The Synthesis and Structure of {[PimPri,But]ZnOH}(ClO4): A Tris(imidazolyl)phosphine Zinc Hydroxide Complex and a Proposed Structural Model For Carbonic Anhydrase

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The zinc hydroxide complex {[PimPri,But]ZnOH}(ClO4) is synthesized by the reaction of [PimPri,But] with Zn(ClO4)2·6H2O; {[PimPri,But]ZnOH}(ClO4) is the first structurally characterized monomeric zinc hydroxide complex supported by imidazole functionalities and is therefore an excellent structural model for the active site of carbonic anhydrase.

Carbonic anhydrase (CA), a ubiquitous zinc enzyme found in both plants and animals, has the essential function of catalysing the equilibration of hydrogencarbonate with carbon dioxide and water [eqn. (1)].[1]

$$CO_2 + H_2O \rightleftharpoons HCO_3^- + H^+ \qquad (1)$$
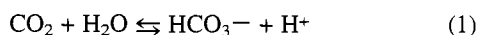
The active site of the enzyme is composed of a pseudo-tetrahedral zinc centre coordinated to the nitrogen donors of three histidine imidazole groups, with the remaining coordination site occupied by the catalytically active moiety, namely a hydroxide or water ligand, depending upon pH.[2] In order to provide insight in to the nature of the catalytic cycle, considerable effort has been directed toward the syntheses of complexes that model either, or both, the structure and function of the active site.[3–13] Despite these numerous studies, however, only two four-coordinate zinc hydroxide complexes supported by nitrogen donor ligands, namely the tris(3-*tert*-butyl-5-methylpyrazolyl)hydroborato complex [TpBut,Me]ZnOH[7a] and the triazacyclododecane derivative [(tacd)Zn-(OH)]+,[13b,14] have been structurally characterized. The latter, however, is actually a hydrogen-bonded trimer in the solid state, *i.e.* [(tacd)Zn(OH)]3(ClO4)3·(HClO4). Even though [TpBut,Me]-ZnOH and [(tacd)Zn(OH)]+ do indeed resemble the active site of carbonic anhydrase in that both exhibit a common [ZnN3O] coordination sphere, their structural similarity to the enzyme is limited by the fact that the nitrogen donors are not imidazolyl-based ligands. In this paper, we describe the synthesis and structure of the first well-defined monomeric four-coordinate zinc hydroxide complex that is supported by imidazole functionalities.

Many tridentate, tripodal, imidazolyl-based ligands, *e.g.* tris(imidazolyl)phosphine, tris(imidazolyl)carbinol and tris-(imidazolyl)alkane derivatives, have been used previously to model the function of carbonic anhydrase.[4–6] Such systems, however, have not yet afforded structurally characterized examples of four-coordinate zinc-hydroxide or zinc-aqua complexes. Nevertheless, it seemed reasonable to consider that an appropriately substituted tris(imidazolyl)derivative should allow for the isolation of a monomeric zinc hydroxide
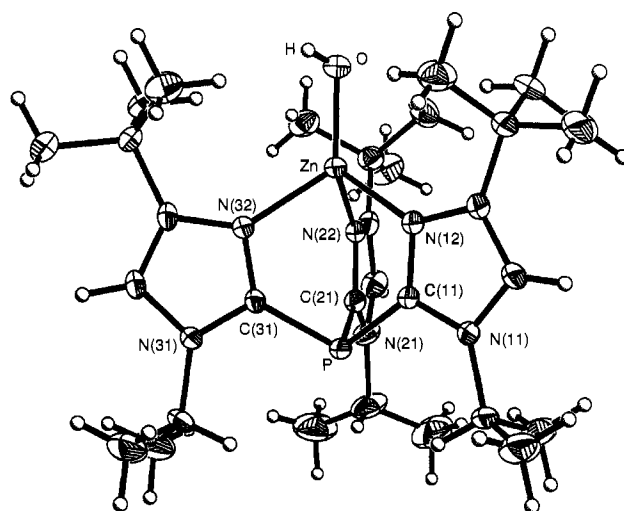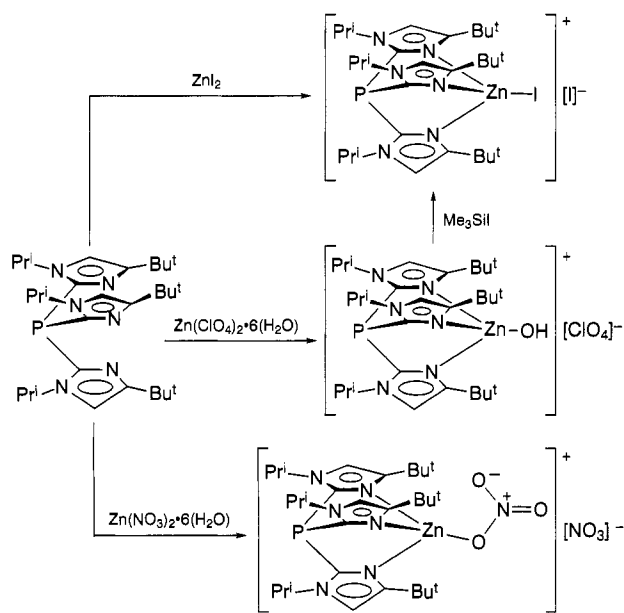

