a variety of aldehydes, Scheme 1. The tach moiety is an effective mimic of the tris-histidine coordination as a water molecule bound to Zn(tach)²⁺ has a p*K*_a of 7.95,⁸ similar to that of the analogous water molecule in CA (*ca.* 7). On coordination to a metal the ligand enforces a face capping tridentate nitrogen coordination geometry around the metal, see *e.g.* Scheme 2. Using this new ligand system, we have synthesised and structurally charac-



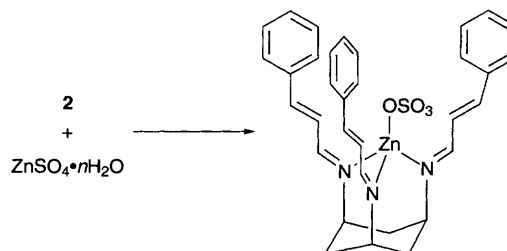
Scheme 1 Synthesis of ligands by **1** and **2** condensation of aldehyde with *cis,cis*-1,3,5-triaminocyclohexane

terised preliminary model complexes that possess a sterically crowded, hydrophobic superstructure, similar to that observed in the active site of CA.

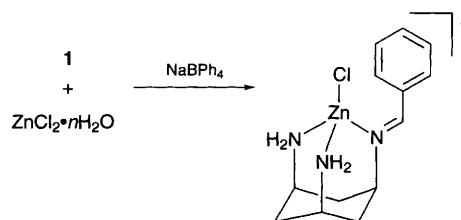
We have prepared the molecules *cis,cis*-1,3,5-tri-(*E*)-benzylideneaminocyclohexane **1** in 75% yield⁹ and *cis,cis*-1,3,5-tri-(*E,E*)-cinnamylideneaminocyclohexane **2** in 62% yield[†] from the condensation of tach with benzaldehyde and cinnamaldehyde respectively. Addition of **1** to zinc chloride (in the presence of sodium tetraphenylborate) and **2** to zinc sulfate affords two new complexes, {*r*-1-[(*Z*)-benzylideneamino-κ*N*]-*c*-3,5-diamino-κ²*N,N'*-cyclohexane}chlorozinc(II) tetraphenylborate (**3**)‡ and [*cis,cis*-1,3,5-tri-(*Z,E*)-cinnamylideneamino-κ³*N,N',N''*-cyclohexane](sulfato-κ*O*)zinc(II)] (**4**)§ in 69 and 89% yield respectively. In the case of **1**, complexation causes partial hydrolysis of the ligand (Scheme 3). **2** complexes to zinc without decomposition. The crystal structures of the complexes¶ have been determined.

The structure of **3** (Fig. 1) shows that zinc complexation has forced the hydrolysis of two of the three imine bonds to afford a novel unsymmetrical ligand.¶ There is evidence of steric strain in the structure between the chloride anion and the remaining benzyl arm, N(1)–C(7)–C(8) 126.8(4)° and N(1)–C(7)–C(8)–C(13) 28.3(7)°. Presumably the steric strain has facilitated the partial hydrolysis of **1**. The zinc coordination geometry is highly distorted from tetrahedral, the N(1)–Zn–Cl(1) angle of 132.7(1)° is particularly large and the other N–Zn–Cl angles also exceed the tetrahedral angle. A tetraphenylborate anion and a methanol molecule complete the structure.

