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Models for the Interaction of Zn²⁺ with DNA. Syntheses and X-ray Structural Characterizations of Two Polymeric Tetrahedral Zinc Complexes of Monomethyl Phosphate Esters of Cytidine and Deoxycytidine 5′-Monophosphate Nucleotides

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The complexes $Zn(CMOMeP)_2$, $C_{20}H_{30}N_6O_{16}P_2Zn\cdot9H_2O$, and $Zn(dCMOMeP)_2$, $C_{20}H_{30}N_6O_{14}P_2Zn\cdot11H_2O$, were prepared and investigated by single-crystal X-ray methods (CMOMeP and dCMOMeP are the monoanionic ligands cytidine 5′-monophosphate and 2′-deoxycytidine 5′-monophosphate with the phosphate groups methylated, respectively). The complexes are isomorphous and crystallize in the trigonal system, space group $P3_221$, with $\alpha = \beta = 90.0°$, $\gamma = 120.0°$, and $Z = 3$. $Zn(CMOMeP)_2$ has $a = b = 11.261$ (6) Å, $c = 27.050$ (22) Å, and $V = 2970.4$ Å³, and $Zn(dCMOMeP)_2$ has $a = b = 11.087$ (2) Å, $c = 26.553$ (6) Å, and $V = 2826.8$ Å³. The data were collected at 297 K for $Zn(CMOMeP)_2$ and at 120 K for $Zn(dCMOMeP)_2$. The structures were solved by direct methods and refined by variable block–block-diagonal least-squares analysis using 2646 observed reflections to an R value of 0.056 for $Zn(CMOMeP)_2$ and using 3608 observed reflections to an R value of 0.093 for $Zn(dCMOMeP)_2$. The coordination geometry about Zn is a distorted tetrahedron with the metal coordinating to two nucleotides at N(3) and to two phosphate oxygens on different phosphate groups. The two bases coordinated through N(3) are in the "head-to-tail" configuration. Each nucleotide is coordinated to two Zn atoms, at N(3) and at one phosphate oxygen, leading to a polymeric species. The Zn atom is on a twofold axis, as is one water molecule. There is an intramolecular interaction between Zn and O(2) (Zn⋯O(2) = 2.70 Å for $Zn(CMOMeP)_2$ and 2.72 Å for $Zn(dCMOMeP)_2$). The four bases in the nucleotides associated with each Zn stack in two pairs that are equivalent, with an average separation of 3.59 Å and a 4.3° angle between the planes of the bases for $Zn(CMOMeP)_2$. The sugar conformation for $Zn(dCMOMeP)_2$ is disordered and has equal populations of 3′-endo, anti, gauche⁺ and 2′-endo, anti, gauche⁺. For $Zn(CMOMeP)_2$, the sugar conformation is 3′-endo, anti, gauche⁺. These structures are the first examples of direct Zn to phosphate O coordination for a phosphodiester group. The presence of Zn-to-base binding and Zn-to-phosphate group binding in these and other Zn nucleotide complexes is discussed in terms of the effects of Zn²⁺ on DNA structure and stability.

Introduction

Zinc is important in many chemical and biochemical processes involving nucleic acids.[1] For example, Zn²⁺ is not effective in degrading DNA[2] but is very effective in degrading RNA.[3] Zinc is also found in many nucleic acid processing enzymes and bind proteins.[4–8] Although the function of the Zn is not fully understood, some evidence suggests that it binds directly to the nucleic acid.[6]

The influence of Zn²⁺ on DNA structure and on DNA rewinding on cooling after denaturation indicates that Zn²⁺ can bind to both the bases and the phosphate groups.[9] For example, Zn²⁺ increases the melting temperature of DNA but this effect maximizes at ratios of Zn/P of ca. 1. This behavior suggests phosphate binding at low ratios and base binding at high ratios. This ability to bind to both types of groups could be an important feature of the unusually high capability of Zn²⁺ in promoting essentially complete renaturation of DNA melted in the presence of Zn²⁺ at a ratio of Zn/P of 4:1.[9,10] Studies in the literature suggest that Zn²⁺ binds primarily to GC-rich regions of DNA.[11] However, Zn²⁺ is in the middle range of metal ions promoting the B → Z conversion of poly[d(G-C)]·poly[d(G-C)].[12] Base-binding metals generally facilitate B → Z conversion whereas phosphate binding metal ions are relatively ineffective.[12]

The fact that Zn²⁺ is spectroscopically invisible makes it difficult to gain direct insight into the binding mode of Zn²⁺ to nucleic acids and their components.[1] Thus X-ray crystal structure analysis of isolated solids could be especially helpful in elucidating Zn²⁺ binding to nucleic acid derivatives. Despite this need and the importance of Zn in nucleic acid biochemistry, there have been relatively few studies involving isolated and structurally characterized Zn complexes with nucleic acid components, particularly nucleotides.[1,13–15] All, except three,[1,16] of the structurally characterized metal complexes of mononucleotides involve phosphate monoesters that carry two negative charges per phosphate group, in the normal protonation state. Consequently, the role of the phosphate groups either through direct metal

binding or through electrostatic interaction with the metal, may be overemphasized in comparison to the nucleotide monomer unit in nucleic acids where the phosphodiester group carries only one negative charge.

