

X-Ray Structural Study of a Zinc(II) Inclusion Complex of a Phenolate-pendant Cyclam[#]

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Abstract. The molecular structure of phenol-pendant cyclam-zinc(II) complex, **4a**, has been determined by X-ray structure analysis. Crystals of **4a** · ClO₄ · CH₃OH (C₁₆H₂₇N₄OZn · ClO₄ · CH₃OH) are monoclinic, space group *P*2₁/*n*, with four molecules in the unit cell of dimensions *a* = 31.198(2) Å, *b* = 8.426(1) Å, *c* = 8.214(1) Å, and β = 93.96(1)°. The structure was solved by the heavy atom method and refined anisotropically to *R* = 0.044, *R*_w = 0.062 for 1551 independent reflections. The complex assumes a five-coordinate, square pyramidal geometry, where zinc(II) is surrounded by the cyclam moiety in a planar fashion with the pendant phenolate anion occupying an axial position. An extremely short Zn—O(phenolate) bond distance of 1.983(5) Å, in conjunction with the 0.288 Å displacement of Zn(II) above the cyclam N₄ plane toward the phenolate, accounts for the extremely low p*K*_a value of 5.8 for the pendant phenol. These facts about **4a**, in comparison with the previous findings for the Ni(II) (**4b**) and Cu(II) complexes (**4c**) with the same ligand, illustrate well the characteristics of zinc(II) ion coordination properties.

Key words. Charles Pedersen, crown ethers, phenol-pendant cyclam-zinc(II) complex, crystal structure.

Supplementary Data relating to this article are deposited with the British Library as Supplementary Publication No. SUPS211g (4 pages).

1. Retrospect

From July 20–23, 1987 I had the honor to organize the 12th International Symposium on Macrocyclic Chemistry at Hiroshima. That year marked the 20th anniversary of Crown Ethers. In 1967, Charlie orally presented his discovery in Nikko, Japan. We therefore decided to dedicate this symposium to him, and to place a citation to Charlie on the first page of the abstracts and to send a copy to him before the meeting. The citation is reproduced here.

The following is a response letter from him, which reached me just a day before the opening. I thought it my duty to read this letter at the opening ceremony. I believe that Charlie would allow me to exhibit the original copy to all the readers of this journal.

[#] This paper is dedicated to the memory of the late Dr C. J. Pedersen.

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In Honor of

Mr. Charles J. Pedersen

Your discovery of Crown Ethers has been a tremendous break-through and has had a great impact on chemistry.

In celebrating the 20th Anniversary of this landmark discovery, we dedicate this symposium to you, expressing our sincerest respect and profound gratitude to you.

Hiroshima, July 20, 1987

12th International Symposium on

Macrocyclic Chemistry

on behalf of all the participants,

Eiichi Kimura, Chairman

Charles J. Pedersen
57 Market Street
Salem, N. J. 08079

Professor Eiichi Kimura
Chairman, XII ISMC
Hiroshima University
School of Medicine
1-2-3 Kasumi, Minami-ku
Hiroshima 734, Japan

July 10, 1987

Dear Professor Kimura:

Thank you for expediting the printing of the abstract so that I might see it before the opening of the Symposium.

I must confess that tears welled up in my eyes when I saw the beautiful ^a page with your kind and eloquent dedication. I will always treasure it and I thank you and your collaborators with all my heart.

Most men achieve "Immortality" through their progeny. I have no child of my own. Possibly, the Crown Ethers will serve, in a small way, to mark my footstep on earth.

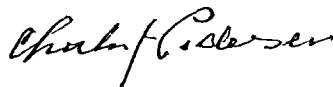
I am impressed more than ever by the scope of the intrusion of Crown Ethers into chemistry. I will enjoy reading the abstracts more carefully at my leisure.

Can you doubt that I greatly regret not being with you on July 20, 1987?

Dr. Herman E. Schroeder brings to all of you my cordial greetings.

