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Phosphine Analogues of Cisplatin. Synthesis and X-ray Structure of Bis(μ-hydroxo)bis(bis(trimethylphosphine)platinum(II)) Dinitrate and Its Reactivity with 1-Methylcytosine. X-ray Structure of Bis(μ-1-methylcytosinato-N^3,N^4)bis(bis(trimethylphosphine)platinum(II)) Dinitrate

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The complex *cis*-$[(PMe_3)_2Pt(\mu\text{-}OH)]_2(NO_3)_2$ has been prepared and characterized by multinuclear ^1H, ^{31}P, and ^{195}Pt NMR spectroscopy. The dimeric nature of the cationic complex found in solution has been confirmed in the solid state by single-crystal X-ray analysis. The compound crystallizes in the monoclinic system, space group $P2_1/n$, with $a = 15.511$ (7) Å, $b = 12.315$ (5) Å, $c = 6.964$ (4) Å, $\beta = 97.67$ (4)°, and $Z = 2$. The structure was solved by heavy-atom methods and refined by least-squares techniques to $R = 0.048$ for 2748 unique data ($I \geq 3\sigma(I)$). The cationic unit *cis*-$[(PMe_3)_2Pt(\mu\text{-}OH)]_2^{2+}$ contains bridging hydroxo ligands with the Pt atoms in a distorted square-planar geometry. The P-Pt-P and O-Pt-O angles are 95.4 (1) and 75.9 (4)°, respectively. The $P_4Pt_2O_2$ skeleton is planar with a rather short O···O distance (2.54 (1) Å). The reaction of this complex with 1-methylcytosine (1-MeCy) has been investigated, in H_2O and dimethyl sulfoxide (DMSO), by ^{31}P NMR spectroscopy. *cis*-$[(PMe_3)_2Pt(\mu\text{-}OH)]_2^{2+}$ reacts with the nucleobase, at room temperature in a few hours, with deprotonation of the exocyclic amino group and metal coordination of the cytosinate ligand. The main reaction product is the dinuclear complex *cis*-$[(PMe_3)_2Pt(\mu\text{-}1\text{-}MeCy(-H))]_2(NO_3)_2$, which has been characterized in solution by multinuclear NMR spectroscopy and in the solid state by single-crystal X-ray analysis. The complex crystallizes in the triclinic system, space group $P\bar{1}$, with $a = 10.320$ (4) Å, $b = 10.431$ (5) Å, $c = 17.426$ (8) Å, $\alpha = 92.39$ (4)°, $\beta = 99.13$ (4)°, $\gamma = 94.54$ (5)°, and $Z = 2$. The structure was solved by heavy-atom methods and refined to $R = 0.038$ for 5900 unique data ($I \geq 3\sigma(I)$). The two deprotonated 1-MeCy molecules bridge two *cis*-$(PMe_3)_2Pt$ moieties in a N^3,N^4 head-to-tail fashion to form a dinuclear species in which the coordination planes of the two metal atoms form a dihedral angle of 46.2°. At 80 °C, in H_2O or DMSO solution, the complex dissociates to the corresponding mononuclear species. The molecular structures and the solution state of the prepared complexes are discussed with reference to those of the amine analogues.

Introduction

Since the discovery of the anticancer activity of *cis*-$[(NH_3)_2PtCl_2]$, the coordination chemistry of DNA-relevant biomolecules has been extensively investigated.[1] All the structurally characterized platinum adducts of nucleobases (in their neutral or deprotonated forms), nucleosides, and nucleotides, stabilized by neutral ligands, are restricted to complexes of amines[2] or bis(amines).[3] We have previously shown that some bis(phosphine) complexes of platinum(II) exhibit a high reactivity toward pyrimidinic nucleosides, and in a few cases their adducts were isolated and spectroscopically characterized.[4] As an example, the reaction of $[L_2Pt(\mu\text{-}OH)]_2^{2+}$ (where L_2 are 1,1′-bis(diphenylphosphino)ferrocene and 1,2-bis(diphenylphosphino)ethane) with thymidines gave the corresponding adducts $[L_2Pt(thymidinate)S]^+$, in which the thymidinate anion is N^3-bonded and S is a molecule of solvent (dimethyl sulfoxide, DMSO, or dimethylformamide, DMF). The interaction of the same hydroxo complexes with cytidines gave a complex mixture of products, only partially characterized by spectroscopic methods.[5]

In this paper we report on the synthesis of the complex *cis*-$[(PMe_3)_2Pt(\mu\text{-}OH)]_2(NO_3)_2$ and its characterization in solution by multinuclear NMR spectroscopy and in the solid state by single-crystal X-ray analysis. Moreover, the interaction of this water-soluble complex with a representative nucleobase has been investigated. In H_2O or DMSO, 1-methylcytosine (1-MeCy) undergoes a facile deprotonation of the exocyclic amino group to give as main reaction product the dinuclear adduct *cis*-$[(PMe_3)_2Pt(\mu\text{-}1\text{-}MeCy(-H))]_2^{2+}$, which has been isolated as a nitrato salt and characterized by single-crystal X-ray analysis. This structure represents the second example of a platinum(II) complex in which the deprotonated nucleobase bridges two metal centers in a N^3,N^4 head-to-tail fashion.[6]

Results

Synthesis and X-ray Structure of *cis*-$[(PMe_3)_2Pt(\mu\text{-}OH)]_2(NO_3)_2$. Addition of 2 equiv of $AgNO_3$ to a suspension of *cis*-$[(PMe_3)_2PtCl_2]$ in water causes the immediate precipitation of AgCl. By solvent removal under vacuo the white complex *cis*-$[(PMe_3)_2Pt(NO_3)_2]$ can be recovered in virtually quantitative yield. The IR spectrum (in Nujol mull) of the solid lacks the typical absorptions of the ionic nitrate groups,[7] as well as those attributable to coordinated water molecules.

The dinitrato complex is very soluble in water and other donor solvents in which it forms the corresponding solvent complexes, likely *cis*-$[(PMe_3)_2PtS_2]^{2+}$ (S = H_2O, DMSO, DMF). Addition of a large excess of NO_3^- (1 M $NaNO_3$) to a water solution of *cis*-$[(PMe_3)_2Pt(NO_3)_2]$ does not modify significantly its ^{31}P and ^{195}Pt NMR spectra. This implies that the nitrato ligands are quantitatively replaced by water upon dissolution of *cis*-$[(PMe_3)_2Pt(NO_3)_2]$.