In order to obtain more realistic models of metal binding to nucleic acids, we are studying metal complexes with mononucleotides further esterified at the phosphate group with a methyl or an ethyl group. This phosphate grouping is similar in charge (mononegative) and geometry to the internal phosphate group in DNA. We have recently described structures of two octahedral Zn complexes with the monomethyl phosphate esters of guanosine 5′-monophosphate and inosine 5′-monophosphate nucleotides.[1] Only metal-to-base binding was observed.

In this report, we describe in detail the structure of the Zn complex of the monomethyl phosphate esters of cytidine 5′-monophosphate and deoxycytidine 5′-monophosphate. These compounds are similar and novel in that they are the first examples

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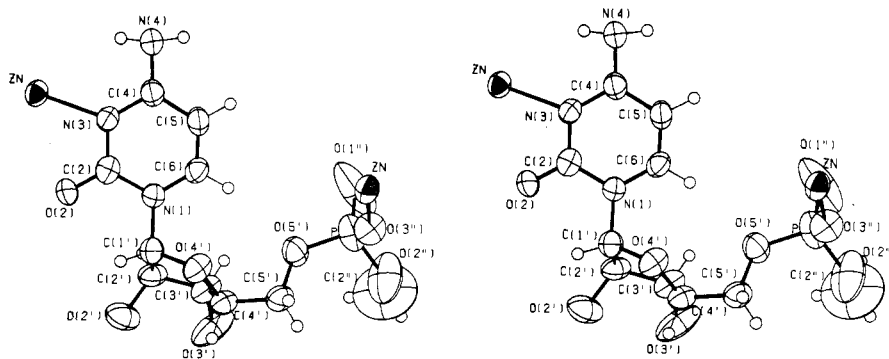[‡] Universität Stuttgart.

Figure 1. Atomic numbering for the CMOMeP ligand with Zn coordination sites indicated.

of a direct bond between a phosphodiester group and Zn^{2+}, an interaction of potentially great relevance to nucleic acid biochemistry.

Experimental Section

Preparations. The methylation and subsequent zinc complexation of the nucleotides cytidine 5′-monophosphate and 2′-deoxycytidine 5′-monophosphate were accomplished as previously described,[1] and products will be designated Zn(CMOMeP)$_2$ and Zn(dCMOMeP)$_2$, respectively. Crystals were grown by vapor diffusion of acetone into an aqueous solution of the complex (*T* ca. 4 °C). Crystals of both complexes disintegrate due to loss of water of crystallization upon exposure to air. Anal. Calcd for Zn(C$_{10}$H$_{15}$N$_3$O$_8$P)$_2$·7H$_2$O: 27.81; H, 5.14; N, 9.73. Found: C, 27.74; H, 4.84; N, 9.93. Anal. Calcd for Zn(C$_{10}$H$_{15}$N$_3$O$_7$P)$_2$·5H$_2$O: C, 30.18; H, 5.07; N, 10.56. Found: C, 30.21; H, 4.93; N, 10.53. The stoichiometry found by X-ray analysis for Zn(CMOMeP)$_2$ is Zn(C$_{10}$-H$_{15}$N$_3$O$_8$P)$_2$·9H$_2$O and for Zn(dCMOMeP)$_2$ is Zn(C$_{10}$H$_{15}$N$_3$O$_7$P)$_2$·11H$_2$O.

X-ray Data Collection, Structure Determination, and Refinement. Diffraction data were measured in an ω-scan mode with a Syntex P1 diffractometer for Zn(dCMOMeP)$_2$, those for Zn(CMOMeP)$_2$ were measured with the same diffractometer upgraded to a Nicolet P3F system, and both used graphite-monochromatized Mo Kα radiation (λ = 0.710 69 Å) with a variable scan rate of 2.0–24.0° min^{-1} and a scan width of 0.75°. Data set resolution etc. are further characterized in Table I. Stationary background counts were measured at the beginning (bgd1) and at the end (bgd2) of each scan with a total background to scan time, Tr = 1. Intensities were calculated from the total scan count (Ct) and background counts by the relationship I = [Ct + Tr(bgd1 + bgd2)]. The intensities were assigned standard deviations according to the formula $\sigma^2(I)$ = [Ct + Tr^2(bgd1 + bgd2)]. Data were collected under the criteria +$h \leq k$, ±l. There were no significant variations in the three periodically measured reference reflections for the Zn(dCMOMeP)$_2$ crystal (constant to within 2.5%); during the measurement of the last 1500 data, those for the Zn(CMOMeP)$_2$ crystal displayed a systematic decrease to 80% of their initial values (intensities were appropriately corrected). Lorentz and polarization corrections were made. Absorption corrections were judged to be unnecessary due to the low value of μ. See Table I for further characterization of the data sets.

The initial structure determination for Zn(dCMOMeP)$_2$ was accomplished with MULTAN80;[17a] that for Zn(CMOMeP)$_2$ was derived from it. Development of the structural models was carried out with the XRAY[17b] program library (version of 1976). Equations for the scattering factors, F_o, f', and f'', for the atoms are given in ref 17c. In Zn(CMOMeP)$_2$, O(W5) exhibited resolvable disorder. In Zn(dCMOMeP)$_2$, O(W6) had large thermal parameters, but the refinement proceeded more smoothly when it was included. In addition, the 2′-deoxyribose moiety is conformationally disordered. Examination of difference Fourier maps indicated that the two conformers were present with essentially equal populations. An overall scale factor, all appropriate atomic coordinates, and anisotropic temperature factors for non-hydrogen atoms were refined by variable block–block-diagonal least-squares techniques. The quantity minimized was $\sum(|F_o - F_c|)^2$. Where possible, hydrogen atoms (calcu-

