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Models of the active sites of zinc-containing enzymes: the structure of acetato[hydrotris(3-*tert*-butyl-5-methylpyrazol-1-yl)borato]zinc(II)

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The zinc complex acetato[hydrotris(3-*tert*-butyl-5-methylpyrazol-1-yl)borato]zinc(II) has been prepared and structurally characterised as a model of the active sites of the zinc-containing enzymes carbonic anhydrase and dihydroorotase. Crystals are monoclinic, space group $P2_1/n$, a 15.995(2), b 19.861(4), c 10.530(2) Å, β 90.00(2)°, Z 4 and the structure has been refined to a residual of 0.048 based on 4096 reflections. The complex deviates from C_3 symmetry as a consequence of interactions between the tripod ligand and the fourth ligand bound to the Zn atom. The Zn–N (tripod) bond lengths are affected by the degree of steric crowding but bonds to the fourth ligand are not. Comparison with the I^-, OH^- and HCO_3^- forms of human carbonic anhydrase I confirms that the complexes with tripodal ligands are excellent structural models for the active site of this enzyme.

A common motif across a number of zinc-containing enzymes is the co-ordination of the metal ion by three histidine imidazole groups. Consequently tripodal ligands bearing three nitrogen-containing aromatic rings such as pyridyl, pyrazolyl or imidazolyl groups form an excellent basis for modelling of these active sites. The enzyme carbonic anhydrase (CA) has received the most attention in this respect with a number of recent reports of structural models of the active site.[1–10] Most of these models have employed tris(pyrazolyl) borate ligands because they provide the three aromatic donor groups and are readily prepared and elaborated. Our own interest is in dihydroorotase (DHOase), the enzyme that catalyses the conversion of *N*-carbamyl-L-aspartate into L-dihydroorotate, the third reaction in the *de novo* biosynthesis of pyrimidine nucleotides.[11] Inhibitors of DHOase are potential anticancer agents and some have also shown excellent promise as antimalarial agents.[12] It is therefore an excellent target for structure-based drug design, however at present no crystal structure is available. Using site-directed mutagenisis, it has recently been confirmed that the active site of DHOase contains a zinc ion co-ordinated by three histidine imidazole groups and that a number of other peptide side chains are important for maintaining maximum activity.[13] The current model of this active site, developed to explain these observations,[13] is shown in Fig. 1. The mechanism of action involves co-ordination of *N*-carbamyl-L-aspartate to the zinc atom followed by ring closure to give L-dihydroorotate.[11,13,14] Our structure–activity studies on a number of natural substrates and inhibitors of DHOase have revealed an acute sensitivity to the orientation of the substituents on the rings.[15,16] Recently, we have commenced an investigation of the structures of their zinc complexes in order to establish the preferred sites of interaction between zinc and the natural and synthetic substrates[17,18] and the next phase of the project is to use tripodal ligands with and without hydrogen-bonding sides chains to mimic the active site and to shed light on the role of the peptide side chains. The putative active site of DHOase contains a four- or five-co-ordinate zinc atom and in order to limit access to the metal in our models we have chosen the tripodal ligands L^1 and L^2 both of which have *tert*-butyl substituents on each of the arms.

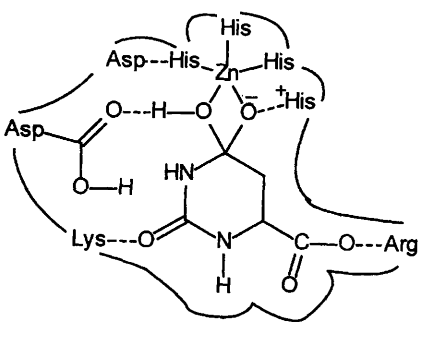
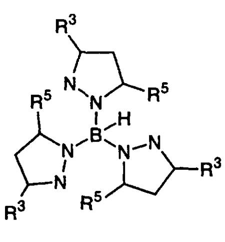
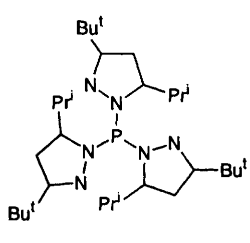


Fig. 1 Schematic view of the proposed active site of DHOase





L^1 $R^3 = Bu^t, R^5 = H$
L^2 $R^3 = Bu^t, R^5 = Me$
L^3 $R^3 = Pr^i, R^5 = Pr^i$
L^5 $R^3 = Ph, R^5 = H$

L^4

Experimental

Chemicals

All reagents and solvents were of laboratory grade obtained from commercial sources, with no further purification unless otherwise noted.