The aquo complex *cis*-$[(PMe_3)_2Pt(H_2O)_2]^{2+}$ exhibits a fairly strong acidic behavior. In fact, a 0.135 M solution of *cis*-$[(PMe_3)_2Pt(NO_3)_2]$ at 25 °C has a pH value of 1.75. The $^{31}P\{^1H\}$ NMR spectrum of the same solution shows a strong singlet at δ −25.31, symmetrically flanked by ^{195}Pt satellites (see Table I), attributable to the undissociated species *cis*-$[(PMe_3)_2Pt(H_2O)_2]^{2+}$. Moreover, a weaker resonance (intensity ratio ca. 1:5) is observed at slightly higher field (δ − 25.57), which occurs as an apparent

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Table I. ^{195}Pt and ^{31}P NMR Parameters[a]

compd[b]	solvent	δ_P, ppm ($^1J_{^{195}Pt-^{31}P}$, $^3J_{^{195}Pt-^{31}P}$)[c] [$J_{^{31}P-^{31}P}$][d]	δ_{Pt},[d] ppm {$J_{^{195}Pt-^{195}Pt}$}
$(PMe_3)_2PtCl_2$	DMSO-d_6	-22.35, s (3469)	
$(PMe_3)_2Pt(S)_2^{2+}$	D_2O	-25.25, s (3742)	-4348, t
	DMSO-d_6	-24.9, s (3738)	
$[(PMe_3)_2Pt(\mu\text{-}OH)]_2^{2+}$	D_2O	-25.58, s (3398), (10)*	-3920, tt {240}
$[(PMe_3)_2Pt(1\text{-}MeCy(-H))]^+$	D_2O	-28.52 (3264) -30.41, m (3121) [24.4]	
	DMSO-d_6	-27.77 (3221) -29.14, m (3135) [24.4]	-3821, d,d
$[(PMe_3)_2Pt(\mu\text{-}1\text{-}MeCy(-H))]_2^{2+}$	D_2O	-32.75 (3135) -33.03, m (3293) [26.2]	
	DMSO-d_6	-31.91 (3066) -32.44, m (3269) [26.2]	-3911, d,d

[a] All J values are in Hz. [b] All compound have cis-phosphine ligands; s = singlet, d = doublet, t = triplet, d,d = doublet of doublets, t,t = triplet of triplets, and m = AB multiplet. [c] Asterisk indicates ^3J value. [d] Negative values of δ at higher field from aqueous Na_2PtCl_6.

Table II. Crystal Data for *cis*-$[(PMe_3)_2Pt(\mu\text{-}OH)]_2(NO_3)_2$

empirical formula; mol wt	$C_{12}H_{38}N_2O_8P_4Pt_2$; 852.3
cryst dimens, mm	0.12 × 0.20 × 0.08
cryst syst	monoclinic
space group	$P2_1/n$
cell dimens	
a, Å	15.511 (7)
b, Å	12.315 (5)
c, Å	6.964 (4)
β, deg	97.67 (4)
Z; $F(000)$	2; 808
V, Å^3	1318.3 (1.1)
calcd dens, g/cm^3	2.147
wavelength, Å	0.7107
linear abs coeff, cm^{-1}	103.4
no. of unique cor rflns (up to 2θ = 64°)	4543
no. of reflns with $I \geq 3\sigma(I)$	2748
function minimized	$\sum w(\Delta F)^2$
no. of params	77
rflns/param	36
final residual R (w = 1); R_g[a]	0.048; 0.057
max Δ/σ	0.07

[a] $R_g = [\sum \Delta F^2 / \sum (wF_o)^2]^{1/2}$.

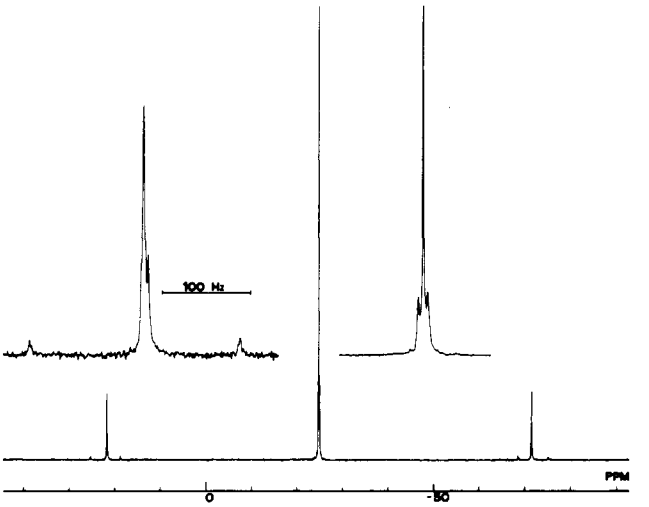

Figure 1. $^{31}P\{^1H\}$ NMR spectrum of *cis*-$[(PMe_3)_2Pt(NO_3)_2]$ in D_2O solution after addition of 1 equiv of NaOH, at 27 °C.

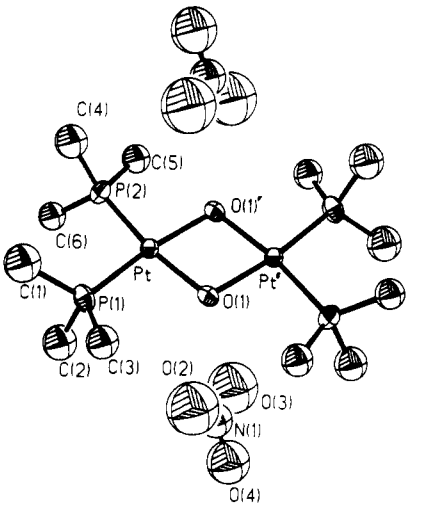

Figure 2. ORTEP drawing of the molecular structure of *cis*-$[(PMe_3)_2Pt(\mu\text{-}OH)]_2(NO_3)_2$ projected on the coordination plane.

singlet with ^{195}Pt satellites ($J_{^{195}Pt-^{31}P}$ = 3400 Hz). The addition of 1 equiv of NaOH results in the immediate disappearance of the lower field resonance and the concomitant increase of that centered at δ -25.57. A detailed inspection of this latter resonance reveals the presence of weaker satellites symmetrically flanking the main resonances, as shown in Figure 1.

