Inorganica Chimica Acta, *152* (1988) 125–134

The Crystal Structures of Four Models for the Binding to DNA of Cisplatinum Derivatives Containing a Bidentate Tertiary Diamine

JOHN D. ORBELL*[#], MAX R. TAYLOR*, SALLY L. BIRCH, SHARON E. LAWTON, LOUISE M. VILKINS
School of Physical Sciences, The Flinders University of South Australia, Bedford Pk., S.A. 5042, Australia
and LISA J. KEEFE
The Institute for Cancer Research, Fox Chase Cancer Centre, Philadelphia, Pa. 19111, U.S.A.

(Received November 19, 1987)

Abstract

The compounds *cis*-[(TMED)Pt(9-MeG)$_2$](PF$_6$)$_2$·2H$_2$O (**1**), *cis*-[(TMED)Pt(9-EtG)$_2$](ClO$_4$)$_2$·2H$_2$O (**2**), *cis*-[(TMED)Pt(DMX)$_2$](PF$_6$)$_2$·4H$_2$O (**3**) and *cis*-[(TMED)Pt(TMX)$_2$](PF$_6$)$_2$·xH$_2$O ($x \approx 4$) (**4**), where TMED = *N*,*N*,*N*′,*N*′-tetramethylethylenediamine, 9-MeG = 9-methylguanine, 9-EtG = 9-ethylguanine, DMX = 1,3-dimethylxanthine and TMX = 1,3,9-trimethylxanthine, have been prepared and structurally characterised by X-ray methods. Compound **1** crystallises in space group *Pn*, with $a = 10.675(1)$, $b = 12.970(1)$, $c = 12.016(1)$ Å, $\beta = 97.05(1)°$, $Z = 2$. Compound **2** crystallises in space group *Pbca*, with $a = 13.886(1)$, $b = 31.742(4)$, $c = 14.958(2)$ Å, $Z = 8$. Compound **3** crystallises in space group *C*2/*c*, with $a = 37.557(4)$, $b = 12.215(2)$, $c = 15.823(3)$ Å, $\beta = 90.47(1)°$, $Z = 8$. Compound **4** crystallises in the space group *C*2/*c*, with $a = 38.516(5)$, $b = 12.078(2)$, $c = 16.219(2)$ Å, $\beta = 97.88(1)°$, $Z = 8$. Compounds **3** and **4** are structurally similar. Each [(TMED)Pt(Base)$_2$]$^{2+}$ cation shows square-planar coordination to Pt with the two independent purine ligands coordinated through N7 and arranged in a head-to-tail conformation. The structures are compared with each other and with related compounds in terms of their base/base and base/coordination plane dihedral angles, and their different crystalline environments.

Introduction

The targeting of specific sites on DNA by metal coordination complexes such as the antitumour cisplatinum drugs is coming under increasing scrutiny [1]. This is motivated in part by a desire to elucidate the mode of action of a growing number of metal chemotherapeutic agents [2] and to place their development on a more rational basis. The more general objective is to understand the broad nature of metal-nucleic acid interaction which is a fundamental, albeit poorly understood, area of biochemistry.

Much valuable information has been obtained by the study of simple model systems. For example, solid state and solution studies of compounds such as *cis*-PtL$_2$(purine-N7)$_2$ (where L$_2$ is a bidentate amine ligand and N7 indicates the coordination site), have provided insights into the nature of possible intrastrand crosslinkages. The *cis*-coordinated G(N7)–Pt–G(N7) intrastrand crosslinkage between two adjacent guanines on the same strand of DNA is widely regarded as being the major and possibly the critical lesion by which the cisplatinum drugs block DNA replication bringing about cell death [3].

The bulkiness of the coordinated amine L or L$_2$ and the exocyclic substituent(s) on the coordinated nucleobase(s) in the vicinity of the Pt atom binding site plays a major role in the formation and subsequent geometry of such interactions. Thus it has been previously demonstrated from X-ray analyses of model systems that the critical geometrical features of an intrastrand cross-linkage (as reflected in the base/base and base/coordination plane dihedral angles) are related to the nature and number of exocyclic substituents contiguous to the Pt atom binding site [4]. Furthermore, recent NMR studies of such systems strongly suggest that the preference of the cisplatinum drugs for the guanine residues in DNA has a steric basis [1]. It has also been recognized that, after an initial monofunctional attack on G(N7) by a cisplatinum moiety, rotation about the Pt-N7 bond, which is required to consolidate a potentially lethal intrastrand crosslinkage, can be hindered by the clash of substituents on the coordinated amine and nucleobase [5].

In the light of the above it is not surprising that the effectiveness of the cisplatinum drugs is strongly influenced by the nature of the amine ligand(s) L or L$_2$. For example, the cytotoxic activity of these

---

*Authors to whom correspondence should be addressed.

[#] New address: St. Vincent's Institute for Medical Research, 9 Princes St., Fitzroy, Vic. 3065, Australia.

0020-1693/88/$3.50

TABLE I. Crystallographic Data

Compound Formula	1 $[Pt(C_6N_2H_{16})(C_6N_5OH_7)_2]$-$(PF_6)_2 \cdot 2H_2O$	2 $[Pt(C_6N_2H_{16})(C_7N_5OH_9)_2]$-$(ClO_4)_2 \cdot 2H_2O$	3 $[Pt(C_6N_2H_{16})(C_7N_4O_2H_8)_2]$-$(PF_6)_2 \cdot 4H_2O$	4 $[Pt(C_6N_2H_{16})(C_8N_4O_2H_{10})_2]$-$(PF_6)_2 \cdot xH_2O$
M_r	967.56	900.58	1033.7	
Crystal system	monoclinic	orthorhombic	monoclinic	monoclinc
Space group	*Pn*	*Pbca*	*C2/c*	*C2/c*
a (Å)	10.675(1)	13.886(1)	37.557(4)	38.561(5)
b (Å)	12.970(1)	31.742(4)	12.215(2)	12.078(2)
c (Å)	12.016(1)	14.958(2)	15.823(3)	16.219(2)
α (°)	90	90	90	90
β (°)	97.05(1)	90	90.47(1)	97.88(1)
γ (°)	90	90	90	90
U (Å^3)	1651.1	6593.0	7258.7	7482.5
D_c (g cm^{-3})	1.946	1.814	1.892	
Z	2	8	8	8
Crystal dimensions (mm^3)	0.30 × 0.18 × 0.075	0.25 × 0.17 × 0.125	0.26 × 0.22 × 0.013	0.26 × 0.22 × 0.025
μ (cm^{-1})	43.39	47.06	42.67	41.3 ($x = 4$)
θ_{max} (°)	25.0	26.1	25.0	25.0
No of reflections collected	5417	6498	5842	1817
No used in refinement	3978	4054	3707	1817
No of variables	511	372	378	172
$R(F^2)$		0.068	0.101	
$R_w(F^2)$		0.087	0.117	
$R(F)$	0.020	0.045	0.059	0.092
$R_w(F)$	0.022			0.120
Max. shift/error final cycle	0.23	0.91	0.11	0.08

compounds is found to decrease along the series: $NH_3 \approx NH_2R > NHR_2 > NR_3$ [6]. This may be wholly or in part due to intramolecular steric effects.