Physical methods

The NMR spectra were recorded on a Bruker AC200 instrument (200 MHz for ^1H and 50 MHz for ^{13}C) using $CDCl_3$ as the solvent, infrared spectra on a Perkin-Elmer Series 1600 FTIR spectrometer as KBr discs.

Syntheses

Compounds L^1 and L^2 were synthesized as their potassium and thallium salts as described by Trofimenko *et al.*[19]

[Zn(L^1)I]. The salt TlL^1 (0.0226 g, 39.7 μmol) was dissolved in acetone (5 cm^3) and a solution of ZnI_2 (0.0136 g, 42.6 μmol) in 3 ethanol (3 cm^3) was added dropwise. The bright yellow precipitate of TlI was filtered off and the pale yellow filtrate left to crystallise. Yield 0.0210 g (92%). NMR: ^{1}H, δ 7.80 (3 H, d, J = 1, pyrazolyl C^{5}H), 6.31 (3 H, d, J = 1 Hz, pyrazolyl C^{4}H), and 1.38 [27 H, s, $C(CH_3)_3$]; ^{13}C, δ 155.8 (pyrazolyl C^3), 140.5 (pyrazolyl C^5), 103.7 (pyrazolyl C^4), 31.7 [$\mathit{C}(CH_3)_3$] and 29.9 [$C(\mathit{C}H_3)_3$]. IR: 2962s, 2903m, 2887m, 2518 [m, ν(B–H)], 1502s, 1458m, 1384s, 1363s, 1340s, 1258m, 1213m, 1196s, 1170m, 1102m, 1061m, 1025m, 928w, 878w, 831w, 786s, 736s, 721m, 578w and 492w cm^{-1}. The structure was determined and confirmed the results obtained previously.[4]

[ZnL^2(O$_2$CMe)]. To a stirred solution of zinc(II) acetate dihydrate (1.00 g, 4.56 mmol) in water (10 cm^3) was added a solution of KL^2 (0.100 g, 0.220 mmol) in tetrahydrofuran (1 cm^3). About 1 min after the addition a white precipitate was evident. The mixture was allowed to stir for 1 h, and then extracted with chloroform. The chloroform extract was dried with anhydrous Na_2SO_4, filtered, and the solvent removed on a rotary evaporator to give the product. Yield 0.107 g (89%). NMR: ^{1}H, δ 5.84 (3 H, s, pyrazolyl C^{4}H), 2.39 (9 H, s, pyrazolyl C^{5}CH$_3$), 2.12 (3 H, s, O_2CCH_3), 2.05 (1 H, br, BH) and 1.36 [27 H, s, $C(CH_3)_3$]; ^{13}C, δ 175.6 ($O_2\mathit{C}CH_3$), 163.6 (pyrazolyl C^3), 144.3 (pyrazolyl C^5), 102.9 (pyrazolyl C^4), 31.6 [$\mathit{C}(CH_3)_3$], 30.2 [$C(\mathit{C}H_3)_3$], 23.5 ($O_2C\mathit{C}H_3$) and 12.9 (pyrazolyl C^5CH$_3$). IR: 2960s, 2558 [m, ν(B–H)], 1653 [s, ν(C=O)], 1542s, 1476m, 1424s, 1383s, 1364s, 1339m, 1317s, 1246w, 1189s, 1070s, 1028m, 985w, 929w, 857w, 834w, 789m, 769s, 734w, 680w, 649m, 614w and 520m cm^{-1}. Microanalysis data were not obtained because of the variable loss of solvent from the solid.

X-Ray crystallography

Crystals of [ZnL^2(O$_2$CMe)] suitable for structure analysis were obtained by slow evaporation of a toluene solution of the complex. A crystal was mounted a on glass fibre with cyanoacrylate resin and cell constants were determined by a least-squares fit to the setting angles of 25 independent reflections collected on a Rigaku AFC7-R four-circle diffractometer employing graphite-monochromated Cu-Kα radiation.