These spectral features are consistent with the presence of the dinuclear species, with bridging hydroxo ligands, *cis*-$[(PMe_3)_2Pt(\mu\text{-}OH)]_2^{2+}$. As the natural abundance of ^{195}Pt is 33.7%, for such a dinuclear cation the $^{31}P\{^1H\}$ NMR spectrum can be interpreted as resulting from the superposition of the singlet due to the isotopomer that contains no ^{195}Pt nuclei and the A part of the $A_2A'_2X$ and $A_2A'_2XX'$ multiplets (X' = ^{195}Pt) deriving from the contribution of the two isotopomers *cis*-$[(PMe_3)_2{}^{195}Pt(\mu\text{-}OH)_2Pt(PMe_3)_2]^{2+}$ and *cis*-$[(PMe_3)_2{}^{195}Pt(\mu\text{-}OH)_2{}^{195}Pt(PMe_3)_2]^{2+}$, respectively. The spectral analysis gave values of long-range coupling constant ($|^2J_{^{195}Pt-^{195}Pt}|$ = 240 Hz, $|^3J_{^{195}Pt-^{31}P}|$ = 10 Hz, respectively) in the range observed for related phosphine complexes with halogen,[8] sulfur,[9] and carboxylate[10] as bridging ligands. A further confirmation of the dinuclear nature of the hydroxo complex was obtained by its $^{195}Pt\{^1H\}$ NMR spectrum. As expected, the metal resonance occurs as a well-resolved triplet of triplets centered at δ -3920 with the separation within each triplet corresponding to $^1J_{^{195}Pt-^{31}P}$ and $^3J_{^{195}Pt-^{31}P}$ (Table I). The contribution of the isotopomer containing two ^{195}Pt nuclei is detectable as weak satellites symmetrically flanking the main resonance.

Both ^{31}P and ^{195}Pt NMR data clearly indicate that complex *cis*-$[(PMe_3)_2Pt(\mu\text{-}OH)]_2^{2+}$ is the only detectable species obtained by addition of 1 equiv of OH^- to *cis*-$[(PMe_3)_2Pt(NO_3)]_2$. This dinuclear hydroxo complex has been isolated and further characterized by single-crystal X-ray analysis.

The molecular structure of the complex is shown in Figure 2, and the structural parameters are collected in Table III.

The geometry around the Pt atoms is distorted square planar, the O(1)-Pt-(O)' bond angle being 75.4 (4)°, and the complex

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Table III. Selected Bond Lengths (Å) and Angles (deg), with Their Esd's in Parentheses, of *cis*-$[(PMe_3)_2Pt(\mu\text{-}OH)]_2(NO_3)_2$

Pt-P(1)	2.231 (3)	Pt-P(2)	2.228 (4)
Pt-O(1)	2.08 (1)	P(1)-C(1)	1.87 (3)
P(1)-C(2)	1.80 (2)	P(1)-C(3)	1.78 (2)
P(2)-C(4)	1.81 (2)	P(2)-C(5)	1.79 (2)
P(2)-C(6)	1.80 (2)	N(1)-O(2)	1.20 (4)
N(1)-O(3)	1.18 (4)	N(1)-O(4)	1.23 (3)
Pt-O(1)′	2.06 (1)		
P(2)-Pt-O(1)	169.8 (3)	P(1)-Pt-O(1)	94.7 (3)
P(1)-Pt-P(2)	95.4 (1)	Pt-P(1)-C(3)	111.9 (6)
Pt-P(1)-C(2)	115.3 (8)	Pt-P(1)-C(1)	117.3 (8)
C(2)-P(1)-C(3)	104 (1)	C(1)-P(1)-C(3)	102 (1)
C(1)-P(1)-C(2)	104 (1)	Pt-P(2)-C(6)	118.6 (6)
Pt-P(2)-C(5)	110.5 (6)	Pt-P(2)-C(4)	114.6 (7)
C(5)-P(2)-C(6)	101.9 (8)	C(4)-P(2)-C(6)	105.9 (9)
C(4)-P(2)-C(5)	103.7 (9)	O(3)-N(1)-O(4)	112 (2)
O(2)-N(1)-O(4)	129 (2)	O(2)-N(1)-O(3)	118 (2)
Pt-O(1)-Pt′	104.1 (4)	P(2)-Pt-O(1)′	94.0 (3)
O(1)-Pt-O(1)′	75.9 (4)		

Table IV. Crystal Data for *cis*-$[(PMe_3)_2Pt(\mu\text{-}1\text{-}MeCy(-H))]_2(NO_3)_2$

empirical formula; mol wt	$C_{22}H_{48}N_8O_8P_4Pt_2$; 1066.7
crystal dimens, mm	0.6 × 0.3 × 0.3
crystal syst	triclinic
space group	$P\bar{1}$
cell dimens	
a, Å	10.320 (4)
b, Å	10.431 (5)
c, Å	17.426 (8)
α, deg	92.39 (4)
β, deg	99.13 (4)
γ, deg	94.54 (5)
Z; $F(000)$	2; 1032
V, Å^3	1843.5 (1.4)
calcd dens, g/cm^3	1.92
wavelength, Å	0.7107
linear abs coeff, cm^{-1}	78.8
no. of unique cor rflns (up to 2θ = 64°)	10760
B_F equiv reflns, %	2.4
no. of rflns with $I \geq 3\sigma(I)$	5900
function minimized	$\sum w(\Delta F)^2$
no. of params	357
rflns/param	17
final residual R (w = 1); R_g[a]	0.038; 0.042
max Δ/σ	0.03

[a] $R_g = [\sum \Delta F^2 / \sum (wF_o)^2]^{1/2}$

has crystallographic C_i symmetry. Other major distortions arise from the larger P(1)-Pt-P(2) angle (95.4 (1)°) and the smaller P(2)-Pt-O(1) one (169.8 (3)°). The $P_4Pt_2O_2$ skeleton is planar; only the atoms O(1) and O(1)′ (related to O(1) by $-x$, $1-y$, $1-z$) deviate by ±0.05 Å from the plane containing the P_4Pt_2 atoms. This feature agrees with the "inner-core" planarity found in $[(dppf)Pt(\mu\text{-}OH)]_2(BF_4)_2\cdot CH_2Cl_2$[11] and $[(NH_3)_2Pt(\mu\text{-}OH)]_2(NO_3)_2$,[12] but it is in contrast with the bending of the dihydroxy bridge in the closely related complex $[(PEt_3)_2Pt(\mu\text{-}OH)]_2(BF_4)_2$,[13] in which the dihedral angle between the two PtP_2O_2 halves is substantial (36.4°). This interesting feature has been explained with the existence of hydrogen bonds between the BF_4^- ion and the bridging hydroxy groups.

In the present complex there is a rather short distance between the hydroxo ligands and the nitrato anions (O(1)···O(2) = 2.96 (3) Å), and the bond angle Pt-O(1)···O(2) (113°) is suitable for hydrogen bonding. However such interaction does not appear to modify significantly the planarity of the $P_4Pt_2O_2$ skeleton. The Pt-P distances (average 2.23 Å) are in excellent agreement with the values found in the related PEt_3 derivative.[13] The nitrate group is planar within 0.03 Å, the bond lengths are in the range 1.18–1.22 Å, and the dihedral angle between the dimeric cation and the nitrate ions is 59°. Some of the nitrate ions are disordered, as shown by the high thermal factors for which values of U_{eq} up to 0.198 Å^2 have been observed.