The above considerations have led us to investigate by X-ray structural analysis the detailed geometries and flexibilities of a series of model systems involving the $[TMED]Pt^{2+}$ moiety, TMED being the bulky bidentate ligand tetramethylethylenediamine. The bulk on the coordinated purine bases has also been manipulated by varying the degree of alkylation. The crystal and molecular structures of four compounds have been determined and the molecules examined in terms of their relative base/base and base/coordination plane dihedral angles as part of a continuing program to investigate the role of steric factors in the binding of metal species to DNA.

Experimental

Reagents

A stock of $Pt(TMED)I_2$ was prepared from K_2PtCl_4 [7]. The K_2PtCl_4 was prepared from H_2PtCl_6 (May and Baker) by the method of Keller [8]. Nucleobases were purchased from Sigma; Me_2SO-d_6 was supplied by Aldrich. Common chemicals were obtained from other scientific supply houses.

Preparation of [Pt(TMED)B$_2$](Anion)$_2$, B = 9-MeG, 9-EtG, DMX or TMX

Four compounds were prepared from $Pt(TMED)I_2$ using established procedures for analogous systems [9]. Crystals suitable for X-ray analyses were obtained by evaporation from the following aqueous/DMF solutions: B = 9-MeG (counterion = PF_6^-, 5% DMF); B = 9-EtG (ClO_4^-, 10%); B = DMX (PF_6^-, 5%); B = TMX (PF_6^-, 20%). Approximate density measurements and preliminary X-ray data were consistent with the formulations $[Pt(TMED)B_2](anion)_2 \cdot xH_2O$ which were later confirmed by full X-ray analyses.

Crystallography

Data for unit cell dimensions and intensity data were collected at room temperature on a CAD-4 diffractometer using graphite-monochromated Mo Kα X-radiation. Crystal data and details of the data collection are summarised in Table I.

One unique set of data was collected for **1**, **2** and **3** and two quadrants for **4**. Three standard reflections were measured regularly during data collection and no significant variation in intensity of these standard reflections was observed. Absorption corrections were applied by Gaussian quadrature. All data with $F^2 > 0$ were included in the calculations. The structures were solved by a combination of Patterson and Fourier methods. For compound **1**, hydrogen atoms, other than those of the methyl group and the water molecules, were located in difference Fourier maps, but for the other compounds hydrogen atom positions could not be reliably found. The structures were refined by full-matrix least-squares techniques using blocks of parameters, minimising $\Sigma w \Delta F$ for **1** and **4** and $\Sigma w \Delta F^2$ for **2** and **3**.

For compound **1**, the parameters that were varied in the final refinement cycles included positional coordinates for all atoms, isotropic temperature factor coefficients for hydrogen atoms and anisotropic ones for all other atoms. For compounds **2** and **3**, the anions were constrained to have ideal stereochemistry with oxygen and fluorine atoms following chlorine and phosphorus respectively. Hydrogen atoms were placed in calculated positions and were constrained to follow the relevant carbon and nitrogen atoms. Individual isotropic temperature factor coefficients were refined for fluorine atoms, hydrogen atoms and oxygen atoms of perchlorate, with those of the hydrogen atoms further constrained so that those bonded to the same carbon atom had the same value. All other atoms were refined as for **1**. For compound **4**, the temperature factors of the platinum atom and the two phosphorus atoms were refined with anisotropic temperature factor coefficients while for carbon, nitrogen and oxygen atoms isotropic temperature factors were refined. Hydrogen and fluorine atoms were placed at calculated positions, but neither their positional coordinates nor their isotropic temperature factors were refined. Crystals of **4** were of much poorer quality than those of the other compounds and the data did not warrant a more detailed refinement. Scattering factors were taken from Cromer and Mann [10] for all atoms except hydrogen which were taken from Stewart, Davidson and Simpson [11]. Correction terms for anomalous scattering were taken from Cromer and Liberman [12]. Numerical details about the refinements are given in Table I. Computer programs of the XTAL package were used in the structure solution and refinement [13]. Atomic coordinates and equivalent isotropic temperature factors for the non-hydrogen atoms are listed in Table II.

^{1}H NMR Results

^{1}H NMR spectra obtained for crystals **1** and **2** were compared with the spectra for the free 9-MeG and 9-EtG ligands. All chemical shifts are in ppm from Me_4Si with Me_2SO as the solvent. For both complexes, the H8 proton shows the largest shift upon platination: 0.39 and 0.59 ppm downfield for **1** and **2** respectively. Downfield shifts of these magnitudes for the H8 proton have been observed for a number of related systems [9]. It is not clear, however, why such a large difference in magnitude exists between these two complexes. The $N2H_2$ exocyclic amino resonances for the uncomplexed

TABLE II. Atomic Coordinates and Isotropic or Equivalent Isotropic Temperature Factor Coefficients for 1, 2, 3 and 4