Fig. 1 ORTEP drawing of the cation in {[PimPri,But]ZnOH}(ClO4). Selected bond lengths (Å) and angles (°): Zn–O 1.860(5), Zn–N(12) 2.086(5), Zn–N(22) 2.088(5), Zn–N(32) 2.073(6); O–Zn–N(12) 121.7(2), O–Zn–N(22) 118.9(3), O–Zn–N(32) 124.6(3), N(12)–Zn–N(22) 94.5(2), N(22)–Zn–N(32) 94.0(2), N(12)–Zn–N(32) 95.9(2)].
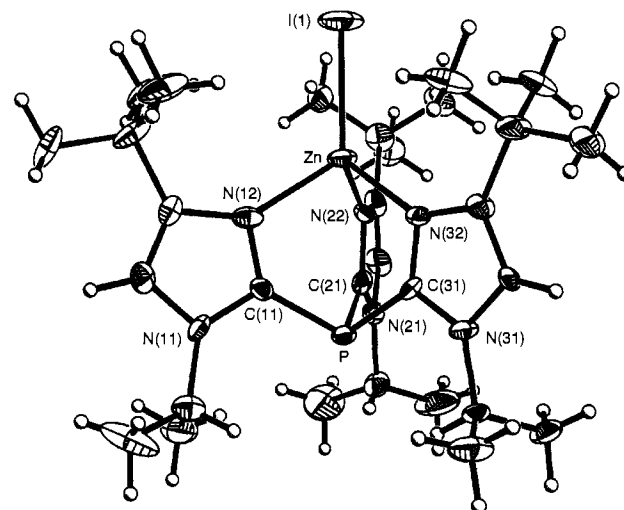

Scheme 1

Fig. 2 ORTEP drawing of the cation in {[PimPri,But]ZnI}I. Selected bond lengths (Å) and angles (°): Zn–I(1) 2.516(3), Zn–N(12) 2.091(15), Zn–N(22) 2.114(15), Zn–N(32) 2.076(14); I(1)–Zn–N(12) 120.5(4), I(1)–Zn–N(22) 121.6(4), I(1)–Zn–N(32) 119.4(3), N(12)–Zn–N(22) 95.8(6), N(22)–Zn–N(32) 96.2(5), N(12)–Zn–N(32) 97.7(6).