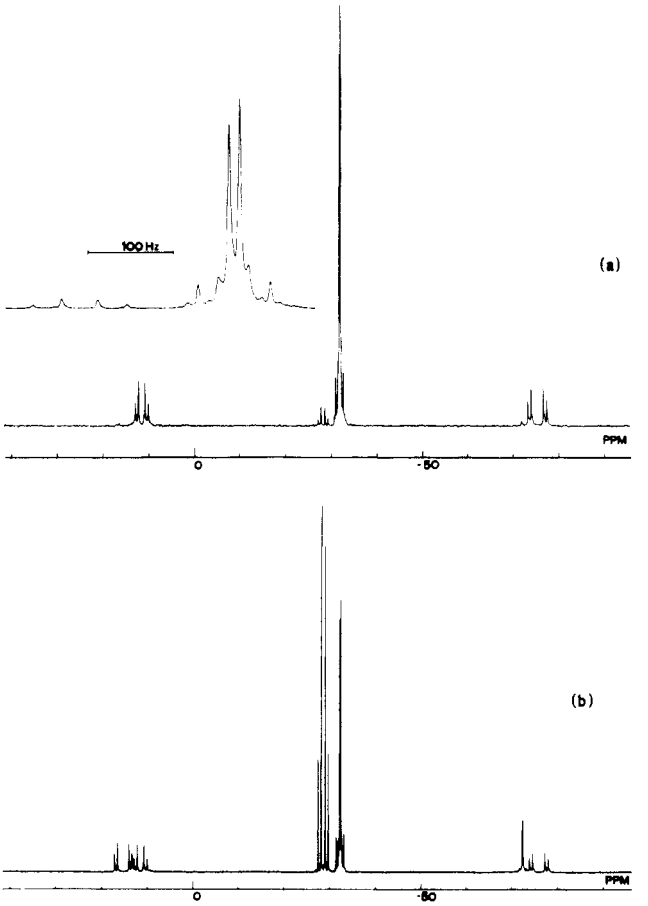

Figure 3. $^{31}P\{^1H\}$ NMR spectra (in DMSO-d_6, at 27 °C) of a mixture of *cis*-$[(PMe_3)_2Pt(\mu\text{-}OH)]_2(NO_3)_2$ and 1-MeCy (in 1:2 molar ratio) (a) after 24 h at 27 °C and (b) after heating at 80 °C for ca. 24 h.

Reactivity of *cis*-$[(PMe_3)_2Pt(\mu\text{-}OH)]_2(NO_3)_2$ with 1-Methylcytosine. When 1 equiv per Pt of 1-MeCy is added to a DMSO-d_6 solution of *cis*-$[(PMe_3)_2Pt(\mu\text{-}OH)]_2(NO_3)_2$, a complex change in the ^{31}P NMR spectrum is observed after a few hours at room temperature. The final spectrum of the reaction mixture is reported in Figure 3a, and the corresponding data are collected in Table I.

The higher field multiplet is an AB pattern with a high second-order character ($\Delta\delta/J_{AB}$ = 0.76) symmetrically flanked by two sets of satellites attributable to close- and long-range ^{195}Pt–^{31}P coupling effects.

The ^1H NMR spectrum shows the exocyclic amine proton resonance as a broad singlet at δ 6.97, which intensity accounts for a single proton. The phosphine methyl resonances occur as two well-resolved doublets, with diverse J_{PtH} and J_{PtP} values, in agreement with the chemical unequivalence of the PMe_3 ligands observed in the ^{31}P NMR spectrum. If the reaction is carried out in D_2O, a similar ^{31}P NMR spectrum is obtained, the only difference being the relative intensity of the two sets of multiplets (ca. 5:1). In both solvents the less intense multiplet displays an AB pattern with very similar $^1J_{PtP}$ values (Table I), without long-range coupling effects. When the reaction mixture is heated at 80 °C for several hours, the high-field multiplet is quantitatively replaced by this latter multiplet (Figure 3b).

As a whole, these results suggest that the main reaction product, formed at room temperature, may contain the deprotonated nucleobase bridging two *cis*-$(PMe_3)_2Pt$ moieties to give of the dinuclear species *cis*-$[(PMe_3)_2Pt(\mu\text{-}1\text{-}MeCy(-H))]_2^{2+}$. The complex has been isolated by fractional crystallization of the reaction mixture, and its molecular structure was determined by single-crystal X-ray analysis.

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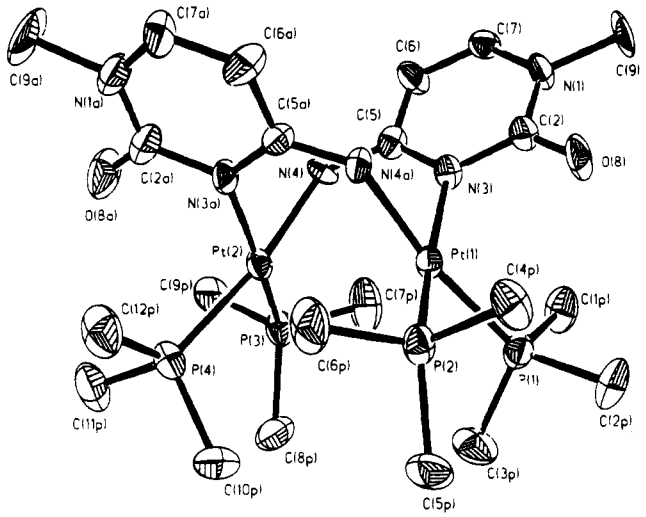

Figure 4. *cis*-$[(PMe_3)_2Pt(\mu\text{-}1\text{-}MeCy(-H))]_2^{2+}$ cation with the numbering of the atoms. Nitrate groups are omitted for clarity.