Atom	x	y	z	$1000U_{eq}$
$[Pt(TMED)(9\text{-}MeG)_2](PF_6)_2 \cdot 2H_2O$				
Pt	0	0.18980(1)	0	27
N11	−0.1502(4)	0.3469(4)	−0.3687(3)	43
C21	−0.2725(8)	0.3254(6)	−0.4127(7)	46
N21	−0.3095(6)	0.3655(7)	−0.5161(5)	66
N31	−0.3522(5)	0.2731(5)	−0.3594(4)	42
C41	−0.2996(6)	0.2391(5)	−0.2588(5)	35
C51	−0.1768(9)	0.2549(7)	−0.2095(8)	34
C61	−0.0928(7)	0.3134(5)	−0.2611(5)	37
O61	0.0184(5)	0.3357(4)	−0.2345(4)	49
N71	−0.1611(9)	0.2066(5)	−0.1051(9)	34
C81	−0.2734(5)	0.1632(4)	−0.0942(4)	34
N91	−0.3581(5)	0.1814(4)	−0.1857(4)	34
C91	−0.4923(5)	0.1502(5)	−0.1987(5)	48
N12	−0.1575(4)	−0.1626(3)	0.0259(3)	37
C22	−0.1213(7)	−0.2341(5)	−0.0464(5)	38
N22	−0.1702(7)	−0.3294(4)	−0.0394(6)	55
N32	−0.0441(4)	−0.2142(3)	−0.1215(3)	37
C42	−0.0071(6)	−0.1141(5)	−0.1190(5)	32
C52	−0.0390(6)	−0.0379(4)	−0.0482(5)	33
C62	−0.1220(5)	−0.0580(5)	0.0312(5)	32
O62	−0.1578(5)	−0.0002(4)	0.1000(4)	44
N72	0.0207(5)	0.0533(4)	−0.0763(4)	33
C82	0.0878(4)	0.0290(4)	−0.1582(4)	38
N92	0.0747(5)	−0.0730(4)	−0.1883(4)	37
C92	0.1408(6)	−0.1284(5)	−0.2681(4)	53
N1	0.1676(9)	0.1743(6)	0.1060(9)	40
N2	−0.0230(6)	0.3245(4)	0.0854(5)	39
C1	0.1816(9)	0.0710(7)	0.1589(7)	58
C2	0.2758(7)	0.1934(7)	0.0436(9)	70
C3	−0.1216(9)	0.3082(7)	0.1620(8)	67
C4	−0.0580(9)	0.4154(5)	0.0142(7)	63
C5	0.1638(6)	0.2512(6)	0.1982(5)	59
C6	0.1021(7)	0.3490(6)	0.1521(6)	58
P1	−0.0368(1)	0.1023(1)	0.4855(1)	36
F1	−0.0647(9)	0.2070(6)	0.4387(9)	192
F2	−0.1406(9)	0.1165(6)	0.5594(9)	186
F3	0.0709(9)	0.0829(7)	0.4128(7)	165
F4	−0.1273(6)	0.0430(6)	0.3974(7)	151
F5	0.0048(9)	−0.0070(5)	0.5364(6)	152
F6	0.0565(8)	0.1551(9)	0.5842(8)	133
P2	0.0108(2)	0.5530(1)	0.4490(1)	60
F7	−0.0646(9)	0.6071(8)	0.3539(8)	204
F8	−0.1001(9)	0.5589(6)	0.5244(9)	169
F9	0.1211(9)	0.5447(8)	0.3839(9)	206
F10	0.0904(9)	0.4998(9)	0.5496(8)	198
F11	0.0586(9)	0.6622(5)	0.4904(9)	150
F12	−0.0461(9)	0.4465(5)	0.4109(7)	152
Ow1	0.2482(7)	0.3026(7)	−0.3122(7)	96
Ow2	−0.5131(9)	0.4376(7)	0.2919(7)	136
$[Pt(TMED)(9\text{-}EtG)_2](ClO_4)_2 \cdot 2H_2O$				
Pt	0.01589(3)	0.11862(1)	0.20627(3)	35
N11	−0.1567(7)	0.2519(3)	0.1462(7)	53
C21	−0.099(1)	0.2875(4)	0.1252(9)	58
N21	−0.1473(9)	0.3241(3)	0.1106(8)	77
N31	−0.0055(8)	0.2862(3)	0.1197(7)	56
C41	0.0316(8)	0.2470(3)	0.1422(7)	44
C51	−0.0193(9)	0.2117(3)	0.1639(7)	41
C61	−0.1212(9)	0.2120(4)	0.1665(8)	49
O61	−0.1769(6)	0.1829(3)	0.1808(6)	69
N71	0.0461(6)	0.1794(3)	0.1790(5)	37
C81	0.1321(9)	0.1962(4)	0.1657(7)	48
N91	0.1254(7)	0.2374(3)	0.1438(7)	52
C91	0.204(1)	0.2673(4)	0.123(1)	102
C101	0.290(1)	0.2474(6)	0.090(1)	114
N12	0.2306(7)	0.0830(3)	−0.0479(5)	45
C22	0.1862(9)	0.0754(4)	−0.1276(8)	49
N22	0.2458(8)	0.0623(3)	−0.1957(6)	71
N32	0.0940(8)	0.0806(3)	−0.1428(6)	49
C42	0.0451(8)	0.0918(3)	−0.0684(7)	40
C52	0.0835(8)	0.0978(3)	0.0164(7)	41
C62	0.1837(8)	0.0958(4)	0.0299(8)	46
O62	0.2298(6)	0.1020(3)	0.0996(5)	64
N72	0.0072(7)	0.1090(2)	0.0741(6)	42
C82	−0.0700(9)	0.1101(3)	0.0256(7)	47
N92	−0.0506(7)	0.1002(3)	−0.0621(6)	49
C92	−0.1186(9)	0.0989(4)	−0.1386(8)	59
C102	−0.182(1)	0.1375(5)	−0.140(1)	106
N1	−0.0165(8)	0.0569(3)	0.2362(7)	55
N2	0.0250(7)	0.1273(3)	0.3413(6)	44
C1	0.035(1)	0.0252(4)	0.178(1)	103
C2	−0.123(1)	0.0485(4)	0.226(1)	86
C3	0.127(1)	0.1353(5)	0.3704(9)	76
C4	−0.034(1)	0.1639(4)	0.3750(8)	76
C5	0.011(1)	0.0496(4)	0.3309(9)	72
C6	−0.012(1)	0.0876(4)	0.3867(8)	62
C11	0.0849(3)	0.2902(1)	0.3789(2)	72
O1	−0.0041(3)	0.2868(1)	0.3247(2)	186
O2	0.1493(3)	0.3222(1)	0.3387(2)	168
O3	0.1346(3)	0.2489(1)	0.3807(2)	145
O4	0.0597(3)	0.3029(1)	0.4712(2)	198
C12	0.3036(2)	−0.0234(1)	0.0371(2)	69
O5	0.2765(2)	−0.0569(1)	−0.0270(2)	191
O6	0.3739(2)	0.0055(1)	−0.0051(2)	130
O7	0.3472(2)	−0.0427(1)	0.1177(2)	209
O8	0.2165(2)	0.0006(1)	0.0633(2)	273
Ow1	−0.0660(7)	0.4312(3)	0.1143(6)	90
Ow2	0.0668(9)	0.3703(3)	0.1775(8)	106
$[Pt(TMED)(1,3\text{-}DMX)_2](PF_6)_2 \cdot 4H_2O$				
Pt	0.09442(2)	0.20235(5)	0.00067(4)	45
N11	0.1056(5)	0.333(1)	0.3001(9)	81
C11	0.0863(7)	0.281(2)	0.371(1)	121
C21	0.1316(6)	0.413(2)	0.320(1)	85
O21	0.1367(5)	0.443(1)	0.3910(8)	117
N31	0.1494(4)	0.459(1)	0.2530(9)	66
C31	0.1766(6)	0.539(2)	0.267(1)	111
C41	0.1415(4)	0.419(1)	0.172(1)	57
C51	0.1184(4)	0.335(1)	0.1557(9)	47
C61	0.0987(5)	0.287(2)	0.219(1)	73
O61	0.0774(4)	0.210(1)	0.2106(8)	91
N71	0.1188(3)	0.319(1)	0.0682(7)	51
C81	0.1423(5)	0.391(1)	0.039(1)	62
N91	0.1557(3)	0.454(1)	0.0987(9)	58

