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Platinum(II) Binding to N7 and N1 of Guanine and a Model for a Purine-N^1,Pyrimidine-N^3 Cross-Link of Cisplatin in the Interior of a DNA Duplex

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The preparation and X-ray structures of two dinuclear complexes **4** and **5**, derived from $[(\mathrm{dien})\mathrm{Pt}(\mathrm{GH}\text{-}N^7)]^{2+}$ (**1**), containing the 9-methylguanine anion G (**4**, **5**) and deprotonated 1-methyluracil U (**5**) are reported. $\{[(\mathrm{dien})\mathrm{Pt}]_2(\mathrm{G}\text{-}N^7,N^1)\}(\mathrm{ClO_4})_3\cdot 2\mathrm{H_2O}$ (**4**) and *cis*-$[(\mathrm{NH_3})_2\mathrm{Pt}(\mathrm{U}\text{-}N^3)(\mathrm{G}\text{-}N^1,N^7)\mathrm{Pt}(\mathrm{dien})](\mathrm{ClO_4})_2\cdot 2.5\mathrm{H_2O}$ (**5**) crystallize in the monoclinic (**4**) and triclinic (**5**) systems, space groups $C2/c$ (**4**) and $P\bar{1}$ (**5**). Cell dimensions are $a = 32.494$ (5) Å (**4**), 8.504 (3) Å (**5**), $b = 17.052$ (3) Å (**4**), 13.466 (3) Å (**5**), $c = 11.507$ (2) Å (**4**), 15.736 (3) Å (**5**), $\alpha = 104.34$ (2)° (**5**), $\beta = 104.65$ (3)° (**4**), 108.66 (2)° (**5**), $\gamma = 102.48$ (2)° (**5**), $V = 6168.5$ Å^3 (**4**), 1566.1 Å^3 (**5**), and $Z = 8$ (**4**), 2 (**5**). In both cations, a (dien)$\mathrm{Pt^{II}}$ entity is coordinated to the guanine via N7, whereas the N1 position is either occupied by a (dien)$\mathrm{Pt^{II}}$ (**4**) or a *cis*-$(\mathrm{NH_3})_2\mathrm{Pt(U)}$ (**5**) residue. Coordination of the Pt at N1 takes place from **1** under virtually physiological pH conditions. Compound **5** represents the first example of a hypothetical DNA cross-link of cisplatin with N1 of a purine and N3 of a pyrimidine, two sites normally in the interior of a DNA double helix. Both nucleobases adopt a head–head orientation, thus making **5** a realistic model of a guanine, thymine cross-link. The large dihedral angle of 102° between the two bases and the long separation of 9.5 Å between the alkyl groups of both bases point toward a DNA distortion, which, if realized, should exceed that of the well-known G,G adduct at the DNA periphery by far. In slightly acidic medium, **1** interacts with $\mathrm{Ag^+}$ without deprotonation at N1 but rather $\mathrm{Ag^+}$ binding to N3.

The N7 positions of the purine nucleobases guanine (G) and adenine (A) in the major groove of B-DNA represent the preferred binding sites of *cis*-$(\mathrm{NH_3})_2\mathrm{PtCl_2}$, *cis*-DDP.[2] Simultaneous coordination to two G-N^7 sites of one DNA strand (intrastrand G,G cross-link) occurs most frequently. Models of this type of interaction are available.[3-6] The consequence of this adduct is a severe distortion (kinking) of DNA,[7] possibly related to the mode of action of *cis*-DDP as an antitumor agent. Other established *cis*-DDP–DNA adducts result from AG intrastrand cross-linking, GXG binding (X = base other than G), G,G interstrand crosslinking, monofunctional binding to a single G, and DNA–protein cross-linking of unspecified type.[8] The distribution of these adducts depends to some extent on reaction conditions such as Pt concentration, reaction time, presence of other ions or ligands, etc. There is some indirect evidence that additional minor adducts of yet unknown biological relevance may be formed.[9] Moreover, there appears to be a good chance that as a result of systematic DNA binding studies with Pt coordination compounds other than *cis*-$(\mathrm{NH_3})_2\mathrm{PtCl_2}$, with a more detailed understanding of the effects of base sequence and local DNA structure on Pt binding,[10] as well as additional studies in synergistic binding patterns of Pt(II) and other drugs,[11] the number of types of cross-links eventually will grow further.

