Inorg. Chem. **1995,** *34,* 2487−2489

Characterization of (Trimethyltriazacyclononane)triaquozinc(II) Nitrate. A Nonbridged Isomer

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Received November 24, 1993

Introduction

Macrocyclic polyamine complexes of zinc(II) have been used to model the structures of zinc-containing active sites in enzymes, such as carbonic anhydrase and carboxypeptidases.[1−6] In the 1:1 metal:polyamine model complexes, it has typically been shown, or assumed, that the Zn(II) ion adopts a tetrahedral or square pyramidal coordination environment and that only one water coordinates to the zinc. We had occasion to synthesize the 1,4,7-trimethyl-1,4,7-triazacyclononane Zn(II) complex in attempts to make phosphate diester and DNA hydrolysis agents. The crystal structure of this complex reveals that the Zn(II) ion adopts an octahedral environment, coordinated to the three nitrogens of the macrocycle and also to three aquo ligands. This contrasts with a report that describes a binuclear zinc complex containing the same ligand system. That complex was isolated under similar conditions, except for the choice of counterion, solvent, and pH.[2] The high pK_a value and the long Zn−O bond length for coordinated water in the octahedral Zn(II) complex may have implications for the role of zinc ions in enzymes.

Experimental Section

The nuclear magnetic resonance spectrum (^{1}H) was taken on a GE QE-300 spectrometer, and the significant chemical shifts are reported in ppm (δ units) relative to the solvent peak. The elemental analysis was determined by Desert Analytics, Tucson, AZ. The 1,4,7-trimethyltriazacyclononane ligand was synthesized using known procedures.[7−10] Other reagents were purchased from commercial sources and used without further purification.

Synthesis of [L′Zn(H$_2$O)$_3$](NO$_3$)$_2$·^{1}/$_2$H$_2$O. To a 15 mL solution of $Zn(NO_3)_2 \cdot 6H_2O$ (0.08 M, 348 mg, 1.17 mmol) in ethanol was added a solution of 1,4,7-trimethyltriazacyclononane (L′) (0.08 M, 200 mg, 1.17 mmol) in ethanol. The mixture was heated gently with stirring for 20 min and then allowed to cool to room temperature with stirring for an additional 3 h. Solvent was removed with a rotary evaporator. The residue was washed and rinsed with diethyl ether and then dried to yield 462 mg (95%) of a white solid. Colorless X-ray-quality crystals were obtained on recrystallization from CH_2Cl_2. Mp = >250 °C dec. ^{1}H NMR (D_2O): δ 2.54 (s, 9H), 2.78 (m, 12H). Anal. Calcd for $[L'Zn(H_2O)_3](NO_3)_2 \cdot {}^1/_2H_2O$, $C_9H_{28}N_5O_{9.5}Zn$: C, 25.51; H, 6.66; N, 16.53. Found: C, 25.55; H, 6.44; N, 16.58.

Crystallography. X-ray data for a 0.7 × 0.7 × 0.5 mm crystal of $C_9H_{28}N_5O_{9.5}Zn$ were collected with a Siemens R3m/V automated diffractometer equipped with a Mo X-ray tube and a graphite crystal monochromator. Orientation matrix and unit cell parameters were determined by the least squares fitting of 20 machine-centered reflections ($15° < 2\theta < 30°$) and confirmed by the examination of axial photographs. Intensities of three check reflections were monitored every 197 reflections, throughout the data collection. Structure solutions and data workup were performed on a DEC Microvax II computer with SHELXTL PLUS software. All non-hydrogen atoms were refined anisotropically. Hydrogen atoms were generated in idealized positions for the structure factor calculations but were not refined. One lattice water occupies a special position. Refinement of the enantiomorph factor in the acentric space group led to a value of zero, which suggests twinning of enantiomorphic pairs. Further details of the data collection and refinement are given in the supplementary material.

Potentiometric Titrations. An Orion 501 pH meter equipped with a MI-412 microelectrode was used. All measurements were done at 25 °C in 0.1 M NaNO$_3$. Titrations were performed with 20 and 40 mM $L'Zn(H_2O)_3{}^{2+}$ and with a standardized carbonate-free 0.489 M NaOH solution. Electrode response was standardized with buffer solutions at pH 7.00 and 10.00.