(continued)

TABLE II. *(continued)*

Atom	x	y	z	$1000U_{eq}$
N12	0.2232(4)	0.144(1)	−0.0565(9)	68
C12	0.2431(5)	0.198(2)	−0.125(1)	90
C22	0.2423(6)	0.069(2)	−0.006(1)	72
O22	0.2742(4)	0.057(1)	−0.015(1)	115
N32	0.2236(4)	0.013(1)	0.0540(9)	70
C32	0.2417(5)	−0.070(2)	0.103(1)	97
C42	0.1884(5)	0.035(1)	0.062(1)	56
C52	0.1694(4)	0.104(1)	0.0140(9)	52
C62	0.1964(5)	0.165(1)	−0.054(1)	51
O62	0.1721(3)	0.225(1)	−0.1048(7)	65
N72	0.1344(3)	0.103(1)	0.0384(7)	50
C82	0.1330(5)	0.033(1)	0.101(1)	61
N92	0.1656(4)	−0.015(1)	0.1153(9)	62
N1	0.0701(4)	0.086(1)	−0.0739(8)	59
N2	0.0532(3)	0.302(1)	−0.0376(9)	62
C1	0.0978(7)	0.038(2)	−0.137(1)	116
C2	0.0572(6)	−0.011(2)	−0.026(1)	100
C3	0.0637(6)	0.398(2)	−0.087(2)	131
C4	0.0326(6)	0.339(2)	0.039(2)	132
C5	0.0389(8)	0.137(3)	−0.112(2)	146
C6	0.0290(8)	0.239(2)	−0.090(2)	168
P1	0.0756(1)	0.7024(5)	0.1339(3)	99
F1	0.0997(1)	0.6813(5)	0.2147(3)	144
F2	0.0874(1)	0.5881(5)	0.0965(3)	267
F3	0.0516(1)	0.7235(5)	0.0531(3)	155
F4	0.0639(1)	0.8168(5)	0.1713(3)	262
F5	0.1081(1)	0.7593(5)	0.0886(3)	223
F6	0.0431(1)	0.6456(5)	0.1791(3)	224
P2	0.1985(1)	−0.1508(4)	−0.1764(3)	93
F7	0.2320(1)	−0.1435(4)	−0.1154(3)	223
F8	0.2045(1)	−0.2782(4)	−0.1860(3)	185
F9	0.1650(1)	−0.1581(4)	−0.2373(3)	207
F10	0.1924(1)	−0.0234(4)	−0.1667(3)	220
F11	0.2232(1)	−0.1295(4)	−0.2550(3)	250
F12	0.1737(1)	−0.1721(4)	−0.0978(3)	328
Ow1	0.1869(5)	0.657(1)	0.062(1)	145
Ow2	0.1705(5)	−0.183(1)	0.2216(9)	130
Ow3	0.0205(7)	0.079(2)	0.176(1)	246
Ow4^a	0	0.44(1)	0	399
[Pt(TMED)(1,3,9-TMX)$_2$](PF$_6$)$_2$·xH$_2$O				
Pt	0.09996(5)	0.2049(2)	−0.0363(1)	38^b
N11	0.115(1)	0.335(3)	0.255(2)	58(12)
C11	0.102(2)	0.283(5)	0.329(4)	94(19)
C21	0.137(1)	0.421(4)	0.278(3)	58(14)
O21	0.1417(9)	0.452(3)	0.355(2)	79(11)
N31	0.1517(9)	0.469(3)	0.223(2)	39(9)
C31	0.175(1)	0.563(4)	0.249(3)	56(14)
C41	0.143(1)	0.433(3)	0.144(3)	42(12)
C51	0.126(1)	0.341(3)	0.124(2)	25(10)
C61	0.111(1)	0.283(4)	0.178(3)	54(13)
O61	0.0916(8)	0.197(3)	0.167(2)	65(9)
N71	0.1239(9)	0.324(3)	0.040(2)	50(11)
C81	0.143(1)	0.404(4)	0.015(3)	44(13)
N91	0.1544(9)	0.475(3)	0.075(2)	37(9)
C91	0.175(1)	0.581(4)	0.056(3)	47(13)
N12	0.221(1)	0.157(3)	−0.065(2)	53(11)
C12	0.239(1)	0.216(4)	−0.129(3)	58(13)
C22	0.245(1)	0.093(4)	−0.016(3)	66(16)
O22	0.225(1)	0.082(3)	0.014(2)	88(12)
N32	0.228(1)	0.020(3)	0.043(2)	55(11)
C32	0.252(1)	−0.056(5)	0.088(3)	78(17)
C42	0.193(1)	0.036(3)	0.046(3)	38(12)
C52	0.175(1)	0.103(3)	−0.008(3)	33(11)
C62	0.187(1)	0.168(3)	−0.068(3)	42(13)
O62	0.1708(8)	0.227(3)	−0.125(2)	62(9)
N72	0.1400(8)	0.103(3)	0.011(2)	35(9)
C82	0.140(1)	0.032(4)	0.072(3)	43(12)
N92	0.172(1)	−0.014(3)	0.092(2)	47(11)
C92	0.178(1)	−0.100(4)	0.155(3)	67(16)
N1	0.076(1)	0.090(3)	−0.112(2)	52(11)
N2	0.060(1)	0.307(4)	−0.083(2)	63(11)
C1	0.096(2)	0.056(5)	−0.170(4)	103(22)
C2	0.067(1)	−0.009(5)	−0.076(4)	78(18)
C3	0.044(2)	0.363(6)	−0.021(4)	116(23)
C4	0.072(1)	0.385(5)	−0.143(4)	82(18)
C5	0.048(2)	0.141(6)	−0.174(4)	96(20)
C6	0.039(2)	0.221(8)	−0.137(6)	161(33)
P1	0.0729(3)	0.707(2)	0.0872(9)	63^b
F1	0.048	0.734	0.000	127
F2	0.054	0.803	0.127	127
F3	0.101	0.702	0.167	127
F4	0.043	0.678	0.129	127
F5	0.103	0.778	0.043	127
F6	0.102	0.648	0.020	127
P2	0.2091(5)	−0.160(1)	−0.188(1)	63^b
F7	0.170	−0.121	−0.214	127
F8	0.194	−0.203	−0.103	127
F9	0.250	−0.206	−0.180	127
F10	0.201	−0.278	−0.205	127
F11	0.216	−0.144	−0.280	127
F12	0.213	−0.040	−0.162	127