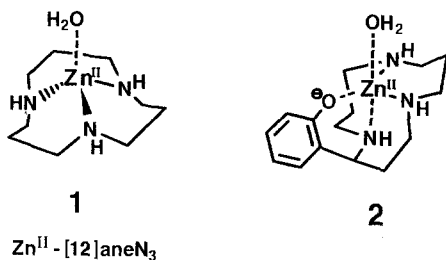
With my best personal regards,

Sincerely yours,

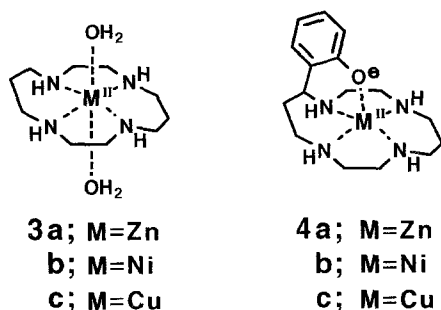


2. Introduction

Although coordination properties of zinc(II) ion have constantly attracted interest, particularly in connection with the bioinorganic chemistry of zinc enzymes, only a few ligands have been designed that permit us to gain deep insight into these properties [1]. Recently, we have discovered that zinc(II) complexes of a macrocyclic triamine complex **1** is a good mimic of carbonic anhydrase [2] and that its phenol-pendant derivative **2** offers an anion (i.e. phenolate) inhibition model of carbonic anhydrase [3]. In the latter complex, intramolecular coordination of the phenolate anion oxygen as the fourth donor is more facile with a consequence of the low pK_a value of 6.8 compared to the proton dissociation of the H_2O bound as the fifth donor which occurs at a much higher pK_a value of 10.7 [3]. In the absence of the phenol-pendant arm, the H_2O bound as the fourth donor in **1** dissociates with a pK_a value of 7.3 at 25°C [2], a value almost equal to that for carbonic anhydrases [4]. The X-ray structure of **2** discloses a five coordinate, trigonal bipyramidal structure, where the phenolate donor is at an equatorial position with the very short Zn—O(phenolate) distance of 1.930(4) Å [3]. From these studies with macrocyclic triamine ligands, we have concluded that Zn(II) ion, when bonded to three neutral amine donors, appears to prefer to interact with an anion (especially an anion with available oxygen donor atoms) as the fourth donor, a fact possibly related to the behavior of Zn(II) ions in carbonic anhydrases which are also bound to three imidazole nitrogens.



We then became interested in whether such a propensity of Zn(II) is present in different environments (e.g. cyclam—Zn(II) complex **3a** [5, 6]). We have thus turned to the phenol-pendant cyclam—Zn(II) complex **4a**, in which Zn(II) is placed in

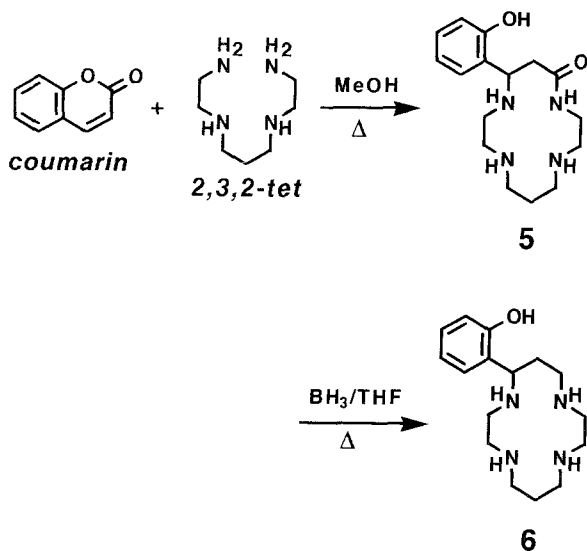


square planar N_4 environment formed by the cyclam. It would be of interest to see how the activity and ligation of the pendant phenol is affected by the basal N_4 donors. We therefore have investigated the X-ray structure and chemical properties of **4a** with reference to **2** and to the pendantless cyclam complex **3a**. Earlier, we had reported X-ray structures of **4b** with Ni(II) [7] and of **4c** with Cu(II) [8]. A comparison of the Zn(II) complex (**4a**) with **4b** and **4c** should reveal characteristic features of Zn(II) coordination properties. It should be emphasized that one of the advantages of the use of macrocyclic ligands is that they can allow selected ligand environments for the encapsulated metal ions, which allow one to detect inherent coordination properties of these metal ions.