Crystal data. $C_{29.5}H_{47}BN_6O_2Zn$, M 593.94, monoclinic, space group $P2_1/n$, a 15.995(2), b 19.861(4), c 10.530(2) Å, β 90.00(2)°, U 3345.2(8) Å^3, Z 4, D_c 1.179 g cm^{-3}, μ(Cu-Kα) 12.25 cm^{-1}, λ(Cu-Kα) 1.5418 Å, F(000) 1268 electrons, θ_{max} 60.0°, T_{max} 0.999, T_{min} 0.892, crystal dimensions 0.45 × 0.25 × 0.10 mm, N 5657, N_o 4096 [$I > 2.5\sigma(I)$], N_{var} 379, maximum shift 0.1σ, R 0.048, R' 0.056* and $w = 1/[\sigma^2(F_o)]$, ρ_{max} 0.73, ρ_{min} −0.46 e Å^{-3}.

Data reduction and application of Lorentz-polarisation and analytical absorption corrections were carried out using TEXSAN.[20] The structure was solved by direct methods using SHELXS 86[21] and refined using full-matrix least-squares methods with TEXSAN. Hydrogen atoms were included at calculated sites with thermal parameters derived from the parent atoms. Non-hydrogen atoms, with the exception of minor sites of disordered atoms, were refined anisotropically. Scattering factors and anomalous dispersion terms for Zn (neutral Zn) were taken from ref. 22. Anomalous dispersion effects were included in F_c;[23] the values for $\Delta f'$ and $\Delta f''$ were those of Creagh and McAuley.[24] The values for the mass attenuation coefficients were those of Creagh and Hubbell.[25] All other calculations were performed using TEXSAN.

An ORTEP[26] plot is shown in Fig. 2. Bond lengths and angles are presented in Table 1.

Atomic coordinates, thermal parameters and bond lengths and angles have been deposited at the Cambridge Crystallographic Data Centre (CCDC). See Instructions for Authors, *J. Chem. Soc., Dalton Trans.*, 1996, Issue 1. Any request to the CCDC for this material should quote the full literature citation and the reference number 186/219.

Results and Discussion

The structure of [Zn(L^1)I] consists of the neutral complex molecule, located on a crystallographic mirror plane as has been previously reported.[4] The geometry about the Zn atom is distorted tetrahedral with the iodine atom bent slightly away from the three-fold axis of the complex, toward the *tert*-butyl group that lies in the mirror plane. This distortion is most readily defined by the B ··· Zn–I angle which is 177.8°, and the small distortion reflects the equirepulsive interactions between the I atom and the *tert*-butyl groups. The closest I ··· H contacts are 2.95, 2.95 and 3.18 Å.

The structures of two closely related complexes, [Zn(L^3)I] and [Zn(L^4)I] each with iodide co-ordinated to the Zn atom, have been reported recently. Bond lengths and angles about the Zn atom for the three structures are collated in Table 2. The complex [Zn(L^3)I] differs from the other two structures in that it has isopropyl substituents at both the 3 and 5 positions on the pyrazol-1-yl ring, significantly reducing the steric crowding about the iodide ligand. This is reflected in shorter Zn–I and Zn–N bond lengths, though the effect on the former is modest. The complex [Zn(L^4)I] differs in that it has a phosphine bridgehead group and this results in an opening of the N–Zn–N bond angles by 2–3° and closing of the I–Zn–N angles by a similar amount. The Zn–N bond lengths are significantly longer in [Zn(L^4)I] than in [Zn(L^1)I] presumably as a consequence of the greater steric crowding induced by these geometrical changes in the ligand. The Zn–I bond length is not significantly different in the two structures.

The complex [ZnL^2(O$_2$CMe)] crystallises in an apparently orthorhombic cell, however attempts to solve the structure in an orthorhombic space group were unsuccessful. Collection of a full data set for a monoclinic cell with β = 90.00° gave an R_{merge} greater than 40% for the orthorhombic cell. Thus, a solution was attempted in the monoclinic space group $P2_1/n$ and was successful. There is no evidence in the refined structure of additional symmetry having been missed. The structure consists of the neutral complex molecule and a grossly disordered solvent molecule that we have tentatively assigned as being a toluene. The acetate ligand is also disordered, over two sites