As part of a systematic study of models of potential DNA cross-linking adducts of *cis*-DDP, we have in the past prepared and structurally (by X-ray) characterized the following combinations: (i) purine-N^7,purine-N^7, G,G;[6] (ii) pyrimidine-N^3,pyrimidine-N^3,[12] C,C,[13] U,U,[14] T,T,[15] U,C;[16] (iii) purine-N^7,pyrimidine-N^3, G,C,[17] G,U,[18] A,C,[19] A,T.[20] The latter type of adducts could, in principle, form in DNA via an anti → syn conformational change of the purine nucleobase *or* the pyrimidine base with the Pt metal then located either in the helix interior or at the helix periphery. In this paper, we describe the preparation of yet another cross-linking model (iv), viz. between a purine-N^1 and a pyrimidine-N^3 site, likely to be formed only in the interior of a DNA double helix, either in an intrastrand or an interstrand fashion.

The formation of this model cross-link is of some interest chemically because it involves an initial Pt(II) coordination at N7 of guanine, which makes the N1 position subsequently available for platination at virtually biological pH.[21-23] The proposal[24] that *cis*-DDP, after partial denaturation of DNA, could possibly cross-link two DNA strands is based on this chemistry. Formation of N7,N1-diplatinated guanine complexes has been observed in

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several cases,[21,22,25-28] but the products have never been isolated and characterized structurally. Structural data is available, however, for several complexes of Pt(II) with 7,9-dimethylhypoxanthine, a related 6-oxopurine, where metal binding is through N1, since N7 is blocked.[29]

As far as steric considerations concerning a local distortion of DNA caused by a purine-N^1,pyrimidine-N^3 cross-link are concerned, it has been predicted[30] that it would be more severe than that of a purine-N^7,purine-N^7 adduct. Our title compound provided an example to check this prediction, especially since the two bases adopt the proper head-to-head orientation to be expected in a real cross-link of this type in DNA.

Experimental Section

Starting Materials. [(dien)PtI]I,[31] *cis*-(NH$_3$)$_2$PtCl$_2$,[32] *cis*-(NH$_3$)$_2$Pt(1-MeU)$_2$·4H$_2$O,[33] and *cis*-(NH$_3$)$_2$Pt(1-MeU)Cl·H$_2$O[34] were prepared as previously described. 9-Methylguanine (9-MeGH, GH) was purchased from Chemogen, Konstanz, FRG, and 1-methyluracil (1-MeUH, UH) was prepared in a slightly modified version of a published procedure.[35]

Preparation of Compounds. [(dien)Pt(GH-N^7)](ClO$_4$)$_2$ (**1**) was prepared by mixing an aqueous suspension of [(dien)PtI]I (1 mmol in 15 mL of H$_2$O) and an aqueous solution of AgClO$_4$ (1.96 mmol in 10 mL of H$_2$O), stirring it for 5 h at 50 °C, filtering off AgI, and combining the clear solution (pH 3) with solid GH (0.95 mmol). After 8 h at 50 °C, the resulting solution was concentrated by rotary evaporation to a volume of 8 mL and allowed to crystallize at 3 °C. A mixture of colorless needles and colorless cubes (apparently two modifications of **1**) was obtained in 95% yield. Anal. Calcd for $C_{10}H_{20}N_8O_9Cl_2Pt$: C, 18.13; H, 3.04; N, 16.92. Found: C, 18.35; H, 3.03; N, 16.87.

[(dien)Pt(G-N^7)]ClO$_4$·2H$_2$O (**2**) was prepared as follows: An aqueous solution of **1** (0.5 mmol in 10 mL of H$_2$O) was brought to pH $\simeq$ 11.5 by adding 0.1 N NaOH and the solution evaporated to 5 mL and crystallized at 3 °C in a stoppered flask. White needles of **2** were obtained in 74% yield. Anal. Calcd for $C_{10}H_{23}N_8O_7ClPt$: C, 20.08; H, 3.88; N, 18.74; Cl, 5.93. Found: C, 19.8; H, 4.0; N, 18.4; Cl, 6.28.

{[(dien)Pt(GH-N^7)]$_2$Ag}(ClO$_4$)$_5$·4H$_2$O (**3**) was isolated as thin, colorless plates in 65% yield on crystallization of **1** (0.1 mmol) from a 0.2 N solution of AgClO$_4$ in H$_2$O. Anal. Calcd for $C_{20}H_{48}N_{16}O_{26}Cl_5Pt_2Ag$: C, 14.96; H, 3.01; N, 13.97; Ag, 6.72. Found: C, 15.0; H, 3.0; N, 14.3; Ag, 6.99.