Table I. Characterization of the Experimental Crystallographic Parameters

	Zn(dCMOMeP)$_2$	Zn(CMOMeP)$_2$
	Crystal Data	
space group[a]	$P3_221$	$P3_221$
lattice params[b]		
T_{cryst}, K	ca. 120	297 (2)
$a = b$, Å	11.087 (2)	11.261 (6)
c, Å	26.553 (6)	27.050 (22)
no. of reflcns[c]	30	23
2θ range, deg	30.13–37.45	22.04–35.93
V, Å^3	2826.8	2970.4
chem formula	C$_{20}$H$_{30}$N$_6$O$_{14}$P$_2$Zn·11H$_2$O	C$_{20}$H$_{30}$N$_6$O$_{16}$P$_2$Zn·9H$_2$O
M_r	904.01	882.98
Z	3	3
ρ_{calcd}, g cm^{-3}	1.529	1.509
	Crystal Characterization	
size, mm^3	0.5 × 0.5 × 0.5	0.1 × 0.1 × 2.0
color	colorless transparent	colorless transparent
habit	hexagonal prisms	hexagonal needles[d]
μ, cm^{-1}	8.6	8.2
$F(000)$	1422	1410
	Intensity Data Set	
resolution (2θ$_{max}$), deg	55	50
no. of unique data	4809	4067
no. of obsd data ($I \geq 3\sigma(I)$)	3608	2646

[a] Trigonal space group for which the enantiomer was determined from the known chirality of the nucleoside. [b] Space-group requires $a = b \neq c$, $\alpha = \beta = 90°$, $\gamma = 120°$. [c] Lattice parameters were determined by least-squares refinement with angular data from automatically centered reflections in the indicated 2θ range. [d] The crystals of this analogue grew as long needles. Attempts to cut them resulted, without fail, in splitting parallel to the needle axis.

Table II. Characterization of the Crystal Structure Refinements

	Zn(dCMOMeP)$_2$	Zn(CMOMeP)$_2$
R[a]	0.093	0.056
R_w[b]	0.140	0.071
no. of variables refined	244	254
no. of contrib reflcns[c]	4389	3427
weighting scheme[d]		
a	0.16	0.12
b	0.0055	0.0005
c	7 × 10^{-5}	1 × 10^{-5}
σ^e	1.08	1.24

[a] $R = \sum(|F_o - F_c|)/\sum F_o$. [b] $R_w = \sum(w^{1/2}|F_o - F_c|)/\sum w^{1/2}F_o$. [c] Number of reflections used in the refinement. This number includes reflections that had a calculated intensity greater than 3σ(*I*) even if the experimental intensity was less than 3σ(*I*). [d] The weighting scheme used was $w = [\sigma^2(F) + aF_o + bF_o^2 + cF_o^3]^{-1}$. [e] Estimated standard deviation of an observation of unit weight.

lated from known geometry) were included in the structure factor calculations (with isotropic temperature factors) but were not refined. The

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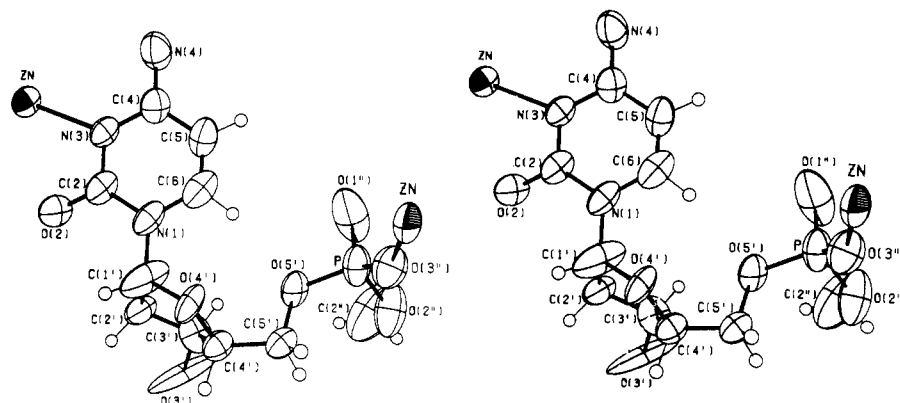
Figure 2. Atomic numbering for the dCMOMeP ligand with Zn coordination sites indicated.

Table III. Final Fractional Atomic Coordinates[a] for Non-Hydrogen Atoms of Zn(CMOMeP)$_2$