The titration data were modeled under the assumption that the following four equilibria were dominant:

$$[L'Zn(H_2O)_3]^{2+} \rightleftharpoons [L'Zn(H_2O)_2(OH)]^+ + H^+ \quad K_{a1} \qquad (1)$$

$$[L'Zn(H_2O)_2(OH)]^+ \rightleftharpoons [L'Zn(H_2O)(OH)_2] + H^+ \quad K_{a2} \qquad (2)$$

$$2[L'Zn(H_2O)_2(OH)]^+ \rightleftharpoons [L'_2Zn_2(\mu\text{-}OH)_2]^{2+} + 4H_2O \quad K_d \qquad (3)$$

$$H_2O \rightleftharpoons OH^- + H^+ \quad K_w \qquad (4)$$

Values for K_{a1} were estimated by fitting the initial portion of the titration curve and neglecting equilibria 2 and 3. Then, the latter portion of the titration curve was fit with the determined values of K_{a1} and K_d fixed. The process was continued in an iterative fashion. The simultaneous equilibria were solved numerically in these calculations using the FindRoot routine in the program Mathematica (Wolfram Research, Inc., Champaign, IL). Values of K_d between 10^{-3} and 10^3 were explored in the fitting process. Exact simulations of the titration curve were generated from the fitted parameters by solving the simultaneous equations (Solve routine in Mathematica) for points along the titration curve. Good agreement was found with pK_{a1} = 10.9, pK_{a2} = 12.3, and K_d = 150.

Results and Discussion

The product isolated from the reaction between $Zn(NO_3)_2 \cdot 6H_2O$ and 1,4,7-trimethyltriazacyclononane is a hexacoordinate Zn(II) complex, chelated to the three nitrogens of the macrocycle and bound to three aquo ligands. The structure of the complex was defined by X-ray crystallography, Figure 1. Crystallographic data, atomic coordinates, and bond lengths and angles are reported in Tables 1−3. The Zn−N bond distances in this complex are 2.147−2.188 Å, which are close to the average Zn−N (N = tertiary amine) bond distance of 2.171 ± 0.068 Å for octahedral zinc, as determined for seven small-molecule crystal structures.[11] The most noteworthy feature of the structure is the trigonal distortion of the octahedron. The N−Zn−N angles of 82.1−82.6° are constrained by the ring size of the macrocycle; however, the O−Zn−O angles of the trans aquo ligands also show a reduction in angle (85.5−86.8°), albeit diminished. There was no evidence in the space-filling models

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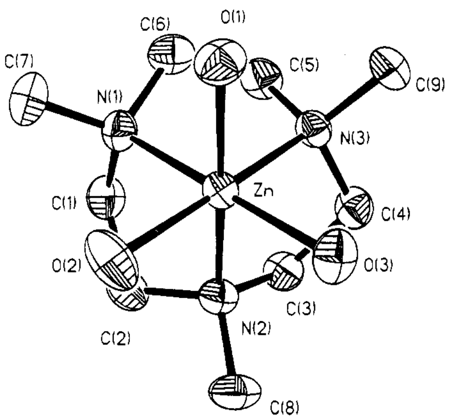

Figure 1. Thermal ellipsoid plot of [L′Zn(H_2O)$_3$](NO_3)$_2$, with 50% probability ellipsoids.

Table 1. Crystallographic Data for [L′Zn(H_2O)$_3$](NO_3)$_2$·$^1/_2$$H_2O$

empirical formula	$C_9H_{28}N_5O_{9.5}Zn$	fw	423.7
a	13.874(4) Å	*T*	20 °C
b	16.909(6) Å	*λ*	0.710 73 Å
c	15.195(4) Å	ϱ_{calc}	1.579 g cm^{-3}
V	3565(2) Å^3	*μ*	14.62 cm^{-1}
Z	8	transm coeff	0.7353−1.0000
space group	*Aba*2	$R(F_o)$	2.35%
		$R_w(F_o)$	2.54%