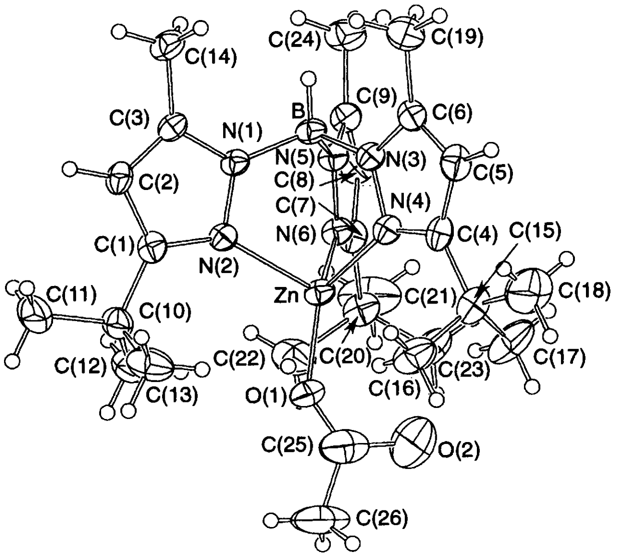


Fig. 2 An ORTEP[26] plot of [ZnL^2(O$_2$CMe)], showing atomic labels (30% thermal ellipsoids)

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* $R = \Sigma(||F_o| - |F_c||)/\Sigma|F_o|$, $R' = \Sigma(w^{\frac{1}{2}}||F_o| - |F_c||)/\Sigma w^{\frac{1}{2}}|F_o|$.

Table 1 Selected bond lengths (Å) and angles (°) for [ZnL^{2}(O$_{2}$CMe)]