atom	x	y	z
Zn	-0.07799 (9)	-0.07799	0
O(3'')	-0.2619 (5)	-0.1058 (5)	-0.0102 (2)
P	-0.3845 (2)	-0.1579 (2)	-0.04227 (7)
O(1'')	-0.4440 (9)	-0.2978 (6)	-0.0613 (2)
O(2'')	-0.4860 (7)	-0.1352 (9)	-0.0089 (2)
C(2'')	-0.622 (1)	-0.179 (2)	-0.0214 (8)
O(5')	-0.3553 (5)	-0.0594 (5)	-0.0883 (2)
C(5')	-0.3100 (7)	0.0820 (7)	-0.0819 (2)
C(1')	-0.1585 (7)	0.1460 (7)	-0.2026 (2)
C(2')	-0.2960 (8)	0.1280 (8)	-0.2191 (2)
O(2')	-0.2769 (6)	0.2558 (5)	-0.2327 (2)
C(3')	-0.3836 (7)	0.0752 (8)	-0.1724 (2)
O(3')	-0.4904 (8)	0.1058 (8)	-0.1690 (2)
C(4')	-0.2764 (6)	0.1491 (7)	-0.1316 (2)
O(4')	-0.1560 (4)	0.1547 (5)	-0.1496 (1)
N(1)	0.1355 (5)	0.0320 (5)	-0.2158 (2)
C(2)	-0.0619 (6)	0.0455 (7)	-0.2588 (2)
O(2)	-0.0247 (5)	0.1455 (4)	-0.2862 (1)
N(3)	-0.0303 (4)	-0.0532 (5)	-0.2704 (1)
C(4)	-0.0775 (6)	-0.1684 (6)	-0.2423 (2)
N(4)	-0.0468 (7)	-0.2646 (6)	-0.2547 (2)
C(5)	-0.1583 (7)	-0.1824 (8)	-0.1989 (2)
C(6)	-0.1824 (6)	-0.0819 (7)	-0.1879 (2)
O(W1)	-0.4833 (9)	0	-0.3333
O(W2)	-0.1371 (6)	-0.4908 (6)	-0.1834 (2)
O(W3)	-0.6995 (8)	-0.158 (1)	-0.2270 (3)
O(W4)	-0.5047 (9)	-0.2336 (8)	-0.2376 (3)
O(W5A)	-0.139 (2)	0.286 (2)	-0.3318 (5)
O(W5B)	-0.354 (2)	-0.143 (2)	-0.3105 (4)

[a] The population parameters for O(W5A) and O(W5B) are 0.54 and 0.46, respectively.

refinements are characterized in Table II.

Results and Discussion

The final non-hydrogen atomic coordinates for bis(cytidine 5'-monophosphate methyl ester)zinc(II), Zn(CMOMeP)$_2$, and bis(2'-deoxycytidine 5'-monophosphate methyl ester)zinc(II), Zn(dCMOMeP)$_2$, are given in Tables III and IV, respectively. The complexes are depicted (with atom labels) in Figures 1 and 2, respectively. Selected bond distances and bond angles are contained in Table V. Tables of observed and calculated structure factors, hydrogen atom coordinates and temperature factors, torsion angles, and least-squares planes are contained in the supplementary material. The two structures are isomorphous. The Zn(CMOMeP)$_2$ complex will be described in detail and features unique to the Zn(dCMOMeP)$_2$ complex will be included for comparison.

The nucleotide ligands do not form discrete complexes, but rather are coupled with two Zn atoms to form "infinite" helical chains with the helix axis parallel to the 3_2 screw axis of the space group and the c axis of the unit cell, Figure 3.

Metal Environment. The Zn(CMOMeP)$_2$ complex has crystallographic 2-fold symmetry; the zinc atom is on a 2-fold axis,

Table IV. Final Fractional Atomic Coordinates[a] for Non-Hydrogen Atoms of Zn(dCMOMeP)$_2$

atom	x	y	z	PP
Zn	-0.07683 (9)	-0.07683	0	
P	-0.3882 (2)	-0.1639 (2)	-0.04546 (6)	
O(1'')	-0.436 (1)	-0.2964 (6)	-0.0701 (3)	
O(2'')	-0.5047 (6)	-0.1624 (9)	-0.0120 (2)	
C(2'')	-0.639 (1)	-0.216 (2)	-0.0345 (6)	
O(3'')	-0.2671 (5)	-0.1099 (6)	-0.0118 (2)	
C(1')	-0.168 (2)	0.141 (2)	-0.2003 (3)	
C(2'A)	-0.2946	0.1533	-0.2177	0.5000
C(2'B)	-0.3309	0.04178	-0.2059	0.5000
C(3')	-0.3788 (8)	0.1153 (9)	-0.1672 (3)	
O(3'A)	-0.4501	0.1853	-0.1748	0.5000
O(3'B)	-0.3731	0.2374	-0.1825	0.5000
C(4')	-0.2694 (6)	0.1649 (7)	-0.1263 (2)	
O(4')	-0.1529 (5)	0.1597 (6)	-0.1477 (1)	
C(5')	-0.3094 (7)	0.0879 (7)	-0.0774 (2)	
O(5')	-0.3642 (5)	-0.0565 (5)	-0.0886 (1)	
N(1)	-0.1398 (6)	0.0293 (7)	-0.2146 (2)	
C(2)	-0.0661 (7)	0.0420 (8)	-0.2571 (2)	
O(2)	-0.0295 (5)	0.1442 (5)	-0.2858 (1)	
N(3)	-0.0329 (5)	-0.0565 (6)	-0.2691 (2)	
C(4)	-0.0814 (8)	-0.1758 (7)	-0.2401 (2)	
N(4)	-0.0484 (9)	-0.2715 (6)	-0.2538 (2)	
C(5)	-0.1628 (9)	-0.1924 (8)	-0.1970 (2)	
C(6)	-0.1863 (7)	-0.094 (1)	-0.1849 (3)	
O(W1)	-0.482 (2)	0	-0.3333	
O(W2)	-0.117 (2)	-0.490 (1)	-0.1809 (6)	
O(W3)	-0.697 (1)	-0.158 (2)	-0.2448 (5)	
O(W4)	-0.479 (2)	-0.219 (2)	-0.2498 (8)	
O(W5)	-0.111 (3)	0.295 (3)	-0.3380 (8)	
O(W6)	-0.03 (1)	-0.514 (5)	-0.074 (2)	