^{a}Occupancy factor for Ow4 = 0.36(8). $^b U_{eq}$.

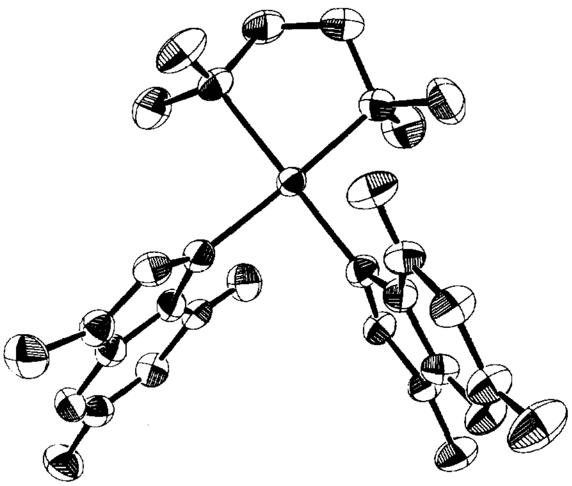

Fig. 1. The [(TMED)Pt(9-MeG)$_2$]$^{2+}$ cation showing thermal ellipsoids plotted at the 50% probability level.

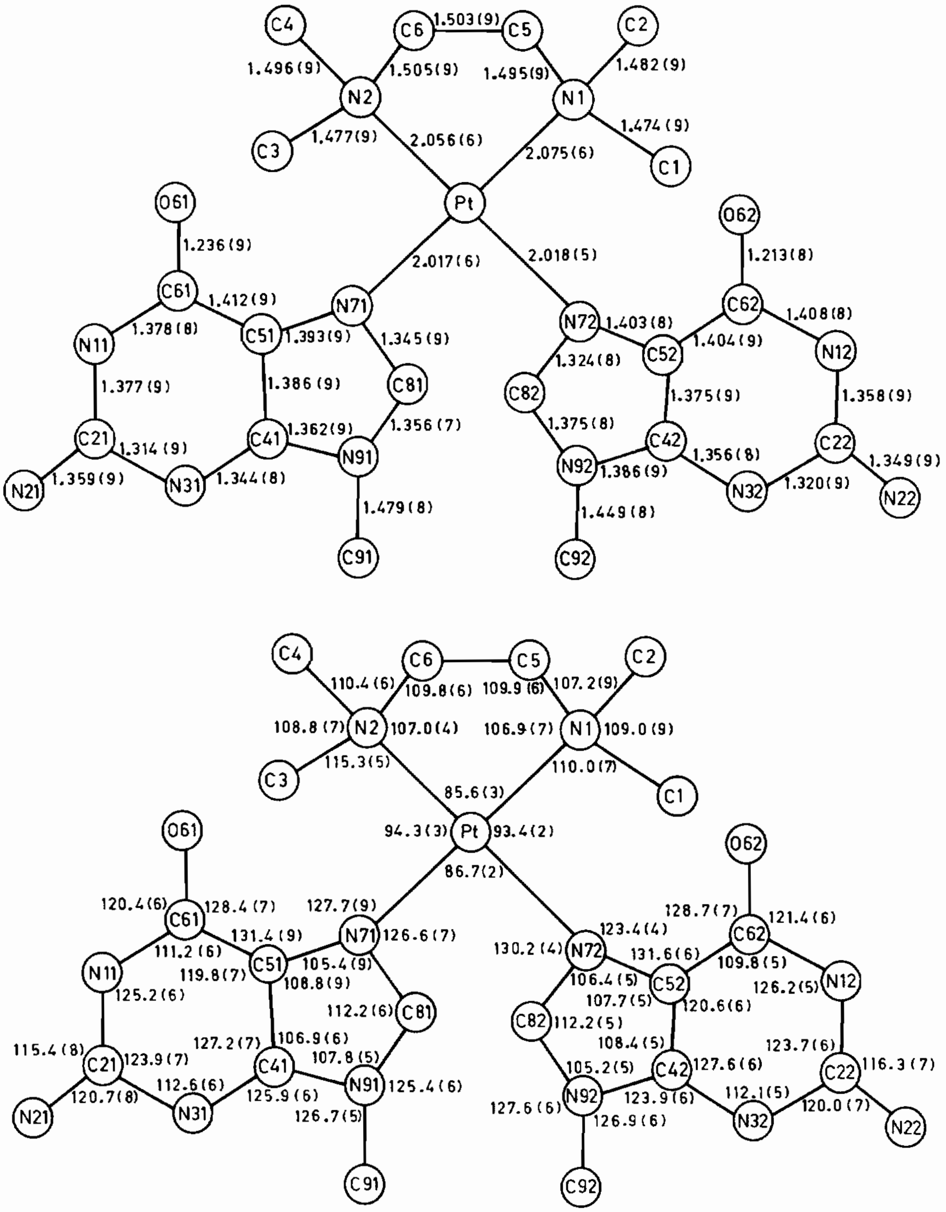

Fig. 2. Interatomic distances (Å) and angles (°) in the cation of **1**. Angles not shown above are Pt–N1–C2 = 112.7(7), C1–N1–C5 = 111.0(9), Pt–N2–C4 = 108.8(5), C3–N2–C6 = 106.6(6)°. Estimated standard deviations are in parentheses.

ligands are broad singlets indicating free rotation about the N2–C2 bond on the NMR time scale. It is noteworthy that for both complexes the NH_2 resonances are shifted markedly downfield (0.29 and 0.39 ppm for **1** and **2**, respectively), even though this group is remote from the N7 binding site. An even larger downfield shift of 0.99 ppm has been observed for the NH_2 resonance of *cis*-$[Pt(NH_3)_2(3\text{-}MeA)_2]^{2+}$ [14], but in this case the amino groups are much closer to the coordination site and are in the vicinity of the filled d_{z^2} orbital normal to the coordination plane. Consistent with data available for other alkylated bases [9], only small shifts are observed for the protons of the 9-CH_3 and 9-C_2H_5 groups upon platination.