Table 2. Atomic Coordinates (×10^4) and Equivalent Isotropic Displacement Coefficients (Å^2 × 10^3) for [L′Zn(H_2O)$_3$](NO_3)$_2$·$^1/_2$$H_2O$

	x	*y*	*z*	*U*(eq)[a]
Zn	2199(1)	6294(1)	5000	24(1)
O(1)	2111(2)	5368(1)	5932(2)	41(1)
O(2)	1581(2)	7017(1)	5955(2)	46(1)
O(3)	739(1)	5989(1)	4658(2)	40(1)
O(4)	3653(2)	4659(1)	6868(2)	56(1)
O(5)	3307(3)	3642(2)	6088(3)	81(1)
O(6)	3925(3)	3503(2)	7379(2)	74(1)
O(7)	603(2)	4190(2)	5973(2)	64(1)
O(8)	−160(2)	3564(2)	7002(2)	63(1)
O(9)	1045(3)	4292(2)	7313(2)	100(1)
O(10)	0	5000	3306(2)	52(1)
N(1)	3701(2)	6600(1)	5276(2)	31(1)
N(2)	2361(2)	7220(1)	4022(2)	32(1)
N(3)	2851(2)	5584(1)	3991(2)	29(1)
N(4)	3621(2)	3925(2)	6786(2)	43(1)
N(5)	496(2)	4012(2)	6768(2)	46(1)
C(1)	3968(2)	7298(2)	4737(2)	39(1)
C(2)	3092(2)	7754(2)	4427(2)	38(1)
C(3)	2721(2)	6858(2)	3196(2)	36(1)
C(4)	2530(3)	5972(2)	3167(2)	37(1)
C(5)	3915(2)	5607(2)	4093(3)	39(1)
C(6)	4221(2)	5875(2)	4990(3)	40(1)
C(7)	3904(3)	6761(2)	6217(2)	47(1)
C(8)	1461(2)	7664(2)	3850(3)	46(1)
C(9)	2510(3)	4746(2)	3997(3)	39(1)

[a] Equivalent isotropic *U* defined as one-third of the trace of the orthogonalized $\mathbf{U}_{ij}$ tensor.

generated from the X-ray data that the methyl groups of the macrocycle were sterically crowding the aquo ligands.

The Zn−O bond distances in this complex are 2.082, 2.115, and 2.153 Å. They lie at the high end of the average Zn−O distance (O = terminal aquo) of 2.090 ± 0.061 Å determined for 56 structures.[11] This is consistent with the fact that Zn−O distances tend to become longer with increasing coordination number. The average bond distance for a 4-coordinate species is 2.006 ± 0.017 Å. For a 5-coordinate species the average Zn−O distance is 2.078 ± 0.079 Å, and for a 6-coordinate species it is 2.097 ± 0.049 Å.[11] The coordinated aquo ligands also display hydrogen bonding to the nitrate counterions. The O···O distances to the nitrate oxygens bound to O(2) are 2.70 and 2.74 Å. For O(3) the hydrogen-bonded nitrates are at 2.74 and 2.84 Å, and for O(1) they are at 2.83 and 2.91 Å. Although the Zn−O(1) distance is shortest, this aquo ligand shows the weakest hydrogen bonding. Thus, the long Zn−O separations cannot be attributed only to strong hydrogen bonding in the crystalline state. Weak binding of the aquo ligands to hexacoordinate zinc is also reflected by a decreased acidity of the bound water in solution.

Table 3. Selected Bond Lengths (Å) and Angles (deg) in [L′Zn(H_2O)$_3$](NO_3)$_2$·$^1/_2$$H_2O$