Table V. Selected Bond Lengths (Å), with Their Esd's in Parentheses, of *cis*-$[(PMe_3)_2Pt(\mu\text{-}1\text{-}MeCy(-H))]_2(NO_3)_2$

Pt(1)---Pt(2)	3.199 (2)	Pt(1)-P(1)	2.260 (3)
Pt(1)-P(2)	2.264 (3)	Pt(1)-N(3)	2.119 (8)
Pt(1)-N(4a)	2.058 (8)	Pt(2)-P(3)	2.259 (3)
Pt(2)-P(4)	2.264 (3)	Pt(2)-N(4)	2.074 (8)
Pt(1)-N(3a)	2.109 (9)	P(1)-C(1p)	1.84 (1)
P(1)-C(2p)	1.81 (1)	P(1)-C(3p)	1.83 (1)
P(2)-C(4p)	1.83 (1)	P(2)-C(5p)	1.82 (1)
P(2)-C(6p)	1.83 (1)	P(3)-C(7p)	1.83 (1)
P(3)-C(8p)	1.84 (1)	P(3)-C(9p)	1.82 (1)
P(4)-C(10p)	1.85 (1)	P(4)-C(11p)	1.82 (1)
P(4)-C(12p)	1.84 (1)	N(1)-C(2)	1.38 (1)
N(1)-C(7)	1.37 (1)	N(1)-C(9)	1.48 (1)
C(2)-N(3)	1.39 (1)	C(2)-O(8)	1.22 (1)
N(3)-C(5)	1.37 (1)	N(4)-C(5)	1.31 (1)
C(5)-C(6)	1.44 (1)	C(6)-C(7)	1.35 (1)
N(1a)-C(2a)	1.36 (2)	N(1a)-C(7a)	1.36 (2)
N(1a)-C(9a)	1.51 (2)	C(2a)-N(3a)	1.38 (1)
C(2a)-O(8a)	1.24 (1)	N(3a)-C(5a)	1.36 (1)
N(4a)-C(5a)	1.30 (1)	C(5a)-C(6a)	1.44 (2)
C(6a)-C(7a)	1.34 (2)	N(5)-O(1)	1.26 (1)
N(5)-O(2)	1.23 (2)	N(5)-O(3)	1.23 (2)
N(6)-O(4)	1.26 (1)	N(6)-O(5)	1.23 (2)
N(6)-O(6)	1.24 (1)		

X-ray Structure of *cis*-$[(PMe_3)_2Pt(\mu\text{-}1\text{-}MeCy(-H))]_2(NO_3)_2$ (1). An ORTEP drawing of the molecular structure is reported in Figure 4, and the main structural parameters are collected in Tables V and VI. Complex **1** contains a dimeric cation in which two square-planar arrays around each platinum atom are bridged in the cis positions by the 1-methylcytosinato ligands through the N^3 atom and the deprotonated exocyclic amine group N^4 atom.

Each Pt atom is in a distorted square-planar arrangement, the P–Pt–P angles (average 94.8 (1)°) being larger than N–Pt–N (average 84.7 (4)°). Moreover, each Pt atom deviates significantly (average 0.185 Å) from the mean plane passing through the four donor atoms. The N(3)---N(4) and N(3a)---N(4a) bite distances (2.34 (1) and 2.32 (1) Å, respectively) are considerably shorter than the Pt(1)---Pt(2) distance (3.199 (2) Å). As a consequence, the coordination planes of the two metal atoms form a dihedral angle of 46.2°. The two five-membered rings [N(3)–Pt(1)–Pt(2)–N(4)–C(5) and N(3a)–Pt(2)–Pt(1)–N(4a)–C(5a)] are virtually perpendicular (dihedral angle of 93.5 (1)°). The bond lengths and angles within the cytosinato ligand show no significant differences with those of 1-methylcytosine.[14]

The nitrate interactions are typical and fall within a range of distances observed for other platinum(II)–nucleobase complexes.[15]

Table VI. Selected Angles (deg), with Their Esd's in Parentheses, of *cis*-$[(PMe_3)_2Pt(\mu\text{-}1\text{-}MeCy(-H))]_2(NO_3)_2$

N(3)-Pt(1)-N(4a)	84.3 (3)	P(2)-Pt(1)-N(4a)	87.0 (3)
P(2)-Pt(1)-N(3)	165.6 (2)	P(1)-Pt(1)-N(4a)	171.9 (3)
P(1)-Pt(1)-N(3)	92.2 (2)	P(1)-Pt(1)-P(2)	94.9 (1)
Pt(2)-Pt(1)-N(4a)	75.6 (2)	Pt(2)-Pt(1)-N(3)	80.1 (2)
Pt(2)-Pt(1)-P(2)	108.8 (1)	Pt(2)-Pt(1)-P(1)	111.0 (1)
Pt(1)-Pt(2)-N(3a)	79.7 (2)	Pt(1)-Pt(2)-N(4)	76.0 (2)
Pt(1)-Pt(2)-P(4)	110.1 (1)	Pt(1)-Pt(2)-P(3)	109.2 (1)
N(4)-Pt(2)-N(3a)	85.1 (3)	P(4)-Pt(2)-N(3a)	91.5 (2)
P(4)-Pt(2)-N(4)	172.4 (3)	P(3)-Pt(2)-N(3a)	166.7 (3)
P(3)-Pt(2)-N(4)	87.4 (3)	P(3)-Pt(2)-P(4)	94.6 (1)
Pt(1)-P(1)-C(3p)	116.1 (5)	Pt(1)-P(1)-C(2p)	114.1 (4)
Pt(1)-P(1)-C(1p)	116.1 (4)	C(2p)-P(1)-C(3p)	104.4 (6)
C(1p)-P(1)-C(3p)	102.1 (6)	C(1p)-P(1)-C(2p)	102.2 (6)
Pt(1)-P(2)-C(6p)	113.8 (4)	Pt(1)-P(2)-C(5p)	124.7 (4)
Pt(1)-P(2)-C(4p)	107.6 (4)	C(5p)-P(2)-C(6p)	102.5 (6)
C(4p)-P(2)-C(6p)	102.5 (5)	C(4p)-P(2)-C(5p)	103.3 (6)
Pt(2)-P(3)-C(9p)	108.0 (4)	Pt(2)-P(3)-C(8p)	123.2 (4)
Pt(2)-P(3)-C(7p)	115.0 (5)	C(8p)-P(3)-C(9p)	103.2 (6)
C(7p)-P(3)-C(9p)	102.2 (6)	C(7p)-P(3)-C(8p)	102.7 (6)
Pt(2)-P(4)-C(12p)	116.1 (5)	Pt(2)-P(4)-C(11p)	114.9 (4)
Pt(2)-P(4)-C(10p)	115.4 (5)	C(11p)-P(4)-C(12p)	101.0 (6)
C(10p)-P(4)-C(12p)	102.4 (6)	C(10p)-P(4)-C(11p)	105.2 (6)
C(7)-N(1)-C(9)	120.5 (9)	C(2)-N(1)-C(9)	118.1 (9)
C(2)-N(1)-C(7)	121.4 (9)	N(1)-C(2)-O(8)	120.1 (9)
N(1)-C(2)-N(3)	118.0 (8)	N(3)-C(2)-O(8)	121.8 (9)
Pt(1)-N(3)-C(2)	111.1 (6)	C(2)-N(3)-C(5)	121.2 (8)
Pt(1)-N(3)-C(5)	126.1 (6)	Pt(2)-N(4)-C(5)	135.7 (7)
N(3)-C(5)-N(4)	121.3 (8)	N(4)-C(5)-C(6)	119.9 (8)
N(3)-C(5)-C(6)	118.7 (8)	C(5)-C(6)-C(7)	119.1 (9)
N(1)-C(7)-C(6)	121.1 (9)	C(7a)-N(1a)-C(9a)	120 (1)
C(2a)-N(1a)-C(9a)	119 (1)	C(2a)-N(1a)-C(7a)	121 (1)
N(1a)-C(2a)-O(8a)	119 (1)	N(1a)-C(2a)-N(3a)	119 (1)
N(3a)-C(2a)-O(8a)	121 (1)	Pt(2)-N(3a)-C(2a)	112.0 (7)
C(2a)-N(3a)-C(5a)	120.4 (9)	Pt(2)-N(3a)-C(5a)	126.8 (7)
Pt(1)-N(4a)-C(5a)	136.4 (7)	N(3a)-C(5a)-N(4a)	120.8 (9)
N(4a)-C(5a)-C(6a)	120.1 (9)	N(3a)-C(5a)-C(6a)	119.0 (9)
C(5a)-C(6a)-C(7a)	118 (1)	N(1a)-C(7a)-C(6a)	122 (1)
O(2)-N(5)-O(3)	124 (1)	O(1)-N(5)-O(3)	118 (1)
O(1)-N(5)-O(2)	118 (1)	O(5)-N(6)-O(6)	119 (1)
O(4)-N(6)-O(6)	120 (1)	O(4)-N(6)-O(5)	120 (1)