3. Experimental Section

3.1. GENERAL METHODS

IR and UV spectra were recorded on a Shimadzu FTIR-4200 and a Hitachi U-3200 spectrophotometer, respectively. All reagents and solvents used were analytical grade. Phenol-pendant macrocyclic tetraamine **6** was synthesized using our reported procedure [8, 9]. The pH measurement procedure was the same as that previously reported for the complexation of **6** with Cu(II) and Ni(II) ions [8, 10, 11].



3.2. SYNTHESIS OF (Zn(II)-PHENOLATE-PENDANT CYCLAM) \cdot $ClO_4 \cdot CH_3OH$, **4a** \cdot $ClO_4 \cdot CH_3OH$

A solution containing **6** (58 mg, 0.2 mmol) and NaOH (8 mg, 0.2 mmol) in MeOH (5 mL) was added to a solution of $Zn(ClO_4)_2 \cdot 6H_2O$ (74 mg, 0.2 mmol) in MeOH (5 mL) at room temperature. After slow evaporation of the solvent, colorless crystals of **4a** \cdot $ClO_4 \cdot CH_3OH$ were obtained in *ca.* 40% yield. IR (KBr pellet);

3600, 3400 (br), 3250, 2870 (s), 1593 (s), 1478 (s), 1445, 1307 (s), 1100 (br), 952, 885, 864, 775 (s) cm^{-1} . *Anal. Calcd.* for $\text{C}_{16}\text{H}_{27}\text{N}_4\text{OZn} \cdot \text{ClO}_4 \cdot \text{CH}_3\text{OH}$: C, 41.82; H, 6.40; N, 11.48. *Found*: C, 41.79; H, 6.42; N, 11.34.

3.3. CRYSTALLOGRAPHIC STUDY

A colorless crystal with dimensions $0.47 \times 0.36 \times 0.09$ mm of $\mathbf{4a} \cdot \text{ClO}_4 \cdot \text{CH}_3\text{OH}$ was used for data collection. The lattice parameters and intensity data were measured on a Rigaku AFC-5 diffractometer with graphite monochromated MoK_α radiation. The structure was solved by the heavy atom method and refined anisotropically using data corrected for absorption to give $R = 0.044$, $R_w = 0.062$ for 1551 independent observed reflections. All the hydrogen atoms are located in a difference electron density map and refined with isotropic temperature factors. The molecular structure is illustrated in Figure 1. The summary of crystal data and data collection parameters, selected bond lengths and bond angles in comparison to those for $\mathbf{4b}$ and $\mathbf{4c}$ are presented in Tables I, II and III, respectively. The atomic positional parameters and distance to atoms from a plane defined by four cyclam nitrogens are listed in Tables IV and V, respectively.

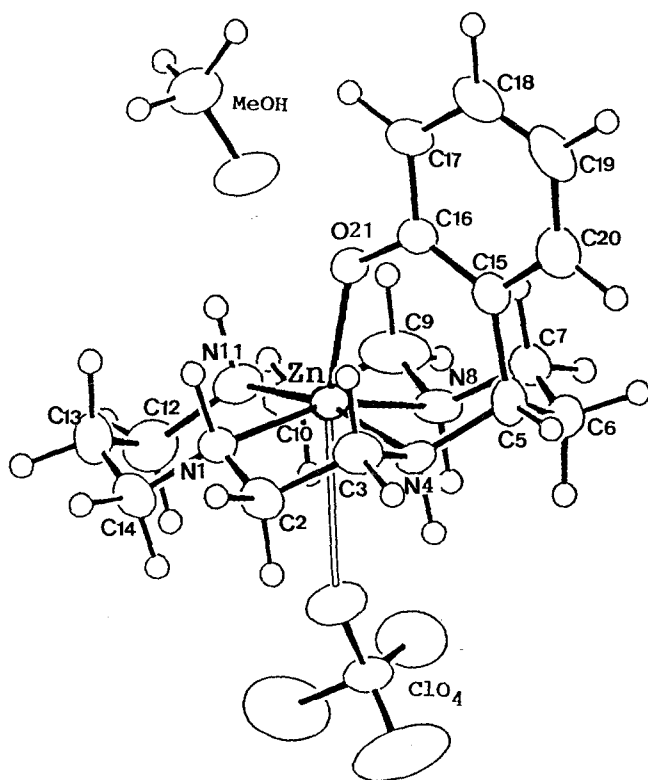


Fig. 1. Molecular structure of $\mathbf{4a} \cdot \text{ClO}_4 \cdot \text{CH}_3\text{OH}$. Atoms are drawn with 30% probability ellipsoids.