	Bond Lengths		
Zn−O(1)	2.115(2)	Zn−O(2)	2.082(3)
Zn−O(3)	2.153(2)	Zn−N(1)	2.188(3)
Zn−N(2)	2.171(3)	Zn−N(3)	2.147(3)
O(4)−N(4)	1.248(3)	O(5)−N(4)	1.243(5)
O(6)−N(4)	1.224(4)	O(7)−N(5)	1.254(4)
O(8)−N(5)	1.237(4)	O(9)−N(5)	1.221(5)
N(1)−C(1)	1.483(4)	N(1)−C(6)	1.487(4)
N(1)−C(7)	1.483(5)	N(2)−C(2)	1.491(4)
N(2)−C(3)	1.482(4)	N(2)−C(8)	1.479(4)
N(3)−C(4)	1.482(4)	N(3)−C(5)	1.485(4)
N(3)−C(9)	1.494(3)	C(1)−C(2)	1.514(4)
C(3)−C(4)	1.523(4)	C(5)−C(6)	1.498(6)
	Bond Angles		
O(1)−Zn−O(2)	86.8(1)	O(1)−Zn−O(3)	86.0(1)
O(2)−Zn−O(3)	85.5(1)	O(1)−Zn−N(1)	95.8(1)
O(2)−Zn−N(1)	96.9(1)	O(3)−Zn−N(1)	177.1(1)
O(1)−Zn−N(2)	177.0(1)	O(2)−Zn−N(2)	95.5(1)
O(3)−Zn−N(2)	96.0(1)	N(1)−Zn−N(2)	82.1(1)
O(1)−Zn−N(3)	95.1(1)	O(2)−Zn−N(3)	178.0(1)
O(3)−Zn−N(3)	95.2(1)	N(1)−Zn−N(3)	82.4(1)
N(2)−Zn−N(3)	82.6(1)	Zn−N(1)−C(1)	108.7(2)
Zn−N(1)−C(6)	102.2(2)	C(1)−N(1)−C(6)	111.9(3)
Zn−N(1)−C(7)	114.2(2)	C(1)−N(1)−C(7)	109.8(2)
C(6)−N(1)−C(7)	109.9(3)	Zn−N(2)−C(2)	103.0(2)
Zn−N(2)−C(3)	108.4(2)	C(2)−N(2)−C(3)	111.7(2)
Zn−N(2)−C(8)	113.5(2)	C(2)−N(2)−C(8)	109.(2)
C(3)−N(2)−C(8)	110.2(3)	Zn−N(3)−C(4)	103.3(2)
Zn−N(3)−C(5)	109.3(2)	C(4)−N(3)−C(5)	112.1(3)
Zn−N(3)−C(9)	113.1(2)	C(4)−N(3)−C(9)	109.2(2)
C(5)−N(3)−C(9)	109.8(2)	O(4)−N(4)−O(5)	118.7(3)
O(4)−N(4)−O(6)	119.7(3)	O(5)−N(4)−O(6)	121.6(3)
O(7)−N(5)−O(8)	120.7(3)	O(7)−N(5)−O(9)	119.2(3)
O(8)−N(5)−O(9)	120.1(3)	N(1)−C(1)−C(2)	112.2(2)
N(2)−C(2)−C(1)	111.5(2)	N(2)−C(3)−C(4)	111.9(3)
N(3)−C(4)−C(3)	111.0(3)	N(3)−C(5)−C(6)	112.6(3)
N(1)−C(6)−C(5)	112.2(3)		

A preparation very similar to the one described in this work led to isolation of the dinuclear complex [L′$_2$Zn$_2$(*μ*-OH)$_2$]ClO_4[2] rather than the monomer. In the previous preparation, the perchlorate salt was used, and the reaction solvent was water, as opposed to 95% ethanol. In addition, a slight excess (1.2 equiv) of the 1,4,7-trimethyl-1,4,7-triazacyclononane ligand was employed previously. The difference in products isolated may arise from the different counterions, solvent systems, and medium basicities (excess amine vs none). This suggests that several equilibria may be important near neutral pH.

Other polyamine zinc complexes with coordinated aquo ligands have been examined. In the 1:1 metal:polyamine ligand complexes, it has typically been shown, or assumed, that the Zn(II) ion adopts a tetragonal or square pyramidal coordination environment in solution and that only one water is coordinated to the zinc.[3,5,6] The isolation of an octahedral species with the present ligand system suggests that this may not always be a safe assumption. With a smaller macrocycle, such as 1,4,7-triazacyclononane, the reduced N−M−N angles better suit an octahedral geometry.[2]

The pK_a of aquated Zn^{2+} ions is approximately 9−10;[6,12,13] however, chelation may significantly influence the acidity of