Results and Discussion

The Molecular Geometries of the (TMED)PtB$_2$$^{2+}$ Cations

The cation of **1** is shown in Fig. 1 and is representative in its general features of the cations of **2**, **3** and **4**. Bond lengths and angles for the cation of **1** are

TABLE III. Bond Lengths (Å) and Angles (deg) in the Pt Coordination Plane

	1	2	3	4
Pt–N1	2.075(6)	2.061(9)	2.06(1)	2.00(4)
Pt–N2	2.056(6)	2.043(9)	2.05(1)	2.03(4)
Pt–N71	2.017(6)	2.017(8)	2.00(1)	2.03(3)
Pt–N72	2.018(8)	2.004(9)	2.02(1)	2.03(3)
N1–Pt–N2	85.6(3)	85.8(4)	84.9(5)	86(1)
N2–Pt–N71	94.3(3)	93.3(3)	94.5(5)	93(1)
N71–Pt–N72	86.7(2)	87.6(3)	86.2(5)	86(1)
N72–Pt–N1	93.4(2)	93.3(3)	94.4(5)	94(1)

TABLE IV. Data for some Intramolecular Contacts in the Cations

Compound	Pt···O61 (Å)	Pt···O62 (Å)	Δ_1 (deg)[a]	Δ_2 (deg)[b]
1	3.420(5)	3.294(5)	1.1(9)	−6.8(6)
2	3.387(8)	3.412(8)	−0.1(7)	−0.2(7)
3	3.39(1)	3.39(1)	3(1)	2(1)

[a] Δ_1 = (Pt–N71–C51) – (Pt–N71–C81). [b] Δ_2 = (Pt–N72–C52) – (Pt–N72–C82).

shown in Fig. 2. Figure 2 also defines the labelling of the atoms of the complex cations. The substituents of **2**, **3** and **4** not included in this diagram, are given their conventional numbering. In all of the structures, the coordination geometry about Pt(II) is planar within experimental error; the four equatorial positions are occupied by the nitrogen atoms of the two *cis*-bound purine bases (labelled N71 and N72) and the nitrogen atoms of the bidentate TMED ligand (N1 and N2). In each case the two coordinated nucleobases are arranged in a head-to-tail fashion such that the cation possesses approximate C_2 molecular symmetry. Bond lengths and angles for the PtN_4 coordination planes are listed in Table III and are typical of those reported in related systems [9]. It is evident from the data in Table II that the atomic coordinates in **1** were determined with significantly higher precision than those in **2**, **3** and **4**; therefore the bond lengths and angles of the latter three structures are not presented in detail. For the most part, bond lengths and angles in the nucleobases and the TMED ligand of complexes **1**–**4** have expected values within experimental error. Comments on several unusual bond lengths and angles in **3** and **4** will be reserved until these structures have been refined using improved data; the crystals used in the present study were very thin and of marginal quality.

The Pt···O6 distances for complexes **1**–**3** are given in Table IV. For related systems this distance is typically in the range 3.37–3.49 Å and no significant participation of the 6-oxo group in metal binding is suggested [9]. However, many 6-oxopurine complexes are stabilized by interligand hydrogen bonding between the 6-oxo group and a coordinated primary amine which pulls the O6 atom away from the filled d_{z^2} orbital of the platinum. For the compounds studied here, such interligand hydrogen bonding is not possible and these systems are more conducive to the formation of a Pt···O6 interaction. In this regard, an interesting feature of **1** is the difference between the two Pt···O6 intramolecular distances. While the Pt···O61 distance of 3.420(5) Å is consistent with those previously reported, the Pt···O62 distance of 3.294(5) is significantly shorter and may be indicative of the onset of chelation for this ligand. To our knowledge, this is the shortest such distance reported to date. The magnitude of the distance is reflected in the considerable asymmetry of the exocyclic bond angles at N71 (Table IV).

It is interesting to note in **1** and **2** that the distances of closest approach of the oxo-substituents to the methyl groups of the TMED ligands (O61··· C4, 3.17 Å, O62···C1, 3.72 Å in **1** and 3.57 Å, 3.83 Å in **2**) are significantly different, and in **1** in particular, that O62 is closer to platinum and further away from a methyl group than O61. The distortion of the 5-membered ring formed by platinum coordination to TMED in **1** and **2** is such that the methylene groups (C5 and C6) are on opposite sides of the plane defined by N1, Pt and N2. The effect of the distortion is to create an asymmetry in the two sets of methyl groups covalently bonded to N1 and N2; thus C4 is pitched towards O61. It is a feature of these structures that the bases are arranged in the head-to-tail conformation. This is opposite to what one would expect on the basis of the least amount of steric interaction between the O6's and the TMED methyl groups. However, the possibility of weak C(methyl)–H···O attraction should be considered. For the cation of **1**, it may be that O62 affords a possible interaction with platinum, albeit weak, at the expense of an O6–methyl interaction.

In **3** the Pt···O6(1,2) interatomic distances are identical and C5 and C6 are less than two standard deviations from the least-squares PtN_4 plane. This extra symmetry may be more apparent than real however, because the carbon atoms of TMED in this structure all show very high apparent thermal motion. It may be that these results are an average of the two extreme puckered conformations. Unfortunately, the structures for **3** (and **4**) are not accurate enough to allow meaningful comment on their Pt···O6 distances.

Crystal Structures

The unit cell contents of **1**, **2** and **3** are shown as stereopairs in Figs. 3, 4 and 5. The structure of **4** is closely related to **3** and is not reproduced here.