Table I. Summary of crystal data and data-collection parameters for $4a \cdot \text{ClO}_4 \cdot \text{CH}_3\text{OH}$.

| | |
|-------------------------------------|------------------------------------------------------------------------------------------------|
| formula | $\text{C}_{16}\text{H}_{27}\text{N}_4\text{OZn} \cdot \text{ClO}_4 \cdot \text{CH}_3\text{OH}$ |
| formula wt. | 488.3 |
| crystal systm | monoclinic |
| space group | $P2_1/n$ |
| cell dimensions | |
| <i>a</i> (Å) | 31.198(2) |
| <i>b</i> (Å) | 8.426(1) |
| <i>c</i> (Å) | 8.214(1) |
| β (deg) | 93.96(1) |
| <i>V</i> (Å ³) | 2154.0(2) |
| <i>Z</i> | 4 |
| density calc. (g cm ⁻³) | 1.506 |
| crystal color | colorless |
| crystal dimensions (mm) | 0.47 × 0.36 × 0.09 |
| radiation | MoK_α (graphite monochromated) |
| μ (mm ⁻¹) | 1.340 |
| temperature (°C) | 25 |
| 2θ range, deg | 2–50 |
| index range | (± <i>h</i> , − <i>k</i> , + <i>l</i>) |
| diffractometer | Rigaku AFC-5 |
| scan width, deg | 1.1 + 0.5 tan θ |
| phasing | heavy atom method |
| refinement | block-diagonal least-squares method |
| no. of measd refl. | 4353 |
| no. of indep refl. | |
| with $ F_0 > 3\sigma(F_0)$ | 1551 |
| final <i>R</i> | 0.044 |
| final <i>R_w</i> | 0.062 |
| weighting scheme | $w = [(\sigma_{\text{count}})^2 + (0.03 \times F_0)^2]^{-1}$ |

Table II. Comparison of selected bond distances (Å) for **4**.

| | 4a ^a | 4b ^b | 4c ^c |
|----------|-----------------|-----------------|-----------------|
| M—N(1) | 2.115(7) | 2.072(6) | 2.035(4) |
| M—N(4) | 2.067(7) | 2.051(5) | 2.003(4) |
| M—N(8) | 2.120(7) | 2.085(6) | 2.037(5) |
| M—N(11) | 2.110(7) | 2.078(5) | 2.018(5) |
| M—O(21) | 1.983(5) | 2.015(5) | 2.145(4) |
| M—O(1C1) | 2.765(11) | 2.402(7) | 3.135(6) |

^a Estimated standard deviation in parentheses.^b From Ref. [7].^c From Ref. [8].

Table III. Comparison of selected bond angles (deg) for **4**.

| | 4a ^a | 4b ^b | 4c ^c |
|---------------|------------------------|------------------------|------------------------|
| N(1)—M—N(4) | 83.9(3) | 85.6(2) | 86.0(2) |
| N(1)—M—N(11) | 94.4(3) | 92.7(2) | 93.3(2) |
| N(4)—M—N(8) | 93.6(3) | 96.6(2) | 94.3(2) |
| N(8)—M—N(11) | 83.8(3) | 84.9(2) | 85.5(2) |
| N(4)—M—O(21) | 91.6(2) | 88.8(2) | 87.5(2) |
| N(8)—M—O(21) | 96.5(3) | 94.1(2) | 98.0(2) |
| M—O(21)—C(16) | 126.1(5) | 126.9(4) | 127.4(3) |

^a Estimated standard deviation in parentheses.^b From Ref. [7].^c From Ref. [8].Table IV. Atomic positional parameters ($\times 10^4$) and equivalent isotropic temperature factors for **4a** · ClO₄ · CH₃OH.