[a] PP is the population parameter for the indicated atoms. If not specified, the position is fully occupied.

as is one water molecule. Four nucleotides are coordinated to each Zn ion, two through the base N(3) atom and two through the phosphate O(3'') atom, in an approximately tetrahedral arrangement about the metal. These two structures are the first examples of a Zn in a tetrahedral environment coordinating to two nucleic acid bases of nucleotides. All reported Zn–nucleic acid complex crystal structures have an approximate tetrahedral metal environment[15] except for the two octahedral Zn complex structures cis-[Zn(GMOMeP)$_2$(H$_2$O)$_4$] and cis-[Zn(IMO-MeP)$_2$(H$_2$O)$_4$], where GMOMeP and IMOMeP are the monoanionic ligands guanosine 5'-monophosphate and inosine 5'-monophosphate with the phosphate group methylated.[1] Each CMOMeP in the Zn(CMOMeP)$_2$ complex coordinates to two Zn atoms (Figure 4) leading to a polymeric species. The Zn atom lies on a crystallographic 2-fold axis, requiring the complex to have C_2 symmetry. Symmetry operations on a unique CMOmeP ligand, e.g. L1 in Figure 4, provide for the interactions between Zn and three additional ligands, L2–L4 in Figure 4.

The Zn(CMOMeP)$_2$ and Zn(dCMOMeP)$_2$ structures can be compared to other metal complex structures containing CMP. The
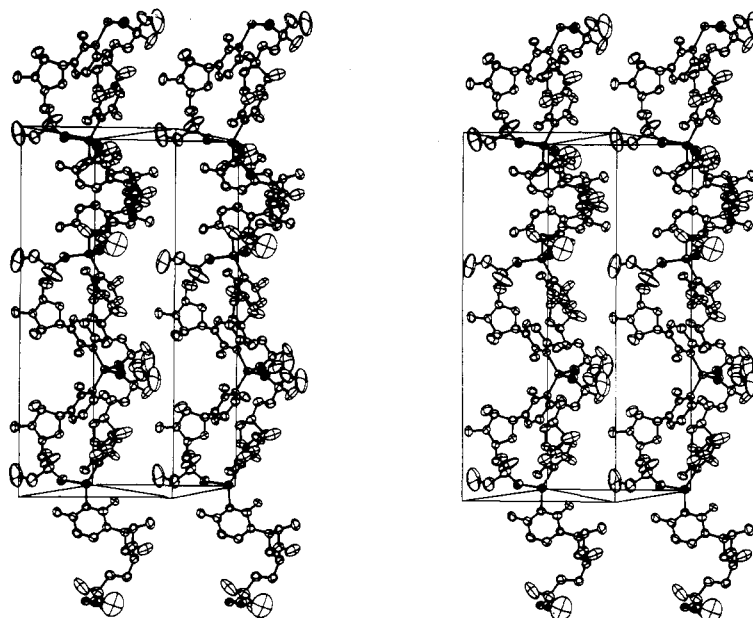
Figure 3. Packing diagram, without waters, projected in the a,c plane, showing the helical arrangement of $Zn(CMOMeP)_2$.
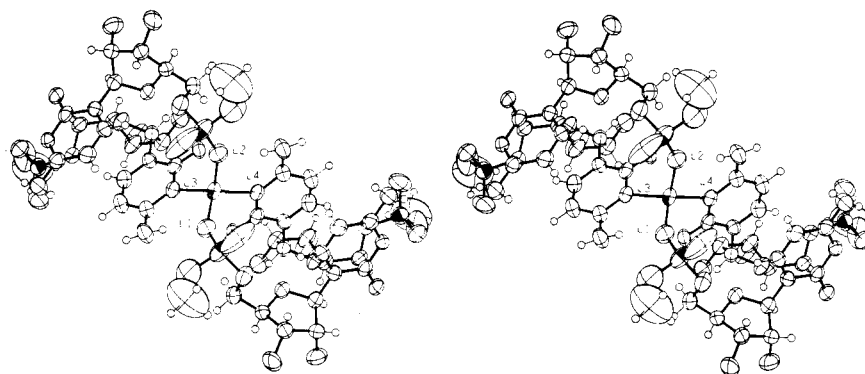
Figure 4. Molecular structure of the $Zn(CMOMeP)_2$ complex where the nucleotide is generated by the following transformations: L1 is x, y, z; L2 is $x - 1, y, z$; L3 is $x, y - 1, z$; L4 is $-y, x - y - 1, z - 0.333$.

Table V. Selected Bond Lengths (Å) and Bond Angles (deg) for $Zn(CMOMeP)_2$

A. Selected Bond Lengths			
Zn–O(3″)	1.953 (6)	N(1)–C(2)	1.390 (8)
Zn–N(3)	2.003 (4)	N(1)–C(6)	1.349 (9)
P–O(3″)	1.481 (5)	C(2)–N(3)	1.361 (1)
P–O(5′)	1.588 (5)	C(2)–O(2)	1.235 (8)
P–O(1″)	1.463 (7)	N(3)–C(4)	1.362 (8)
P–O(2″)	1.574 (9)	C(4)–C(5)	1.44 (1)
O(2″)–C(2″)	1.39 (2)	C(4)–N(4)	1.34 (1)
C(1′)–N(1)	1.47 (1)	C(5)–C(6)	1.32 (1)