In particular, the interatomic contacts N(4a)---O(1) and N(4)---O(5) (3.02 (1) and 3.10 (1) Å, respectively) and the intermolecular contacts C(7a)---O(3) (at $-x$, $1-y$, $1-z$) and C(7)---O(1) at $-x$, $1-y$, $1-z$) represent the only possible hydrogen bonds, while the remaining interactions are at or greater than the van der Waals contact distances.

Discussion

The results of this work indicate that the removal of the chloride ligands in *cis*-$[(PMe_3)_2PtCl_2]$ gives the water-soluble cation *cis*-$[(PMe_3)_2Pt(H_2O)_2]^{2+}$, characterized by a remarkable proton dissociation according to the equilibrium reaction eq 1.

$$cis\text{-}[(PMe_3)_2Pt(H_2O)_2]^{2+} \rightleftharpoons H^+ + \tfrac{1}{2}cis\text{-}[(PMe_3)_2Pt(\mu\text{-}OH)]_2^{2+} \quad (1)$$

As shown by direct pH measurements and by the detection of its deprotonated form by ^{31}P NMR spectroscopy, the aquo complex *cis*-$[(PMe_3)_2Pt(H_2O)_2]^{2+}$ appears to be much more acidic than the corresponding amino derivative.[16] The measure of the acidity constants of *cis*-$[(PMe_3)_2Pt(H_2O)_2]^{2+}$ and a detailed investigation on the equilibrium reaction eq 1 will be reported elsewhere.

Addition of 1 equiv of OH^- to an aqueous solution of *cis*-$[(PMe_3)_2Pt(NO_3)_2]$ leads to the quantitative formation (by ^{31}P NMR) of the hydroxo complex *cis*-$[(PMe_3)_2Pt(\mu\text{-}OH)]_2(NO_3)_2$, which can be isolated in good yield by simple evaporation of its solution. A comparison of the relevant structural data of this

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Table VII. Comparison of Some Structural Data for Bis(μ-hydroxy)diplatinum(II) Complexes

	Pt–O, Å	O–Pt–O, deg	Pt···Pt, Å	O···O, Å	Pt–O–Pt, deg
$[(NH_3)_2Pt(\mu\text{-}OH)]_2(NO_3)_2$[a]	2.03 (1)	81.3 (4)	3.085 (1)	2.64 (1)	98.9 (9)
$[(PEt_3)_2Pt(\mu\text{-}OH)]_2(BF_4)_2$[b]	2.13 (1)	79.4 (6)	3.121 (1)	2.72 (2)	94 (2)
$[(dppf)Pt(\mu\text{-}OH)]_2(BF_4)_2\cdot 2CH_2Cl_2$[c]	2.10 (1)	79.4 (4)	3.227 (1)	2.68 (1)	100.6 (7)
$[(PMe_3)_2Pt(\mu\text{-}OH)]_2(NO_3)_2$	2.07 (1)	75.9 (4)	3.261 (1)	2.54 (1)	104.1 (4)

[a–c] See refs 12, 13, and 11, respectively.

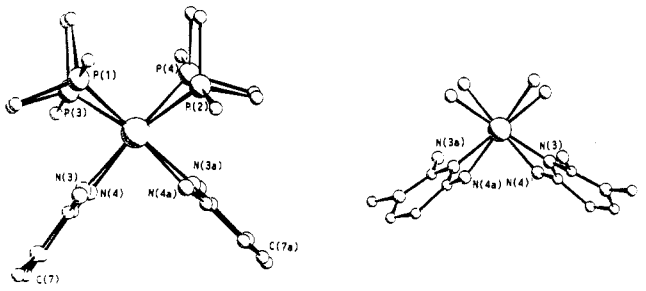
compound with those of the above-mentioned bis(μ-hydroxy)-platinum(II) complexes[11–13] is reported in Table VII.

It can be seen that the substitution of the NH_3 ligands with PMe_3 modifies significantly the geometry of the $Pt(\mu\text{-}OH)_2Pt$ unit with an increase of 0.176 Å in the Pt···Pt distance, the consequent shortening of the O···O one (0.10 Å), and the decrease of the Pt–O–Pt angles from 81.3 to 75.9°. Whereas the Pt–O bond length differences in the two cations can reflect the different trans influence of the neutral ligands, the observed angular changes are likely due to the steric effects of the bulkier trimethylphosphine.