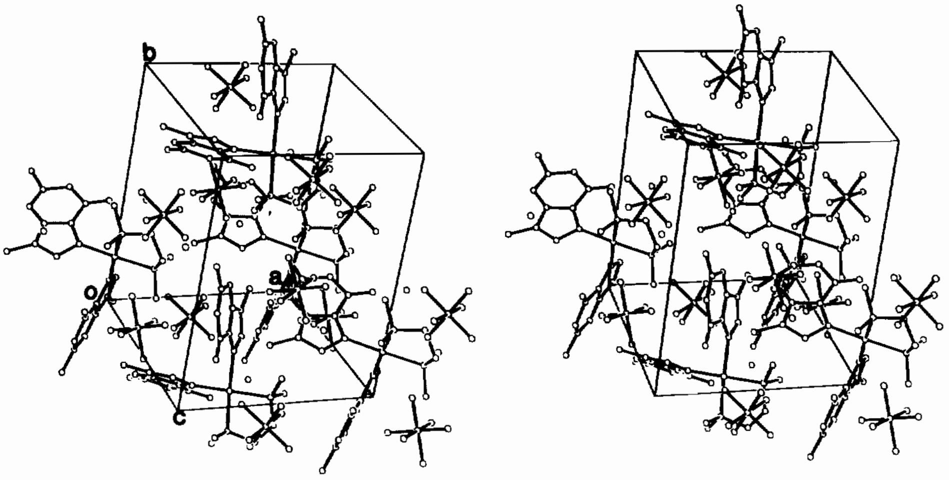

Fig. 3. Stereoscopic diagram of the crystal structure of 1 showing the unit cell outline.

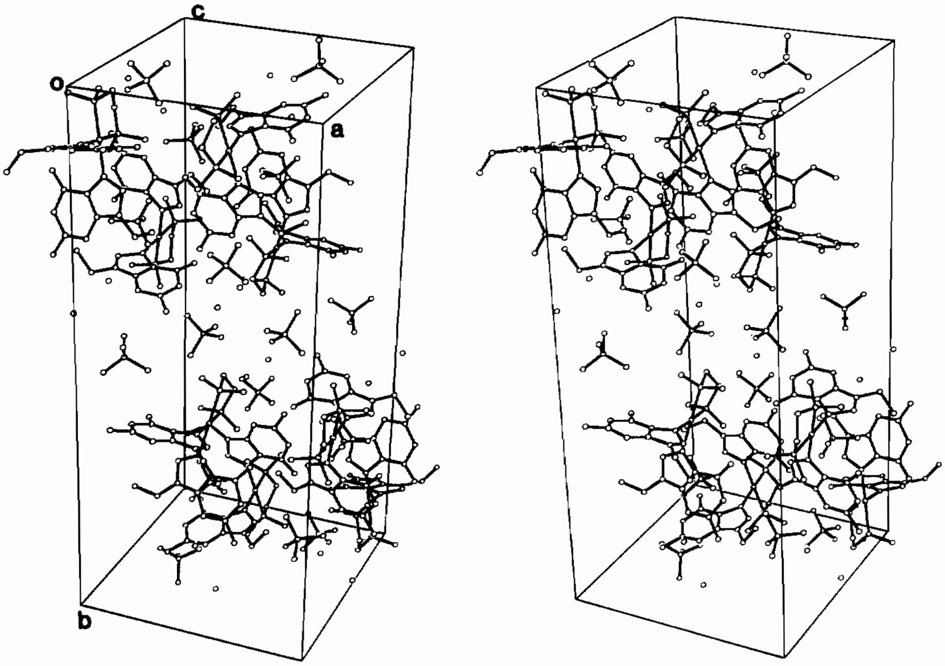

Fig. 4. Stereoscopic diagram of the crystal structure of 2 showing the unit cell outline.

In the structure of **1**, layers of cations and one of the PF_6^- anions (P2) extend perpendicular to *b* and close to the glide plane (Fig. 3). This PF_6^- anion is positioned between the nucleobases of the same cation. These layers are indispersed with layers of the second PF_6^- anion. There is no intermolecular base stacking in this structure. Water molecules link cations and anions by hydrogen bonds, *viz.* Ow1 forms donor hydrogen bonds to O61 and F7 and acceptor ones from N12 and N22 [2.76(1), 2.89(2), 2.93(1), 2.99(1) Å, respectively] in a quasi-tetrahedral arrangement, while Ow2 is more loosely held in hydrogen bonds with O61, N21 and N22 [2.98(1), 3.11(1), 3.11(1) Å] and an ill-defined interaction with fluorine atoms of P1. There is no hydrogen bond to O62. The remaining acidic proton in the structure, that on N11, appears to be involved in a weak bifurcated interaction with F10 and F12.

In the structure of **2**, the layers perpendicular to *b* containing cations and one anion also predominate, and they are much more clearly defined than in **1** (Fig. 4). The perchlorate anion within these layers is centrally positioned in the 'jaws' of the cation. The second perchlorate anion and the two water molecules link layers together near $b = 1/2$. Again there is no intermolecular base–base interaction.

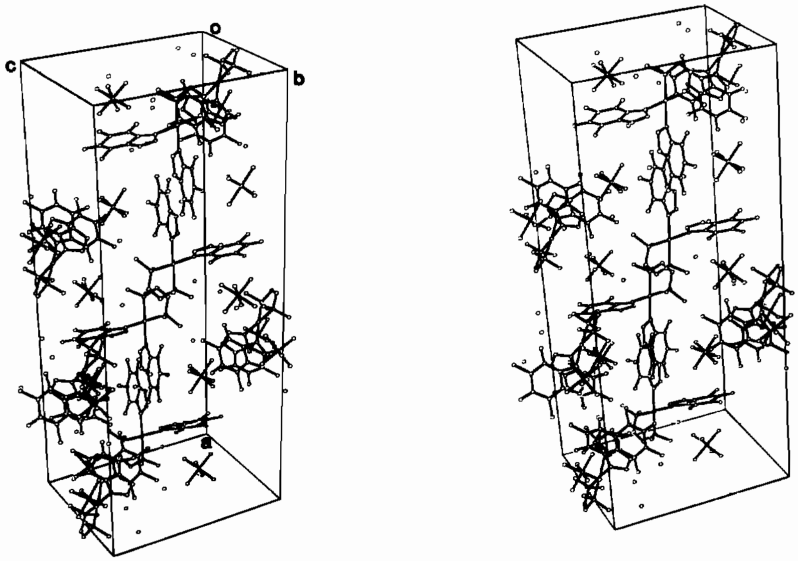

Fig. 5. Stereoscopic diagram of the crystal structure of **3** showing the unit cell outline.