| Atom | <i>x/a</i> | <i>y/b</i> | <i>z/c</i> | <i>B</i> _{eq} (Å ²) |
|---------|------------|------------|------------|------------------------------------------|
| Zn | 1186.4(3) | 2580.8(12) | 1873.4(10) | 3.4 |
| N(1) | 1228(3) | 1246(8) | -291(8) | 4.7 |
| C(2) | 1652(3) | 1555(12) | -852(10) | 4.9 |
| C(3) | 1982(3) | 1707(12) | 612(11) | 4.8 |
| N(4) | 1830(2) | 3024(8) | 1618(8) | 3.8 |
| C(5) | 2082(3) | 3193(12) | 3253(11) | 4.6 |
| C(6) | 1918(4) | 4635(12) | 4112(12) | 6.3 |
| C(7) | 1495(3) | 4520(11) | 4806(11) | 5.1 |
| N(8) | 1122(2) | 4489(8) | 3521(9) | 4.5 |
| C(9) | 693(4) | 4226(13) | 4122(14) | 7.8 |
| C(10) | 388(4) | 4035(14) | 2685(15) | 8.1 |
| N(11) | 508(2) | 2600(10) | 1727(10) | 5.3 |
| C(12) | 279(3) | 2531(14) | 70(16) | 7.8 |
| C(13) | 451(4) | 1125(14) | -931(14) | 7.9 |
| C(14) | 876(4) | 1416(13) | -1583(11) | 6.8 |
| C(15) | 2067(3) | 1655(11) | 4238(10) | 4.4 |
| C(16) | 1716(3) | 671(10) | 4320(9) | 3.7 |
| C(17) | 1759(3) | -735(10) | 5267(10) | 4.2 |
| C(18) | 2141(4) | -1061(11) | 6159(11) | 5.7 |
| C(19) | 2478(3) | -78(14) | 6126(11) | 6.1 |
| C(20) | 2451(3) | 1265(12) | 5130(12) | 5.5 |
| O(21) | 1327(2) | 933(6) | 3550(6) | 3.8 |
| Cl | 1138(1) | 6625(3) | -588(3) | 5.0 |
| O(1Cl) | 1243(4) | 5004(13) | -371(15) | 7.7 |
| O(2Cl) | 957(5) | 7308(15) | 710(15) | 9.5 |
| O(3Cl) | 785(5) | 6631(26) | -1675(24) | 16.6 |
| O(4Cl) | 1424(5) | 7396(19) | -1422(24) | 14.6 |
| C(MeOH) | 461(4) | -1502(14) | 4497(15) | 7.4 |
| O(MeOH) | 568(3) | 69(10) | 4159(11) | 8.6 |

Table V. Distance (Å) to atoms of **4a** from a plane defined by four cyclam nitrogens.

| Atoms | Distance | Atoms | Distance |
|-------|----------|-------|----------|
| Zn | 0.288 | C(6) | 0.387 |
| N(1) | -0.037 | C(7) | 0.735 |
| N(4) | 0.027 | C(9) | 0.357 |
| N(8) | -0.030 | C(10) | -0.373 |
| N(11) | 0.035 | C(12) | -0.872 |
| C(2) | -0.432 | C(13) | -0.493 |
| C(3) | 0.343 | C(14) | -0.926 |
| C(5) | 0.865 | | |

4. Results and Discussion

4.1. CRYSTAL STRUCTURE OF **4a** · ClO₄ · CH₃OH

The side view of the complex is shown in Figure 1. The five-coordinate square-pyramidal coordination geometry around Zn(II) ion is similar to that of the high-spin Ni(II) [7] and Cu(II) [8] complexes. The configurations ('*trans*-III' form) [12] of the macrocyclic ligand (cyclam) are fundamentally identical for the Zn(II), Cu(II), and Ni(II) complexes. The phenolate oxygen O(21) is almost at the apex of the pyramid. The structure of these complexes are similar.