Zn–O(1)	1.870(4)	Zn–N(2)	2.054(3)	C(7)–C(8)	1.386(5)	C(7)–C(20)	1.506(5)
Zn–N(4)	2.051(3)	Zn–N(6)	2.045(3)	C(8)–C(9)	1.378(5)	C(9)–C(24)	1.488(5)
O(1)–C(25)	1.179(6)	O(2)–C(25)	1.318(8)	C(10)–C(11)	1.521(6)	C(10)–C(12)	1.525(5)
N(1)–N(2)	1.373(3)	N(1)–C(3)	1.339(4)	C(10)–C(13)	1.530(6)	C(15)–C(16)	1.510(6)
N(1)–B	1.535(5)	N(2)–C(1)	1.342(4)	C(15)–C(17)	1.526(6)	C(15)–C(18)	1.535(6)
N(3)–N(4)	1.376(3)	N(3)–C(6)	1.354(4)	C(20)–C(21)	1.533(5)	C(20)–C(22)	1.506(6)
N(3)–B	1.544(4)	N(4)–C(4)	1.338(4)	C(20)–C(23)	1.529(6)	C(25)–C(26)	1.410(7)
N(5)–N(6)	1.384(3)	N(5)–C(9)	1.346(4)	C(27)–C(28)	1.28(2)	C(27)–C(29)	1.28(5)
N(5)–B	1.538(5)	N(6)–C(7)	1.341(4)	C(28)–C(29)	1.70(6)	C(28)–C(30)	1.2(1)
C(1)–C(2)	1.399(5)	C(1)–C(10)	1.521(5)	C(29)–C(30)	1.5(1)	C(29)–C(31)	1.24(3)
C(2)–C(3)	1.358(5)	C(3)–C(14)	1.487(5)	C(30)–C(31)	1.74(9)	Zn–O(4)	1.90(2)
C(4)–C(5)	1.389(5)	C(4)–C(15)	1.514(5)	O(3)–C(25)	1.74(2)	O(4)–C(25)	1.08(2)
C(5)–C(6)	1.362(5)	C(6)–C(19)	1.491(5)				
O(1)–Zn–N(2)	111.4(1)	O(1)–Zn–N(4)	125.2(1)	N(4)–N(3)–C(6)	109.5(3)	N(4)–N(3)–B	121.2(3)
O(1)–Zn–N(6)	127.8(2)	O(4)–Zn–N(2)	128.3(5)	C(6)–N(3)–B	129.2(3)	Zn–N(4)–N(3)	109.6(2)
O(4)–Zn–N(4)	125.6(5)	O(4)–Zn–N(6)	109.8(5)	Zn–N(4)–C(4)	143.5(2)	N(3)–N(4)–C(4)	106.9(3)
N(2)–Zn–N(4)	96.3(1)	N(2)–Zn–N(6)	92.2(1)	N(6)–N(5)–C(9)	109.3(3)	N(6)–N(5)–B	121.0(2)
N(4)–Zn–N(6)	95.6(1)	Zn–O(1)–C(25)	138.0(5)	C(9)–N(5)–B	129.4(3)	Zn–N(6)–N(5)	109.6(2)
N(2)–N(1)–C(3)	109.7(3)	N(2)–N(1)–B	120.6(2)	Zn–N(6)–C(7)	143.3(2)	N(5)–N(6)–C(7)	107.1(3)
C(4)–C(5)–C(6)	107.4(3)	N(3)–C(6)–C(5)	107.3(3)	N(2)–C(1)–C(2)	108.8(3)	N(2)–C(1)–C(10)	122.6(3)
N(3)–C(6)–C(19)	122.7(3)	C(5)–C(6)–C(19)	130.0(4)	C(2)–C(1)–C(10)	128.5(3)	C(1)–C(2)–C(3)	106.5(3)
N(6)–C(7)–C(8)	108.8(3)	N(6)–C(7)–C(20)	122.6(3)	N(1)–C(3)–C(2)	108.3(3)	N(1)–C(3)–C(14)	123.1(3)
C(8)–C(7)–C(20)	128.6(3)	C(7)–C(8)–C(9)	107.2(3)	C(2)–C(3)–C(14)	128.6(3)	N(4)–C(4)–C(5)	108.9(3)
N(5)–C(9)–C(8)	107.5(3)	N(5)–C(9)–C(24)	123.0(3)	N(4)–C(4)–C(15)	122.8(3)	C(5)–C(4)–C(15)	128.3(3)
C(8)–C(9)–C(24)	129.5(3)	C(1)–C(10)–C(11)	108.9(3)	C(21)–C(20)–C(22)	108.1(4)	C(21)–C(20)–C(23)	109.2(4)
C(1)–C(10)–C(12)	110.4(3)	C(1)–C(10)–C(13)	109.7(3)	C(22)–C(20)–C(23)	110.0(4)	O(1)–C(25)–O(2)	120.5(6)
C(11)–C(10)–C(12)	109.2(4)	C(11)–C(10)–C(13)	108.4(4)	O(1)–C(25)–C(26)	127.0(7)	O(2)–C(25)–C(26)	112.2(6)
C(12)–C(10)–C(13)	110.2(3)	C(4)–C(15)–C(16)	110.3(3)	O(3)–C(25)–O(4)	98(1)	O(3)–C(25)–C(26)	80.5(7)
C(4)–C(15)–C(17)	108.8(3)	C(4)–C(15)–C(18)	109.7(4)	O(4)–C(25)–C(26)	148(1)	C(28)–C(27)–C(29)	141(5)
C(16)–C(15)–C(17)	109.5(4)	C(16)–C(15)–C(18)	107.5(4)	C(27)–C(28)–C(29)	122(4)	C(27)–C(28)–C(30)	177(3)
C(17)–C(15)–C(18)	111.1(4)	C(7)–C(20)–C(21)	109.5(3)	C(29)–C(28)–C(30)	59(5)	C(27)–C(29)–C(28)	98(3)
C(7)–C(20)–C(22)	110.8(3)	C(7)–C(20)–C(23)	109.2(3)	C(27)–C(29)–C(30)	143(8)	C(27)–C(29)–C(31)	139(9)
C(29)–C(31)–C(30)	57(4)	N(1)–B–N(3)	110.0(3)	C(28)–C(29)–C(30)	45(5)	C(28)–C(29)–C(31)	123(7)
N(1)–B–N(5)	110.4(3)	N(3)–B–N(5)	109.3(3)	C(30)–C(29)–C(31)	78(5)	C(28)–C(30)–C(29)	76(3)
C(3)–N(1)–B	129.6(3)	Zn–N(2)–N(1)	110.2(2)	C(28)–C(30)–C(31)	120(5)	C(29)–C(30)–C(31)	44(3)
Zn–N(2)–C(1)	143.1(2)	N(1)–N(2)–C(1)	106.6(2)	Zn–O(4)–C(25)	146(1)		

Table 2 Average bond lengths (Å) and angles (°) about the Zn atom in a number of [Zn(tripod ligand)X] complexes and the active site of CA I