Table 1 Comparison of the coordination environments about zinc in carbonic anhydrase and structural models

	{[PimPri,But]ZnOH}+a	[TpBut,Me]ZnOHb	[(tacd)Zn(OH)]+c	CA Id	CA IIe
Zn–O/Å	1.860(5)	1.850(8)	1.944(5)	1.9	2.05
Zn–N/Å	2.073(6)–2.088(5)	2.052(5)	2.004(9)–2.042(9)	1.9	2.10–2.12
O–Zn–N (°)	118.9(3)–124.6(3)	123.2(2)	102.5(3)–127.2(3)	98–125	111.1–113.6
N–Zn–N (°)	94.0(2)–95.9(2)	92.8(2)	104.3(4)–107.0(4)	98–117	99.2–115.3

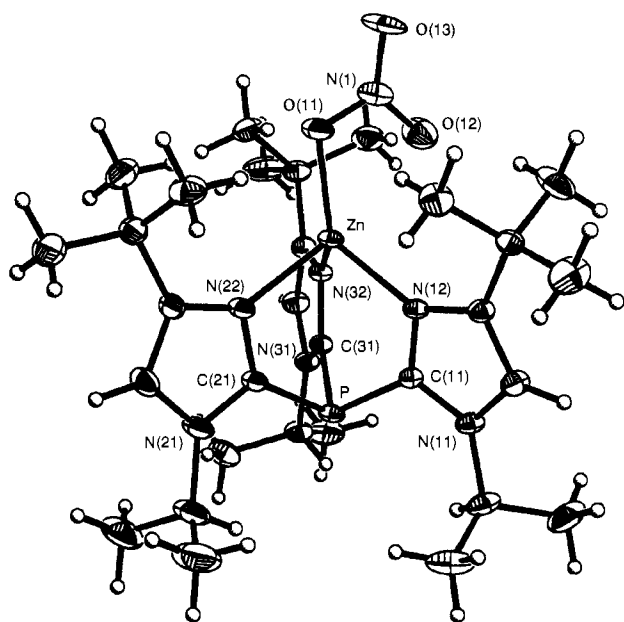a This work. b Ref. 7(a). c Ref. 13(b). d Ref. 2(d). e Ref. 2(a).

Fig. 3 ORTEP drawing of the cation in {[PimPri,But]Zn(ONO2)}(NO3). Selected bond lengths (Å) and angles (°): Zn–O(11) 1.986(4), Zn⋯O(12) 2.518(8), Zn–N(12) 2.054(4), Zn–N(22) 2.074(3), Zn–N(32) 2.048(3), N(1)–O(11) 1.278(6), N(1)–O(12) 1.237(8), N(1)–O(13) 1.217(7); O(11)–Zn–N(12) 121.5(2), O(11)–Zn–N(22) 111.7(2), O(11)–Zn–N(32) 124.1(1), O(11)–N(1)–O(12) 115.8(5), O(11)–N(1)–O(13) 120.3(6), O(12)–N(1)–O(13) 123.9(5), N(12)–Zn–N(22) 93.1(1), N(22)–Zn–N(32) 94.6(1), N(12)–Zn–N(32) 104.2(2).

derivative. By analogy with the tris(pyrazolyl)hydroborato complex [TpBut,Me]ZnOH, in which the bulky *tert*-butyl substituents sustain the monomeric nature of the ZnOH functionality, we have explored the use of the sterically demanding tris[2-(1-isopropyl-4-*tert*-butylimidazolyl)]phosphine ligand [PimPri,But], recently described by Sorrell,[15] for the synthesis of a monomeric tris(imidazolyl)phosphine zinc hydroxide complex.