The four equatorial Zn—N bond lengths of 2.115(7), 2.067(7), 2.120(7) and 2.110(7) Å are slightly longer than the corresponding Cu—N and Ni(high spin)—N bond lengths. This increase in length is caused by the slightly larger ionic radius of Zn(II). The Zn(II) is too large to lie in the plane of the four nitrogens and so is 0.288 Å above the plane (see Figure 2). By contrast, Cu(II) and Ni(II) are coplanar with the four nitrogens of the ligand due to the strong ligand field of cyclam [7, 8]. As a consequence, the Zn—O(21) bond length of 1.983(5) Å is significantly shorter

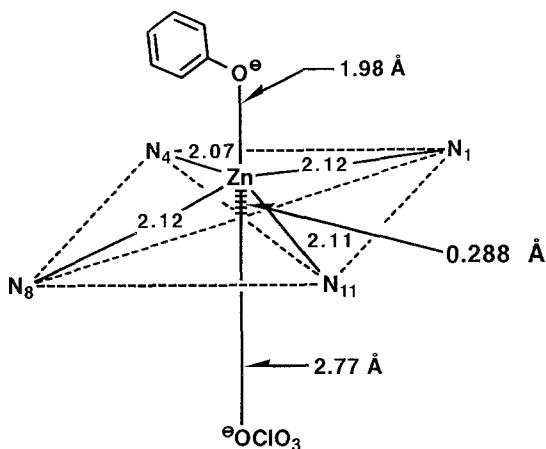


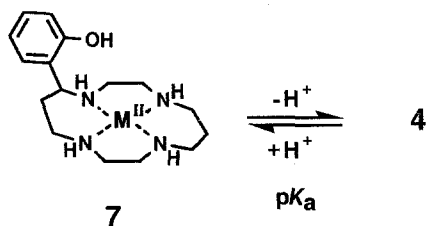
Fig. 2. Coordination geometries around the zinc(II) atom in **4a** · ClO₄ · CH₃OH.

than those in the Cu(II) (2.145(4) Å) and Ni(II) (2.015(5) Å) complexes. Moreover, the Zn—O(21) bond is much shorter than Zn—N bond lengths. These facts lead us to conclude that *zinc ion shifts toward the phenolate anion for the maximum stabilization*. If zinc(II) ion were in the cyclam N₄ plane, it would not be possible for the phenolate group to be brought into a position to bind Zn(II) so strongly. The shortest attainable Zn—O distance in such a structure would be *ca.* 2.0 Å, as estimated by the Dreiding model. The Ni(II) complex assumes almost an ideal square-pyramidal structure.[7]. These facts are compatible with the strong tendency of Zn(II) to bind with an anionic ligand. Being a *d*¹⁰ ion, the Zn(II) ion is not restricted to directional ligand fields and it can come closer to the donor it most favors at the sacrifice of bonding with other neutral nitrogen donors.

Comparing the N₄ complex **4a** with its N₃ counterpart, **2**, the Zn—O⁻ and average Zn—N bond distances in **4a** (1.983(5) Å and 2.10 Å) are longer than those in **2** (1.930(4) Å and 2.07 Å). This is understood in light of its lower coordination number.

4.2. PHENOL-PHENOLATE EQUILIBRIUM IN METAL COMPLEXES

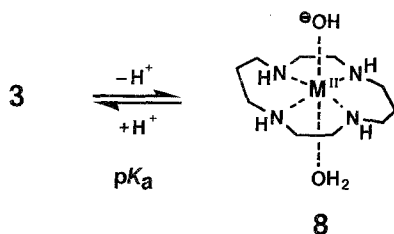
The ease of the axial phenol dissociation (**7** → **4**) was determined using pH-metric and spectrophotometric data and found to vary for each metal ion. These p*K*_a values are directly related to the M(II)—O⁻ bond distances and are as follows: Zn(II) (p*K*_a = 5.8, 25°C and *I* = 0.1 (NaClO₄)) > Ni(II) (p*K*_a = 6.3) > Cu(II) (p*K*_a = 9.2). For comparison, the p*K*_a value of the diprotonated ligand (**6** · 2H⁺) is 8.9 under the same conditions. It is thus concluded that with the Zn(II) complex the pendant phenol is most acidic, which is related to the Zn(II) coordinating properties.