In line with previous observations,[17] the ^{195}Pt NMR chemical shifts of these trimethylphosphine complexes are shifted to higher field of ca. 2750 ppm from the corresponding resonances of amino analogues. In this connection it is interesting to note that the difference of the ^{195}Pt chemical shifts of *cis*-$[(PMe_3)_2Pt(\mu\text{-}OH)]_2^{2+}$ and *cis*-$[(PMe_3)_2Pt(H_2O)_2]^{2+}$ (428 ppm) is surprisingly similar to that reported for the related amino complexes (427 ppm).[18] Such difference has been attributed to the ring strain at the metal center present on the dinuclear complex.[19]

Strict similarities of the coordinating ability of the cytosine ligand toward the metal center in trimethylphosphine and amine complexes of platinum(II) are seen in the reactions of 1-MeCy with *cis*-$[(PMe_3)_2Pt(\mu\text{-}OH)]_2^{2+}$ and *cis*-$[(NH_3)_2Pt(\mu\text{-}OH)]_2^{2+}$,[6] respectively. In both the cases, the reaction with the nucleobase occurs with deprotonation of the exocyclic amino substitutent to give the dinuclear complex in which the cytosinato ligand bridges two *cis*-L_2Pt moieties in a N^3,N^4 head-to-tail fashion. Comparison of equivalent parameters in the two cations, *cis*-$[(PMe_3)_2Pt(1\text{-}MeCy(-H))]_2^{2+}$ (cation **1**) and *cis*-$[(NH_3)_2Pt(1\text{-}MeCy(-H))]_2^{2+}$ (cation of **2**), shows that the major differences lie (i) in the change in Pt···Pt distances from 3.199 (2) Å for **1** to 2.981 (2) Å for **2**, (ii) in Pt–N^3 bond lengths [2.114 (9) Å for **1** and 2.05 (2) Å for **2**], (iii) in N(3)–Pt(1)–N(4a) [84.3 (3)° for **1** and 94 (1)° for **2**], N(4)–Pt(2)–N(3a) [85.1 (1)° for **1** and 93 (1)° for **2**], and Pt(2)–Pt(1)–N(3) [80.1 (2)° for **1** and 83.8 (8)° for **2**] angles, (iv) in the P–Pt–P angles, which are significantly larger (average 94.8 (1)°) than the H_3N–Pt–NH_3 ones (average 90 (1)°), and (v) in the different deviations of the Pt atom from the mean coordination plane defined by the four donor atoms (0.19 and 0.18 Å in **1** vs 0.02 and 0.04 Å in **2**). Furthermore, (vi) the dihedral angle between the two square-planar arrays ("twist" angle) is 46.2 (2)° in **1** and 34 (1)° in **2** and (vii) although the bend angles between the pyrimidine rings are almost the same (102.7 (1)° in **1** and 100 (1°) in **2**) and the two five-membered rings [N(3)–Pt(1)–Pt(2)–N(4)–C(5) and N(3a)–Pt(2)–Pt(1)–N(4a)–C(5a)] are virtually perpendicular (dihedral angle of 93.5 (1)° in **1** and 97 (1)° in **2**) (see Figure 4), the angle between the N(3)···C(7) and N(3a)···C(7a) lines is 79.4 (3)° in **1**, while it is very large in **2** (106 (1)°), as shown in Figure 5, in which the overall features of the two cations can be seen.

Although we cannot ignore the different trans influences of the neutral ligands, we think that the changes observed in **1** and **2** are mainly attributable to the higher steric requirement of the trimethylphosphine compared to that of the amine ligands. The existence of some steric congestion around the metal center in *cis*-$[(PMe_3)_2Pt(1\text{-}MeCy(-H))]_2^{2+}$, resulting from the presence of two phosphines, can be the reason for the rearrangement of **1** when its solutions (in H_2O or DMSO) are warmed at high temperature. As the phosphines maintain their reciprocal cis position and the ^{31}P NMR resonances exhibit coupling effects only with one ^{195}Pt nucleous, we tentatively propose that the new complex is a mononuclear species in which the cytosinato-N^3,N^4 anion acts as a chelating ligand. This binding mode of the cytosinato anion has a precedent in a platinum(IV) amino complex.[20]



1 **2**

Figure 5. *cis*-$[(PMe_3)_2Pt(\mu\text{-}1\text{-}MeCy(-H))]_2^{2+}$ and *cis*-$[(NH_3)_2Pt(\mu\text{-}1\text{-}MeCy(-H))]_2^{2+}$ cations viewed down the Pt(1)–Pt(2) vector.

Experimental Section

Apparatus and Materials. ^1H, ^{31}P, and ^{195}Pt NMR spectra were recorded on a Jeol 90 Q spectrometer. Chemical shifts are given on the δ scale and referenced as follows: internal tetramethylsilane in DMSO-d_6 and sodium 3-(trimethylsilyl)propanesulfonate in D_2O for the proton spectra; external H_3PO_4 (85% w/w) for the phosphorus spectra; external Na_2PtCl_6 (1 M in H_2O) for ^{195}Pt spectra. pH measurements were carried out with a Radiometer PHM 84 research pH meter, by using a KNO_3 salt bridge; the instrument was calibrated with two standard buffers of 0.05 M potassium hydrogen phthalate and 0.05 M potassium tetraoxalate dihydrate from BDH and Merck, respectively. *cis*-$[(PMe_3)_2PtCl_2]$ has been prepared according to the literature method[21] with a yield of 70%. $^{31}P\{^1H\}$ NMR in DMSO-d_6: −22.35, singlet flanked by ^{195}Pt satellites. 1-Methylcytosine was from Sigma.

Preparation of *cis*-$[(PMe_2)_2Pt(NO_3)_2]$. To a suspension of *cis*-$[(PMe_3)_2PtCl_2]$ (0.232 g, 0.554 mmol) in 10 mL of H_2O was added dropwise a solution of $AgNO_3$ (0.188 g, 1.108 mmol) in H_2O (2 mL) under stirring, at room temperature. The reaction mixture was stirred for 4 h and filtered, and the filtrate was evaporated in vacuo. The yield was virtually quantitative. Anal. Calcd for $C_6H_{18}N_2O_6P_2Pt$: C, 15.29; H, 3.85; N, 5.94. Found: C, 14.98; H, 3.67; N, 5.63. ^1H NMR in D_2O: 1.67 (d, $^2J_{P\text{-}H}$ = 12.0 Hz, $^3J_{Pt\text{-}H}$ = 41 Hz).

Preparation of *cis*-$[(PMe_3)_2Pt(\mu\text{-}OH)]_2(NO_3)_2$. A 1-equiv amount of aqueous NaOH (0.5 M) was added to a solution of *cis*-$[(PMe_3)_2Pt(NO_3)_2]$ (450 mg, 0.955 mmol) in H_2O (100 mL). The resulting solution was concentrated in vacuo until a microcrystalline white precipitate was formed. The solid was recovered by filtration, washed with ethanol, and dried in vacuo. The yield was 305 mg, 75%. Anal. Calcd for $C_6H_{19}NO_4P_2Pt$: C, 16.91; H, 4.49; N, 3.29. Found: C, 16.82; H, 4.74; N, 3.18. ^1H NMR in D_2O (phosphine resonances): 1.59 (d, $^2J_{P\text{-}H}$ = 11.7, $^3J_{Pt\text{-}H}$ = 37.2 Hz).