The structure of **4** (Fig. 2) shows an intact ligand **2** coordinated to zinc. The cinnamylidene arms form a rigid cavity around the sulfate anion, which is bound to the fourth coordination site of the zinc. Large Zn–N=C angles, *av.* 130.6(3)°, indicate some steric strain between the cinnamylidene groups and the sulfate anion. The zinc is four-coordinate



Scheme 2 Synthesis of metal complex shown for **2**



Scheme 3 Reaction of **1** with zinc chloride in the presence of NaBPh₄

with an essentially monodentate sulfate anion, Zn–O(1) 1.928(3) Å, having only a weak interaction, Zn···O(4) 2.548(3) Å, between the zinc and a second sulfate oxygen atom. In comparison to **3** the zinc coordination geometry is also distorted from tetrahedral but this time with three dissimilar O(1)–Zn–N angles of 129.5(1), 123.3(1) and 110.0(1)°. A similar zinc coordination geometry has been observed in another CA model, (trispyrazolylborate)nitrate zinc(II).¹⁰ An ethanol molecule held in the 'upper' part of the cavity is hydrogen bonded to O(2) of the sulfate. A methanol molecule completes the structure.

We have prepared zinc complexes of two ligands which exhibit varying degrees of rigid hydrophobic bulk around the

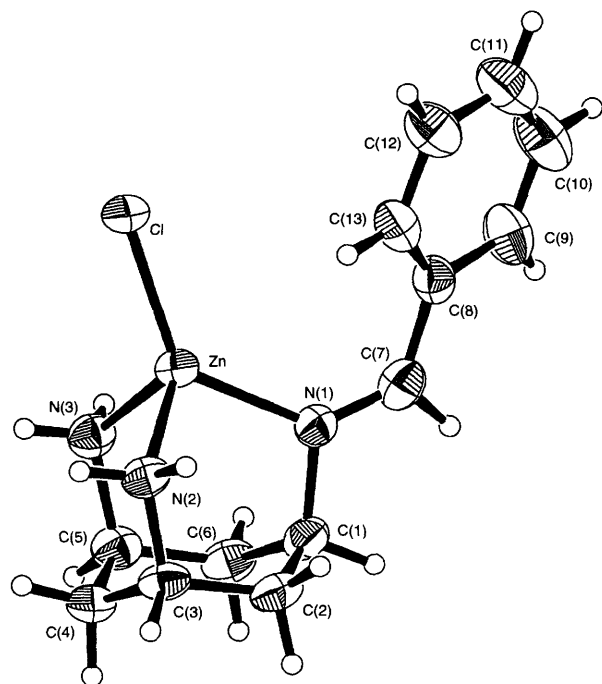


Fig 1 ORTEP plot¹¹ with 30% probability thermal ellipsoids showing the structure of the cation of **3**. Selected bond distances (Å) and angles (°): Zn–N(1) 2.035(3), Zn–N(2) 2.026(3), Zn–N(3) 2.045(3), Zn–Cl 2.195(2), N(1)–Zn–N(3) 95.72(13), N(1)–Zn–Cl 132.68(10), N(2)–Zn–N(1) 97.72(13), N(2)–Zn–N(3) 94.97(13), N(2)–Zn–Cl 115.20(9), N(3)–Zn–Cl 113.12(10).

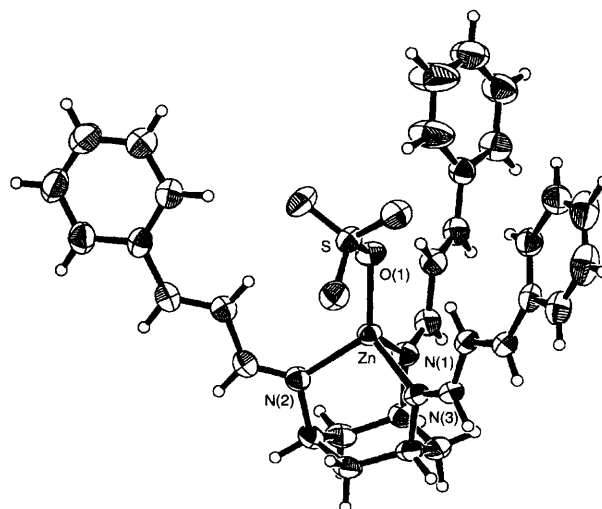


Fig 2 ORTEP plot¹¹ with 30% probability thermal ellipsoids showing molecular structure of **4**. Selected bond distances (Å) and angles (°): Zn–O(1) 1.928(3), Zn–N(3) 2.023(3), Zn–N(2) 2.050(3), Zn–N(1) 2.097(3), Zn–O(4) 2.548(3), O(1)–Zn–N(3) 129.54(13), O(1)–Zn–N(2) 123.31(13), O(1)–Zn–N(1) 110.05(13), N(3)–Zn–N(1) 91.45(14), N(2)–Zn–N(1) 91.60(13), N(3)–Zn–N(2) 100.03(14), O(1)–Zn–O(4) 61.61(13).