B. Selected Bond Angles			
O(3″)–Zn–O(3″)*	104.8 (2)	O(4′)–C(1′)–N(1)	107.2 (6)
O(3″)–Zn–N(3)	101.4 (3)	C(1′)–N(1)–C(2)	117.5 (5)
O(3″)–Zn–N(3)*	111.3 (2)	C(1′)–N(1)–C(6)	122.4 (5)
N(3)–Zn–N(3)*	125.3 (3)	C(2)–N(1)–C(6)	120.0 (7)
Zn–O(3″)–P	148.1 (4)	N(1)–C(2)–N(3)	119.3 (6)
P–O(2″)–C(2″)	124 (1)	N(1)–C(2)–O(2)	120.9 (8)
P–O(5′)–C(5′)	121.4 (4)	C(2)–N(3)–C(4)	120.7 (5)
C(5′)–C(4′)–C(3′)	116.1 (5)	C(2)–N(3)–Zn	180.7 (4)
O(4′)–C(4′)–C(3′)	110.7 (5)	C(4)–N(3)–Zn	130.5 (5)
C(4′)–O(4′)–C(1′)	110.8 (5)	N(3)–C(4)–C(5)	118.9 (7)
C(4′)–C(3′)–C(2′)	101.7 (5)	N(3)–C(4)–N(4)	119.7 (6)
C(3′)–C(2′)–C(1′)	103.1 (5)	C(5)–C(4)–N(4)	121.4 (6)
C(2′)–C(1′)–O(4′)	106.5 (6)	C(4)–C(5)–C(6)	118.5 (6)
C(2′)–C(1′)–N(1)	115.0 (5)	C(5)–C(6)–N(1)	122.4 (6)

ZnCMP crystal structure is particularly suitable for comparison. In ZnCMP, the Zn^{2+} ion also has an approximately tetrahedral environment in which it is coordinated to one cytosine base at N(3), to a phosphate oxygen from two other CMP's, and to one

water oxygen (Table VI). The Zn–N(3) bond lengths in the three Zn complexes are similar (Table VI).[18-24] A common feature of M–CMP complexes is a M···O(2) intramolecular interaction, which ranges from weak (Pt–O(2) length of 2.99 Å[22]) to appreciable (Mn–O(2) length of 2.08 Å[23]). The $Zn(CMOMeP)_2$ and $Zn(dCMOMeP)_2$ complexes also have this intramolecular $Zn···O(2)$ interaction with an intramolecular contact of 2.70 Å for $Zn(CMOMeP)_2$ and 2.72 Å for $Zn(dCMOMeP)_2$. This contact is reflected in the Zn–N–C angles. The Zn–N(3)–C(2) angle is smaller at 108.6° for $Zn(CMOMeP)_2$ than the Zn–N-(3)–C(4) angle of 130.4°. Crystal structure determinations reported to date have demonstrated that the base binds to metals either through N(3) (seven examples, Table VI) or through O(2) (one example); no examples in which N(3) and O(2) are clearly both coordinated equally to the same metal have been reported.
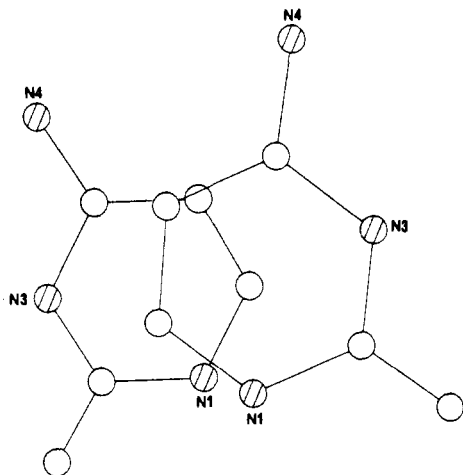
Base Geometry and Stacking Properties. The two bases coordinated through N(3) are in what has been designated as "head-to-tail" configuration and in a "top-to-bottom" intermolecular arrangement with C(2)–N(3)–C(4) as the top half of the molecule and N(1)–C(6)–C(5) as the bottom half.[1] The four bases in the nucleotides associated with each Zn stack in two pairs which

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Table VI. Metal Complexes Containing CMP and CMP Derivatives

compd	M CN[a]	M–N(3), Å	M–O(P), Å	M···O(2), Å	space group	ref
Zn(CMOMeP)$_2$	4	2.00	1.98	2.70	P3$_2$21	this work
Zn(dCMOMeP)$_2$	4	2.00	1.95	2.72	P3$_2$21	this work
ZnCMP	4	2.04	1.82, 1.97	2.69	P2$_1$	18
CoCMP	4	1.99	1.97, 2.00	2.64	P2$_1$	19
CdCMP	5	2.32	2.27, 2.22 2.25	2.92	P2$_1$2$_1$2$_1$	19, 20
CdCMP	7	2.34 2.32	2.38, 2.72 2.62, 2.28 2.29, 2.20 2.19, 2.22	2.58 2.87	C2	21
[Pt(en)CMP]$_2$[c]	4	2.06	1.97	2.99	P2$_1$	22
MnCMP	6	b	2.21	2.08	P2$_1$2$_1$2$_1$	23
CuCMP(dpa)[c]	5	b	2.25		P2$_1$	24

[a] CN = coordination number. [b] M does not bind N3. [c] Abbreviations: en = ethylenediamine, dpa = 2,2'-dipyridylamine.
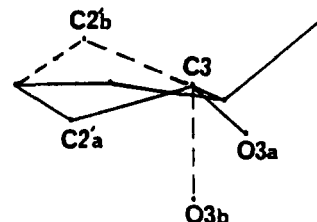

Figure 5. Perspective view of the stacking arrangement of the bases.