Preparation of *cis*-$[(PMe_3)_2Pt(\mu\text{-}1\text{-}MeCy(-H))]_2(NO_3)_2$. A solution of *cis*-$[(PMe_3)_2Pt(\mu\text{-}OH)]_2(NO_3)_2$ (145 mg, 0.170 mmol) and 1-MeCy (42.5 mg, 0.34 mmol) in 3 mL of H_2O was stirred at room temperature for 20 h and then filtered to separate a trace of black precipitate. The solution was evaporated in vacuo, the residue dissolved in EtOH (6 mL), and the resulting solution cooled to 0 °C. Addition of ice-cold Et_2O gave a white microcrystalline precipitate, which was collected by filtration and dried under vacuum. The yield of crude product was 172 mg (95%). The crude product was purified from EtOH/Et_2O, but elemental analyses of several samples gave poorly reproducible results. The crystals suitable for X-ray analysis, grown from EtOH upon slow diffusion of Et_2O, gave

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the following results. Anal. Calcd for $C_{11}H_{24}N_4O_4P_2Pt$: C, 24.77; H, 4.53; N, 10.50. Found: C, 23.91; H, 4.36; N, 9.69. Inspection by microscope showed the crystal surfaces coated with small spots of an amorphous black material, likely platinum. ^1H NMR in DMSO-d_6: cytosine resonances, 7.22 (d, J_{H-H} = 7.0 Hz, H_6), 6.97 (broad singlet, NH), 5.84 (d, J_{H-H} = 7.0 Hz, H_5), 3.14 (s, CH_3); phosphine resonances, 1.75 (d, $^2J_{P-H}$ = 10.9 Hz, $^3J_{Pt-H}$ = 35.6 Hz), 1.48 (d, $^2J_{P-H}$ = 10.5, $^3J_{Pt-H}$ = 30.5 Hz).

Crystallography of *cis*-$[(PMe_3)_2Pt(\mu\text{-}OH)]_2(NO_3)_2$ and *cis*-$[(PMe_3)_2Pt(\mu\text{-}1\text{-}MeCy(\text{-}H))]_2(NO_3)_2$. Transparent, colorless crystals of the μ-hydroxo complex were grown by slow evaporation of a water solution. Details of the crystal data, measurement of intensities, and data processing are summarized in Table II. The intensity data were collected on a Philips PW1100 four-circle diffractometer. Empirical absorption correction, based on ψ scans of three reflections at $\chi \approx 90°$, was applied. The structure was solved by the heavy-atom method and was refined by full-matrix procedures, anisotropically only for Pt, P(1), P(2), and O(1) atoms. No direct determination of the positions of the hydrogen atoms was attempted because of the presence of the heavy Pt atom. The programs used were those of the SHELX package.[22] Fractional coordinates and thermal parameters are given in Table A of the supplementary material. Additional details, including nonessential bond distances and angles, are available as supplementary material. The same apparatus was used for the X-ray analysis of *cis*-$[(PMe_3)_2Pt(\mu\text{-}1\text{-}MeCy(\text{-}H))]_2(NO_3)_2$ (**1**). Characteristics of the data collection processing and refinement are given in Table IV. The structure was solved by the heavy-atom method and refined by full-matrix procedures, anisotropically for all non-hydrogen atoms of the dication and isotropically for the nitrate group atoms. Bond distances and angles are listed in Tables V and VI, respectively.

Fractional coordinates and thermal parameters are reported in Table B of the supplementary material. A table of least-square planes with deviations of the relevant atoms and dihedral angles of **1** is reported as supplementary material (Table C).

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Supplementary Material Available: Tables A–C, listing fractional coordinates and thermal parameters for the two complexes and least-squares planes, deviations of relevant atoms, and dihedral angles for **1** (4 pages); Tables D and E, listing observed and calculated structure factors for both compounds (25 pages). Ordering information is given on any current masthead page.

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Acid Properties of Zinc(II) and Cadmium(II) in Complexation with Macrocyclic Oxo Polyamine Ligands

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The pH-metric titration study of the interaction of Zn^{II} and Cd^{II} ion with dissociable (acidic) hydrogen-containing macrocyclic polyamines **3–10** has served to distinguish inherent acid and coordination properties of these two metal ions. In complexation with monooxocyclam **3** below pH 8, Zn^{II} ion can replace the amide hydrogen and forms a planar 1:1 monooxocyclam complex $[ZnH_{-1}L]^+$ (**14**) containing the hitherto unknown deprotonated amide N^-–Zn^{II} coordination, while Cd^{II} ion does not yield such a complex. A square-pyramidal N_5Zn^{II} complex $[ZnH_{-1}L]^+$ (**16**) is formed with a pyridyl-pendant monooxocyclam **5** at pH <8, as confirmed by an X-ray structure analysis. In contrast, the larger and less acidic Cd^{II} displaces the amide proton of the same ligand to yield $[CdH_{-1}L]^+$ (**18**) at pH >10. The intermediate complex **17** containing a Cd^{II}–O(amide) bond was isolated and characterized by an X-ray structure analysis. A larger sized 16-membered macrocyclic monooxopentaamine, **10**, initially (pH <6) binds more strongly with Cd^{II} than with Zn^{II} using the four secondary nitrogen donors to form $[ML]^{2+}$, **26** and **28**. At higher pH, however, the more acidic Zn^{II} yields a more stable 5-coordinate amide-deprotonated complex, $[ZnH_{-1}L]^+$ (**27**), than the less acidic Cd^{II} does, $[CdH_{-1}L]^+$ (**29**).

Introduction

Recently, the acidic properties of zinc(II) have attracted much attention, as increasing numbers of hydrolytic enzymes (e.g. carboxypeptidases, carbonic anhydrase) are found to contain Zn^{II} in their active centers.[1,2] Unfortunately, the studies to pinpoint the inherent acid properties of the Zn^{II} ion to help understand the specific role of the Zn^{II} ion in those natural complexes are surprisingly limited, due to the following difficulties: (i) Zn^{II}, being a d^{10} metal ion, has few observable chemical properties indicating its environment and activity (i.e. the lack of UV–visible absorptions, magnetic susceptibility).[3] Sometimes, in order to circumvent these drawbacks, Ni^{II}, Co^{II}, Mn^{II}, or isotopic Cd^{II} have been substituted to pursue the action of Zn^{II} in enzymes.[4] (ii) Zn^{II} complexes are usually labile with artificial simple ligands,[5,6] thereby preventing construction of well-defined reactive site in the complicated Zn^{II}–enzyme. (iii) There have been few appropriate ligands available that allow one to focus on the microscopic role of Zn^{II}. Most often, previously designed biomimetic ligands[7,8] worked indiscriminantly with other metal ions, and few comprehensive explanations[9] were provided regarding why the active metal ion ought to be Zn^{II}, but not the other metal ions (e.g. Cu^{II}, Ni^{II}).

It was found that a tridentate, macrocyclic triamine yields a very stable and structurally well-defined Zn^{II} complex **1**,[10–13] which

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