fourth coordination site of the zinc atom. These are the first reported crystal structures of zinc complexes with a single tach-based ligand. The new ligand system is notable insofar as the large number of aldehydes that can be used in the synthesis allows the preparation of a wide range of different superstructures, with the possibility of unsymmetrical cavities. This wide range of ligands provides a basis for modelling many aspects of the CA active site. In future work we will investigate how the hydrophobic superstructure affects the ability of zinc complexes to catalyse the hydration of substrates.

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Footnotes

† **2** was characterised by ¹H NMR spectroscopy, mass spectral analysis and a satisfactory elemental analysis.

‡ *Preparation of 3*: a solution of zinc chloride (0.017 g, 0.13 mmol) and sodium tetraphenylborate (0.044 g, 0.13 mmol) in methanol (3 ml) was added to a solution of **1** (0.050 g, 0.13 mmol) in methanol (5 ml). The combined solution was allowed to stand at room temp. overnight, after which time a quantity of colourless needle crystals precipitated. The crystals were filtered off, washed with methanol and desiccated until dry (0.057 g, 0.09 mmol, 69%).

§ *Preparation of 4*: **2** (0.25 g, 0.53 mmol) and zinc sulfate heptahydrate (0.15 g, 0.53 mmol) were refluxed in methanol (15 ml) for 4 h. The solution was allowed to cool and the fine, white powder was filtered off and desiccated until dry (0.33 g, 0.47 mmol, 89%).

¶ *Crystal data for 3*—C₃₈H₄₃BCIN₃OZn, *M* = 669.4, triclinic, space group *P* $\bar{1}$, *a* = 12.757(4), *b* = 13.025(9), *c* = 10.684(3) Å, α = 97.57(3), β = 102.43(3), γ = 87.77(4)°, *U* = 1718.4(14) Å³, λ = 0.7107 Å, *Z* = 2, *D*_c = 1.29 g cm⁻³, *D*_m = 1.29 g cm⁻³. 4853 reflections measured, 4558 unique. Solution by Patterson methods with SAPI91 and expanded using Fourier techniques with DIRDIF. Full-matrix least-squares refinement on *F*² with SHELXL93 with all non-hydrogen atoms anisotropic and hydrogens refined using a rigid model. Final *R*_F, *wR*_F values on all data were 0.072, 0.105, and *R*_F, *wR*_F values on [*I*_o > 2σ(*I*_o)] data were 0.040, 0.092, goodness of fit on *F*² = 1.014. For **4**—C₃₆H₄₃N₃O₆SZn, *M* = 711.2, monoclinic, space group *P*2₁/*c*, *a* = 9.1092(14), *b* = 15.974(4), *c* = 24.431(6) Å, β = 98.419(14)°, *U* = 3516.7(13) Å³, λ = 0.7107 Å, *Z* = 4, *D*_c = 1.34 g cm⁻³, *D*_m = 1.35 g cm⁻³. 5304 reflections measured, 4665 unique. Solution method and refinement as for **3**. Final *R*_F, *wR*_F values on all data were 0.071, 0.124, and *R*_F, *wR*_F values on [*I*_o > 2σ(*I*_o)] data were 0.042, 0.110, goodness of fit on *F*² = 1.048. Programs used are given in ref. 12. 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.

|| Partial hydrolysis of **1** to give the unsymmetrical ligand can be carried out with a range of transition-metal salts and will be the subject of a future paper.

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