Figure 6. Sugar conformation in the Zn(dCMOMeP)$_2$ complex disordered with equal populations of (a) 2'-endo and (b) 3'-endo.

Table VII. Hydrogen-Bonding Interactions between Adjacent Molecules

H bond	dist, Å	H bond	dist, Å
	1. Zn(CMOMeP)$_2$		
O(2')–O(W2)[a]	2.81 (1)	O(1'')–O(3')[e]	2.97 (1)
O(W2)–O(2')[b]	2.81 (1)	O(1'')–O(2')[e]	2.94 (1)
O(W1)–O(1'')[c]	2.73 (1)	O(W5a)–O(Wa)[f]	2.93 (2)
O(1'')–O(W1)[d]	2.73 (1)	O(W4)–O(W5a)[f]	2.93 (2)
	2. Zn(dCMOMeP)$_2$		
O(W2)–O(3'b)[b]	2.94 (1)	O(W6)–O(W5)[e]	3.03 (9)
O(W1)–O(1'')[c]	2.84 (1)	O(1'')–O(3'b)[i]	2.82 (1)
O(1'')–O(W1)[d]	2.84 (1)	O(1'')–O(W3)[i]	2.90 (4)
O(W6)–O(2'')[g]	2.73 (7)	O(1'')–O(3'a)[i]	2.59 (1)
O(W2)–O(W2)[h]	2.37 (2)	O(W4)–O(W5)[j]	2.54 (5)

[a] x, y + 1, z. [b] x, y − 1, z. [c] −y − 1, x − y, z − 0.333. [d] y − x − 1, −x − 1, z + 0.333. [e] −x − 1, y − x − 1, −z − 0.333. [f] x − y, −y, −z − 0.666. [g] y, x, −z. [h] −x, y − x, −z − 0.333. [i] −x − 1, y − x − 1, −z − 0.333. [j] x − y, −y, −z − 0.666.

are equivalent. The L1 base stacks with the L4 base, and the L2 base stacks with the L3 base (Figure 4). The bases have an average separation of 3.59 Å, a 4.3° angle between the planes, and an overlap of the C(5) and C(6) atoms (Figure 5). This mode of overlap is unusual in comparison with that of other pyrimidine structures.[18,19,25] For example, the ZnCMP structure[18] has the more common base overlap where the N(4) amine group overlaps and interacts with the ring π-electron system of the stacking base. The Zn(CMOMeP)$_2$ structure has no N(4) group overlap (Figure 5).

Sugar Conformation. The sugar least squares plane for atoms C(1'), C(2'), C(3'), C(4'), and O(4') of the Zn(CMOMeP)$_2$ complex forms a dihedral angle of 77.8° with the plane of the base. The Zn(CMOMeP)$_2$ complex is not disordered and is 3'-endo, anti, gauche$^+$. The ZnCMP structure has a 2'-endo, anti, gauche$^+$ sugar conformation and has a base–sugar dihedral angle of 94°.[18] The sugars in the Zn(dCMOMeP)$_2$ complex are conformationally disordered and the Fourier map indicates equal populations of 2'-endo, anti, gauche$^+$ (sugar A) and 3'-endo, anti, gauche$^+$ (sugar B) are present (Figure 6). Various M-CMP complexes exhibit both 2'-endo and 3'-endo sugar conformations. For example, CdCMP is 3'-endo and CoCMP is 2'endo.[19]

Phosphate Group. The angles O(5')–P–O(2'') (104.4°) and O(1'')–P–O(3'') (117.9°) about the phosphate group for Zn-(CMOMeP)$_2$ are similar to the average values of 105.7° and 118.2°, respectively, for the analogous angles found for the other three known metal complexes of the methyl nucleotides, [Pt-(tn)(GMOMeP)$_2$][16] cis-[Zn(GMOMeP)$_2$(H$_2$O)$_4$],[1] and cis-[Zn-(IMOMeP)$_2$(H$_2$O)$_4$].[1]

The Zn–O(P) bond length of 1.98 Å for Zn(CMOMeP)$_2$ is similar to those found for other MCMP complexes where the metal is four-coordinate (Table VI). The Zn–O(P) bond lengths for

complexes with metal coordination numbers greater than four are significantly longer at 2.19–2.62 Å (Table VI).

Hydrogen-Bonding Interactions. The waters of hydration for Zn(CMOMeP)$_2$ hydrogen bond (H bond) with other waters of hydration (O(W3)···O(W2), 2.92 Å), sugar oxygens (O(W2)···O(2'), 2.81 Å) and phosphate oxygens (O(W1)···O(1''), 2.73 Å). The phosphate oxygens also interact with sugar oxygens (O-(1'')–O(3'), 2.97 Å). Table VII contains a complete listing of H-bond interactions for both Zn(CMOMeP)$_2$ and Zn(dCMO-MeP)$_2$.