It should be added that the UV spectra of the phenolate bands of the Zn(II) complex (**4a**) at λ_{\max} 288 nm (ϵ 2600) and of the Ni(II) complex (**4b**) at λ_{\max} 293 nm (ϵ 3700) [8] are almost the same as that of the uncoordinate phenolate anion at λ_{\max} 292 (ϵ 4000). These facts indicate that there is little mixing between the orbitals of those M(II) ions and the phenolate orbital. Namely, there is mainly an ionic interaction between these M(II) ions and the apical O⁻. On the other hand, in the Cu(II) complex (**4c**), the phenolate absorption band is significantly broader with no peak at *ca.* 290 nm [8].

4.3. ACIDITY OF H₂O BOUND TO M(II)-CYCLAM **3**

It is appropriate here to compare the above findings with the p*K*_a values for the H₂O which most likely occupies the axial site and is bound to Zn(II) (**3a**), Ni(II)



(3b), and Cu(II) (3c). The pK_a value of 9.8 (25°C, $I = 0.10$ (NaClO₄)) for Zn(II) was determined pH-metrically. For Ni(II) and Cu(II) complexes, the proton dissociation did not occur until pH *ca.* 11 and we therefore conclude that their pK_a values should be higher than 11. The lowest pK_a for a water in the Zn(II) complex (3a) is reasonable when compared to the complexes of 4.

5. Conclusion

It has been shown that Zn(II) ion shows a strong affinity to bind with an anionic oxygen when the Zn(II) ion was complexed with three nitrogen atoms of a macrocyclic triamine. This study shows that this same tendency is present when Zn(II) ion is coordinated by four nitrogens. In both situations the Zn—O⁻ bond distances are rather short indicating a strong interaction between Zn(II) and O⁻. Thus, the tailored macrocyclic polyamines [13] prove to be a useful tool in studying otherwise undetectable significant properties of the Zn(II) ion and assisting in elucidation of its biochemical significance.

References

1. P. Woolley: *Nature (London)* **258**, 677 (1975). J. T. Groves, and R. R. Chambers, Jr: *J. Am. Chem. Soc.* **106**, 630 (1984).
2. E. Kimura, T. Shiota, T. Koike, M. Shiro, and M. Kodama: *J. Am. Chem. Soc.* **112**, 5805 (1990).
3. E. Kimura, T. Koike, and K. Toriumi: *Inorg. Chem.* **27**, 3687 (1988).
4. Y. Pocker and S. Sarkanen: *Adv. Enzymol.* **47**, 149 (1987). Y. Pocker, J. T. Stone: *J. Am. Chem. Soc.* **87**, 5497 (1965).
5. M. Kodama and E. Kimura: *J. Chem. Soc., Dalton Trans.* 2269 (1977).
6. T. Ito, M. Kato, and H. Ito: *Bull. Chem. Soc. Jpn.* **57**, 2634 (1984). M. Kato and T. Ito: *Inorg. Chem.* **24**, 509 (1985).
7. Y. Iitaka, T. Koike, and E. Kimura: *Inorg. Chem.* **25**, 402 (1986).
8. E. Kimura, T. Koike, K. Uenishi, M. Hediger, M. Kuramoto, S. Joko, Y. Arai, M. Kodama, and Y. Iitaka: *Inorg. Chem.* **26**, 2975 (1987).
9. E. Kimura, T. Koike, and M. Takahashi: *J. Chem. Soc., Chem. Commun.* 385 (1985).
10. E. Kimura, M. Yamaoka, M. Morioka, and T. Koike: *Inorg. Chem.* **25**, 3883 (1986).
11. E. Kimura, T. Koike, H. Nada, and Y. Iitaka: *Inorg. Chem.* **27**, 1036 (1988).
12. V. J. Thöm, C. C. Fox, J. C. A. Boeyens, and R. D. Hancock: *J. Am. Chem. Soc.* **106**, 5947 (1984).
13. Our recent papers about Zn(II) chemistry: E. Kimura, T. Koike, T. Shiota, and Y. Iitaka: *Inorg. Chem.* **29**, 1460 (1990). E. Kimura, and T. Koike: *Comments on Inorg. Chem.* Gordon and Breach Science Publishers: New York, Vol. 11, 285 (1991).