Indeed, the bulky tris(imidazolyl)phosphine [PimPri,But] readily forms a variety of well defined four-coordinate cationic zinc complexes {[PimPri,But]ZnX}+ (X = OH, NO3, I), as illustrated in Scheme 1. Of most significance is the zinc hydroxide complex {[PimPri,But]ZnOH}+, which may be isolated as the perchlorate salt from the reaction of [PimPri,But] with Zn(ClO4)2·6H2O. The molecular structure of {[PimPri,But]-ZnOH}(ClO4) has been determined by X-ray diffraction,† thereby confirming the presence of a discrete monomeric terminal zinc hydroxide complex (Fig. 1). The monomeric nature of {[PimPri,But]ZnOH}+ contrasts with that of the trimeric hydrogen-bonded structure of [(tacd)Zn(OH)]3-(ClO4)3·(HClO4),[13b] but closely resembles that of its neutral analogue [TpBut,Me]ZnOH.[7a] The coordination environments about zinc in these hydroxide complexes are compared, in Table 1, with the corresponding values for carbonic anhydrase. Evidently, both the Zn–O and Zn–N bond lengths in {[PimPri,But]ZnOH}+ are in reasonable accord with those observed in both CA I and CA II. However, the Zn–O bond length in {[PimPri,But]ZnOH}+ is closer to that in CA I than CA II,

whereas the Zn–N bond lengths are between those in CA I and CA II.

The zinc iodide and zinc nitrate complexes, {[PimPri,But]-ZnI}I and {[PimPri,But]Zn(ONO2)}(NO3), are also readily synthesized by the reactions of [PimPri,But] with ZnI2 and Zn(NO3)2·6H2O, respectively. The zinc iodide cation {[PimPri,But]ZnI}+ may also be obtained by treatment of the hydroxide derivative {[PimPri,But]ZnOH}+ with Me3SiI, a reaction that bears some relevance to the observation that iodide is an inhibitor of carbonic anhydrase.[16] Furthermore, the molecular structure of {[PimPri,But]ZnI}I (Fig. 2)† is similar to the coordination environment about zinc in the iodide inhibitor complex of human carbonic anhydrase I,[17] although the Zn–I bond length in {[PimPri,But]ZnI}+ [2.516(3) Å] is notably shorter than that observed in the enzyme iodide complex (2.7 Å).[17,18] The structure of {[PimPri,But]Zn(ONO2)}+ has also been determined by X-ray diffraction (Fig. 3),† revealing the presence of a unidentate nitrate ligand analogous to that in [TpBut]Zn(ONO2).[8,19]

Footnote

† Crystal data: {[PimPri,But]ZnOH}(ClO4)·(Et2O)·(CHCl3) monoclinic, P21/c (No. 14), a = 17.064(5) Å, b = 16.263(4) Å, c = 19.068(4) Å, β = 114.84(2)°, V = 4830(2) Å3, Z = 4, R = 0.0608, Rw = 0.0696. {[PimPri,But]ZnI}I·4(CHCl3) monoclinic, P21/c (No. 14), a = 16.119(4) Å, b = 19.385(4) Å, c = 18.096(3) Å, β = 90.32(2)°, V = 5654(2) Å3, Z = 4, R = 0.0834, Rw = 0.0965. {[PimPri,But]Zn(ONO2)}(NO3)·(MeCN) triclinic, P1̄ (No. 2), a = 10.503(4) Å, b = 13.909(6) Å, c = 14.245(3) Å, α = 104.19(2)°, β = 105.39(2)°, γ = 91.76(3)°, V = 1935(1) Å3, Z = 2, R = 0.0481, Rw = 0.0571. Atomic coordinates, bond distances and angles, and thermal displacement parameters have been deposited at the Cambridge Crystallographic Data Centre. See Information for Authors, Issue No. 1.

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14 Abbreviations: tris(1-pyrazolyl)hydroborato ligands are represented by the abbrevation [Tp$^{R,R'}$], with the 3- and 5-alkyl substituents listed, respectively, as superscripts; tris(2-imidazolyl)phosphines are represented by the abbreviation [Pim$^{R,R'}$], with the 1- and 4-alkyl substituents listed, respectively, as superscripts; tacd = 1,5,9-triazacyclododecane.

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