Base–Sugar Interactions. There is a close contact between C(6) and O(4') of 2.69 Å for Zn(CMOMeP)$_2$ which has a χ_{CN} of 34.2°.[26] This C(6)–H(6)···O(4') hydrogen-bonding interaction is seen for other MCMP complexes such as CdCMP,[19] which has a 2.71-Å contact distance and a χ_{CN} of 16.1°, and ZnCMP with a 2.87 Å contact distance and a χ_{CN} of 56.3°.[18] A comparison of the N(1)–C(1') bond distance and χ_{CN} for several pyrimidine derivatives indicates that the N(1)–C(1') bond length is a maximum of 1.52 Å if χ_{CN} is near 180° and decreases to 1.48 Å as χ_{CN} approaches −140°.[27] The lengthening of the N(1)–C(1')

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bond reflects the steric interactions between the hydrogen attached to C(6) and O(4′).

Relevance to Nucleic Acid Binding. We have previously ascribed the relationship of Zn^{2+} binding to G in DNA to a possible mechanism whereby the Zn^{2+} could facilitate rewinding by enhancing GC base pairing. A recent theoretical study[28] on imidazole H-bonding dimers reveals that Zn^{2+} can greatly stabilize the H-bonding interaction. In our study of the *cis*-[Zn(GMO-MeP)₂(H₂O)₄] octahedral complex, we found that the Zn coordinated to N(7) of both nucleotides.[1] This binding mode allows for Watson–Crick type H bonding to remain intact. The binding mode found here, where N(3) of the cytosine base is coordinated to Zn, would preclude GC base pairing. One could imagine that a phosphate group of one strand and a base for another strand could be involved in the binding. The structure reported here would be consistent with this interaction. It should be noted, however, that one structural type (*cis*-[Zn(GMOMeP)₂(H₂O)₄]) is octahedral whereas the other (Zn(CMOMeP)₂) is tetrahedral.

In Z-DNA, the χ_{CN} torsional angle for GMP corresponds to a syn conformation. In none of the structures we have studied do we find a syn conformation. However, since Zn^{2+} binds to N(7),[1] such an interaction would be expected to stabilize the Z structure since N(7) is in a more open position in Z-DNA as compared to B-DNA.[29] The metal ions that are most effective in the B → Z conversion are base-binding metal ions.[12] However, phosphate-binding metal ions favor B-DNA. Thus, our structural studies, which reveal both base and phosphate binding, are consistent with observations in the literature, such as the midrange

position of Zn^{2+} in B → Z converting ability.[12]

Finally, the angles at the phosphodiester linkage are not greatly different in the two types of structures, *cis*-[Zn(GMOMeP)₂-(H₂O)₄] and Zn(CMOMeP)₂. Therefore, coordination of Zn^{2+} directly to a phosphodiester linkage would not in itself change the structure of B-DNA. Thus, these findings are consistent with the stabilization of DNA structure to melting by Zn^{2+} at low ratios of Zn/P.[9] However, indirect interaction with the phosphate group via coordinated H₂O, as found in the *cis*-[Zn(GMOMeP)₂(H₂O)₄] structure, would also account for the higher melting temperature.

The structures presented in this work and in previous studies[1,13–16] reveal a number of interesting structural features of complexes with nucleotide monophosphates. However, the extension of the results to larger molecules in solution must be made with caution. It certainly will be interesting to compare structural features of Zn complexes of duplexed oligonucleotides with those discussed here.

Registry No. Zn(CMOMeP)₂·9H₂O, 104532-56-1; Zn(dCMO-MeP)₂·11H₂O, 104597-38-8.

Supplementary Material Available: Tables of anisotropic temperature factors, isotropic temperature factors, hydrogen coordinates and temperature factors, bond lengths, bond angles, torsion angles, and least-squares planes and the deviations of individual atoms from these planes and additional packing diagrams (some with hydration) for both structures (21 pages); tables of observed and calculated structure factors (55 pages). Ordering information is given on any current masthead page.

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Synthesis, Characterization, and Electrochemistry of Indium(III) Porphyrins That Contain a Stable Indium–Carbon σ Bond

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The syntheses and spectroscopic properties of a new series of σ-bonded indium porphyrins are reported, and their electrochemical behavior is characterized in different solvents containing 0.1 M tetrabutylammonium hexafluorophosphate as supporting electrolyte. Perfluoroaryl groups (C₆F₄H and C₆F₅) were σ-bonded to indium(III) complexes containing four different types of porphyrin rings. Each neutral complex was characterized by ¹H NMR, ¹⁹F NMR, IR, and UV–visible spectroscopy. All of the complexes could be oxidized or reduced by multiple single-electron transfers. Two reversible reductions were observed in nonaqueous media and corresponded to ring-centered reactions, the first of which generated a stable [(P)In(C₆F₄X)]⁻ radical anion. The compounds could also be oxidized by two one-electron abstractions, but unlike previously described σ-bonded alkylindium (or arylindium) porphyrins, no cleavage of the σ bond occurred following the first oxidation; i.e., the generated radical cations were stable. These two oxidations were shown to be centered at the porphyrin π-ring system. The electrochemistry and spectroscopic properties of the new σ-bonded indium porphyrins were compared with those of other types of indium σ-bonded complexes.

Introduction

A number of different metalloporphyrins with metal–alkyl or metal–aryl σ-bonds have been synthesized and characterized with an aim toward understanding the function and reactivity of several biological molecules.[2] Investigated complexes include metalloporphyrins with 13 different transition and main-group metals.[2]

The most detailed electrochemical studies of σ-bonded metalloporphyrins have involved complexes of Fe,[3–9] Co,[10–13] Ga,[14]

and In.[15] These four groups of metalloporphyrins undergo an electrooxidation that is followed by one or more rapid chemical

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