Complex	Zn–I	Zn–N	I–Zn–N	N–Zn–N	Ref.
[Zn(L^{1})I]	2.518(1)	2.070	122.2	94.3	4
	2.514(1)	2.069	122.0	94.5	This work
[Zn(L^{3})I]	2.493(2)	2.017	123.1	92.9	6
[Zn(L^{4})I]	2.516(3)	2.094	120.5	96.6	9
CA I(I^{-} form)	2.7	1.9	112	108	27
	Zn–O	Zn–O	O–Zn–N	N–Zn–N	
[ZnL^{2}(OH)]	1.850(8)	2.052	123.2	95.6	1
[ZnL^{4}(OH)]	1.860(5)	2.082	121.7	94.8	9
[ZnL^{1}(O$_{2}$CMe)]	1.859(6)	2.081	122.3	93.5	3
[ZnL^{2}(O$_{2}$CMe)]	1.870(4)	2.050	121.5	94.7	This work
[ZnL^{5}(O$_{2}$CPh)]	1.935(5)	2.055	122.4	93.0	10
[ZnL^{2}(MeO$_{2}$CMe)]	1.884(6)	2.034	121.3	94.9	8
[(ZnL^{2})$_{2}$(CO$_{3}$)]	1.850(7)	2.067	122.1	93.5	6
[(ZnL^{3})$_{2}$(CO$_{3}$)]	1.909(6)	2.029	—	92.2	6
[ZnL^{1}(NO$_{3}$)]	1.978(3)	2.052	120.3	95.6	6
[ZnL^{4}(NO$_{3}$)]	1.986(4)	2.059	119.1	97.3	9
[ZnL^{5}(NO$_{3}$)]	1.947(3)	2.033	121.7	—	7
CAI(OH^{-} form)	1.9	1.9	112	108	28
(HCO$_{3}^{-}$ form)	1.8	2.0	115	104	28

with occupancies of 80:20. This disorder takes the form of rotation about the Zn–O bond, positioning the carbonyl oxygen into one of the other two cavities offered by the tripod ligand. The precision associated with the atoms of the minor site is poor and discussion is hereafter limited to the major site. The geometry is similar to that in the iodide complex with a distorted tetrahedral arrangement about the Zn atom and the co-ordinated O (acetate) atom bent away from the three-fold axis, in this case by 11°. There are a number of close contacts between the co-ordinated O atom and the *tert*-butyl groups, the four shortest of which range from 2.42 to 2.76 Å. There are only two close contacts to the non-co-ordinated O (acetate) atom (2.33 and 2.44 Å), but the acetate group is bent away from these H atoms and hence they are responsible for the movement of the co-ordinated O atom off the Zn • • • B axis. In addition, the Zn–O–C angle is opened to 138.0(5)°, evidently in order to relieve these interactions with the non-co-ordinated O atom, and resulting in a large Zn • • • O separation of 3.242 Å. Thus, the acetate ligand is in a highly crowded environment that precludes bidentate binding to the Zn atom.

A large number of [Zn(tripod ligand)X] complexes have been structurally characterised in which X is an anionic O-atom donor. The geometric parameters about the zinc sites of these complexes are collected in Table 2. Variations in the geometry of the tripod are similar to those discussed above with the phosphine bridgehead leading to longer Zn–N bond lengths and/or larger N–Zn–N bond angles and the less sterically crowded ligands having shorter Zn–N bond lengths and smaller N–Zn–N bond angles. There is little variation in the geometry of the tripod ligand when the fourth ligand is an O-atom donor compared to that when it is iodide. The Zn–O bond lengths generally fall in a narrow range from 1.85 to 1.91 Å, the exceptions being the Zn–O (benzoate) at 1.935(5) Å, in which case the tripod ligand has phenyl substituents, and Zn–O (nitrate) at 1.947(3)–1.986(4) Å. Somewhat surprisingly, the bond lengths Zn–O (acetate) and Zn–O (methyl acetate) are not significantly different.

Comparison of the geometries of the [Zn(tripod ligand)X] complexes with that of the active site of human carbonic anhydrase I (HCA I) in the iodide, hydroxide and hydrogencarbonate forms[27,28] (Table 2) confirms that these complexes are excellent structural models for the active site with the geometries being as similar as could be required given the level of precision of the protein structures. Our particular interest is in the enzyme dihydroorotase which is believed to have a similar binding site to that of HCA I. The mechanism of action is thought to involve co-ordination of the Zn atom to a carboxylate group of the substrate, *N*-carbamyl-L-aspartate. The foregoing results give us confidence that the complex [ZnL^2(O$_2$CMe)] will prove to be a reasonable model of the active site of DHOase and we are currently undertaking extended X-ray absorption fine structure studies to test this hypothesis.

Acknowledgements

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