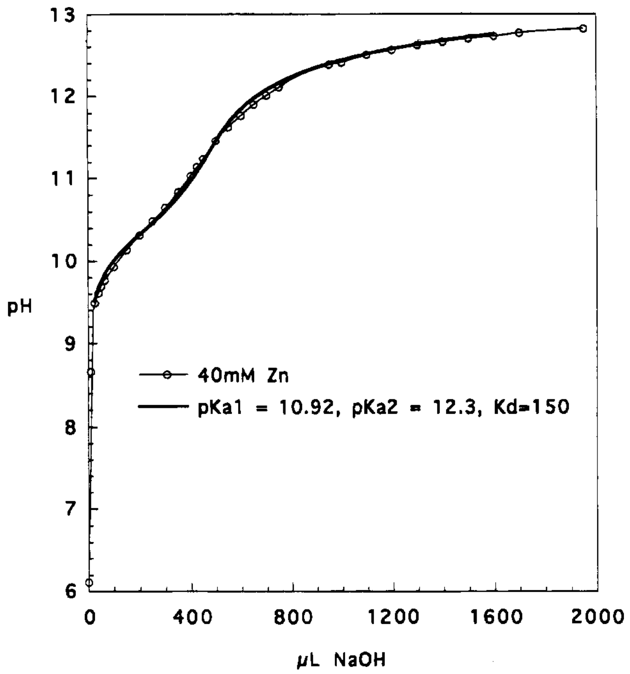

Figure 2. Titration of 5.88 mL of a 40 mM solution of $[L'Zn(H_2O)_3](NO_3)_2$ with 0.489 M NaOH at 20.5 °C. Experimental values are represented by open circles connected by the thin line, and the simulated titration curve is the heavy line.

the Zn(II)$-OH_2$ moiety. For instance, the pK_a for the zinc(II) complex of 1,5,9-triazacyclododecane is 7.3.[14] Though the influence of coordination number on the acidity of the Zn-bound water has been examined, there have been few studies on polyamine model systems other than those for tetra- or pentacoordinated zinc. We were interested in measuring the pK_a of the coordinated water in the $L'Zn(H_2O)_3{}^{2+}$ complex to define the effect of a hexacoordinate environment. This also bears on the dominant structural form present in neutral solution. The titration of 1,4,7-triazacyclononane Zn(II) complexes has been problematic because of precipitation,[14] but that did not pose a problem for the trimethyl derivative. Initial observations showed that aqueous solutions of $L'Zn(H_2O)_3{}^{2+}$ were only very slightly acidic. If one were to assume the slight acidicity arose from a single acid dissociation equilibrium, then the pK_a required was about 10.8. Titrations of the $L'Zn(H_2O)_3{}^{2+}$ complex with NaOH confirmed this qualitative estimate.

The observed titration curve (Figure 2) could be approximated by the sequence of equilibria in eqs 1–4. The estimated values of 10.9 for pK_{a1}, 12.3 for pK_{a2}, and 150 for K_d reproduce the titration curve well. These values are consistent with a weakly acidic parent complex $[L'Zn(H_2O)_3]^{2+}$, yet they also allow the ready formation of a dinuclear complex under weakly basic conditions in concentrated solutions, as encountered in crystallizations.

The high pK_{a1} for bound water agrees with theoretical predictions and limited experimental studies[6,12,15] that show a decreasing coordination number at Zn(II) increases the acidity of bound water. This is attributed to the increase in the total positive charge on zinc and the resulting polarization of bound H_2O. For example, it has been calculated that a difference of 8 pK_a units should occur on going from a tetrahedral to an octahedral zinc(II) environment in a gas-phase model.[15] The present study provides experimental support for this trend, although the magnitude is diminished. The high pK_{a1} found for $[L'Zn(H_2O)_3]^{2+}$ is consistent with a hexacoordinated structure being maintained in solution at pH 7. The high pK_a in the hexacoordinate environment is also consistent with the longer Zn–O bond lengths seen in the octahedral structures. With a longer bond length, the aquo ligand should be less polarized and exhibit an increased pK_a.

The implication of these results for model complexes suggests that aquo ligands in hexacoordinate zinc enzymes will have elevated pK_a's. Thus, in enzymes such as carbonic anhydrase or adenosine deaminase, which require the deprotonation of the zinc-bound water (known as the zinc–hydroxide mechanism)[16–20] for catalysis, a tetracoordinate zinc is preferred over a higher coordination state. There are only a few zinc enzymes which exhibit octahedral metal coordination, including glyoxalase I. The catalytic mechanism of this enzyme does not appear to involve the formation of any metal-bound hydroxide species,[21] and the Zn–O distances are fairly long.[22] The other implication from the structural studies is that adjustment of L–M–L angles from donor atoms on protein chains may be used by living systems to dictate the coordination geometry at zinc. Reduced L–M–L angles will favor higher coordinate structures.

Acknowledgment. This work was supported by the National Science Foundation (Grant CHE-88015958). G.C.S. acknowledges the Public Health Service (Grant T2HG00005A) and the Department of Education Graduate Assistance in Areas of National Need Program for predoctoral fellowships.

Supplementary Material Available: Tables of crystal data, data collection parameters, solution and refinement parameters, anisotropic displacement coefficients, and hydrogen atom coordinates (4 pages). Ordering information is given on any current masthead page.

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