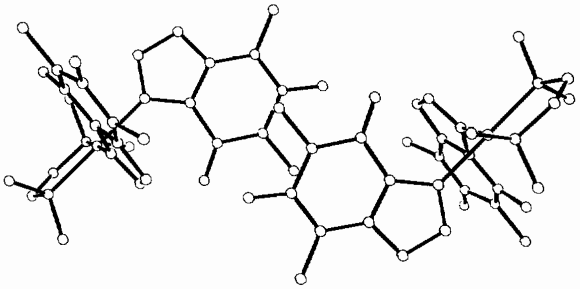

Fig. 6. Intermolecular base stacking in **3** about a centre of symmetry. The view is normal to the base planes.

There is a hydrogen bond between the two water molecules [Ow1–Ow2, 2.75(2) Å]. Ow1 completes a quasitetrahedral arrangement by hydrogen bonding to O6 [2.72(1) Å], and N12 and N22 of the same molecule [3.03(1) and 2.89(1) Å]. Ow2 is less securely held with only one other contact less than 3.15 Å *i.e.* to N31 [2.93(1) Å].

In the structures of **3** and **4** (Fig. 5) the layers are much less pronounced and a small amount of intermolecular base–base stacking occurs. This overlap (Fig. 6) occurs about a centre of symmetry and arises from the nucleobase numbered 2 moving into the 'jaws' of the cation and partially displacing the anion found there in **1** and **2**. The perpendicular distance between the planes is 3.55 Å for **3** and 3.35 Å for **4**. The base overlap is greater in **4** than in **3** with N12 completely overlying C22. DMX has only one proton capable of taking part in hydrogen bonding, consequently there is more water of hydration in **3** providing a solvation sheath around the PF_6^- anions. Both N91 and N92 make strong hydrogen bonds to water molecules [N91–Ow1, 2.80(2) and N92–Ow2, 2.67(2) Å]. The carbonyl oxygen atoms O21 and O22 do not take part in hydrogen bonding, while O61 and O62 make one strong bond each [O61–Ow3, 2.72(3) and O62–Ow2, 2.79(3) Å]. The high thermal motion of the water molecules indicates that they are loosely held in the structure. The extreme of this is Ow4, which appears to have a partially occupied site (Table II). No water molecules could be unequivocally located in **4**. There were many peaks that appeared to represent partially occupied water sites associated with grossly disordered PF_6^- anions.

The Relative Conformations of the Cations

The conformational parameters of interest are the base/base and base/coordination plane dihedral angles, B/B′ and B,B′/PtN_4, respectively. Adopting a previously described convention [4], a compendium of these parameters for the four compounds is given in Table V. When several model systems are compared the B/B′ and B,B′/PtN_4 parameters probe the possible geometries and flexibilities of intra-

TABLE V. Base/Base and Base/PtN_4 Coordination Plane Dihedral Angles (deg)[a]

Compound	Base/Base	Base/Coordination plane	
1	81.3(2)	94.2(2)	85.8(2)
2	87.9(3)	92.6(2)	94.1(2)
3	74.0(4)	83.7(4)	77.6(4)
4	78(1)	78(1)	78(1)

[a] The convention used to define these angles is given in ref. 4.

strand cross-linkages which may form between the various cisplatinum derivatives and adjacent bases on a strand of DNA [4, 9]. The cisplatinum derivatives reported here contain the bidentate tertiary amine TMED. Ligands of this kind cause the drug to be ineffective, although from a consideration of simple model systems the formation of an intrastrand cross-linkage is still feasible, at least with the bases arranged in a head-to-tail configuration.

For head-to-tail model systems which contain 6-oxopurines and primary amines, the B/B′ and B,B′/PtN_4 dihedral angles have been found to be highly variable [9]. In particular, these parameters can be markedly influenced by different crystalline environments. This points to a large degree of flexibility in these systems. One would expect the TMED complexes reported here to be less flexible due to the bulk on the coordinated amine.

It is convenient to divide the four sets of dihedral angles presented in Table V into two groups; **1** and **2**, and **3** and **4**. Those in **1** and **2** are close to 90° and are not unexpected given the steric bulk of the TMED ligand and that intramolecular hydrogen bonding between the exocyclic O6 atom and the amine is precluded. As in previously reported nucleobase systems, the dihedral angles are typically large (>80°).

For **3** and **4** the dihedral angles of the cations are more characteristic of nucleoside-containing model systems [9], and like these systems the relative orientation of the base ligands suggests some intramolecular base/base interaction (Fig. 5). We are currently attempting to grow crystals of the TMED model system with *cis*-coordinated nucleosides or nucleotides to investigate whether smaller dihedral angles and be accommodated as in the corresponding primary amine systems [9], and if so, whether an obvious distortion can be identified.

Supplementary Material

Tables of F_o *versus* F_c, and hydrogen atom coordinates are available from the authors (M.R.T.) on request.

Acknowledgements

The authors gratefully acknowledge the help and support of the members of the crystallographic laboratories at I.C.R. Part of this research was supported by an American Cancer Society Grant BC-242.

References

1 M. D. Reilly and L. G. Marzilli, *J. Am. Chem. Soc., 108,* 6785 (1986).
2 R. Rawls, *Chem. Eng. News*, Oct. 6, 21 (1986).
3 S. E. Sherman, D. Gibson, A. H.-J. Wang and S. J. Lippard, *Science, 230,* 412 (1985).
4 J. D. Orbell, L. G. Marzilli and T. J. Kistenmacher, *J. Am. Chem. Soc., 103,* 5126 (1981).
5 A. T. M. Marcelis, J. L. Van der Veer, J. C. M. Zwetsloot and J. Reedijk, *Inorg. Chim. Acta, 78,* 195 (1983).
6 K. P. Beaumont, C. A. McAuliffe and M. J. Clare, *Chem.-Biol. Interact., 14,* 179 (1976).
7 S. C. Dhara, *Indian J. Chem., 8,* 193 (1970).
8 R. N. Keller, *Inorg. Synth., 2,* 246 (1946).
9 J. D. Orbell, K. Wilkowski, B. de Castro and L. G. Marzilli, *Inorg. Chem., 21,* 813 (1982).
10 D. T. Cromer and J. B. Mann, *Acta Crystallogr., Sect. A, 24,* 321 (1968).
11 R. F. Stewart, E. R. Davidson and W. T. Simpson, *J. Chem. Phys., 42,* 3175 (1965).
12 D. T. Cromer and D. Liberman, *J. Chem. Phys., 53,* 1891 (1970).
13 J. M. Stewart and S. R. Hall, 'The XTAL System of Crystallographic Programs', University of Maryland, 1986.
14 J. D. Orbell, C. Solorzano, L. G. Marzilli and T. J. Kistenmacher, *Inorg. Chem., 21,* 2630 (1982).