{[(dien)Pt]$_2$(G-N^7,N^1)}(ClO$_4$)$_3$·2H$_2$O (**4**) was prepared by adding 1 equiv of NaOH and **1** each to an aqueous solution of [(dien)Pt(H$_2$O)](ClO$_4$)$_2$ (1 mmol in 40 mL of H$_2$O, prepared as with **1**) and keeping the solution (pH $\simeq$ 6.5) for 22 h at 50 °C and 9 h at 70 °C. After the solution was concentrated to 10 mL, a crude, yellow product was isolated, which, on recrystallization from water, gave **4** as colorless cubes in 54% yield. Anal. Calcd for $C_{14}H_{36}N_{11}O_{15}Cl_3Pt_2$: C, 15.36; H, 3.31; N, 14.07; Cl, 9.71. Found: C, 15.52; H, 3.16; N, 14.37; Cl, 9.82.

cis-[(NH$_3$)$_2$Pt(U-N^3)(G-N^1,N^7)Pt(dien)](ClO$_4$)$_2$·2.5H$_2$O (**5**) was prepared in the following way: A solution of *cis*-(NH$_3$)$_2$Pt(U-N^3)Cl·H$_2$O (0.5 mmol in 20 mL of H$_2$O) was converted to the aqua complex (0.48 mmol of AgClO$_4$, 48 h at 20 °C), AgCl was filtered off, and NaOH (0.5 mmol) and **1** (0.5 mmol) were added. The mixture (pH $\simeq$ 7.5) was kept at 70 °C for 3 days, filtered, evaporated to a 3-mL volume, and passed over a Sephadex G10 column. A mixture of **5** and NaClO$_4$ was eluted

Table I. Crystallographic Data for **4** and **5**

compd	**4**	**5**
formula	$C_{14}H_{36}N_{11}O_{15}Cl_3Pt_2$	$C_{15}H_{35}N_{12}O_{13.5}Cl_2Pt_2$
fw	1095.058	1060.615
space group	*C*2/*c*	$P\bar{1}$
a, Å	32.494 (5)	8.504 (3)
b, Å	17.052 (3)	13.466 (3)
c, Å	11.507 (2)	15.736 (3)
α, deg		104.34 (2)
β, deg	104.65 (3)	108.66 (2)
γ, deg		102.48 (2)
V, Å^3	6168.5	1566.1
Z	8	2
d_{calcd}, g cm^{-3}	2.358	2.249
d_{measd}, g cm^{-3}	2.32	2.25
cryst size, mm	0.3, 0.3, 0.2	0.05, 0.1, 0.6
μ, cm^{-1}	90.2	88
θ_{range}, deg	2–25	2–25
no. of unique reflcns	5620	5503
no. of reflcns used in calcns ($F_o \geq 2\sigma(F_o)$)	4853	5061
R	0.071	0.054
$R_w(F)$	0.072[a]	0.049[b]

[a] $w^{-1} = \sigma^2(F) + 0.001F^2$. [b] $w^{-1} = \sigma^2(F) + 0.00025F^2$.

Table II. Atomic Coordinates and Equivalent Isotropic Temperature Factors of {[(dien)Pt]$_2$(G-N^1,N^7)}(ClO$_4$)$_3$·2H$_2$O (**4**)

atom	*x*	*y*	*z*	U_{eq},[a] Å^2
Pt1	0.5903 (1)	0.2893 (1)	0.1000 (1)	0.043 (1)
Pt2	0.7084 (1)	0.2155 (1)	0.6332 (1)	0.034 (1)
N10	0.5943 (5)	0.2092 (8)	−0.0332 (13)	0.069 (6)
C10	0.5971 (11)	0.2544 (15)	−0.1444 (17)	0.127 (15)
C11	0.5750 (8)	0.3323 (16)	−0.1489 (22)	0.104 (11)
N11	0.5871 (5)	0.3693 (8)	−0.0328 (14)	0.076 (6)
C12	0.5650 (9)	0.4360 (11)	−0.0039 (24)	0.107 (12)
C13	0.5745 (8)	0.4555 (10)	0.1273 (20)	0.103 (11)
N12	0.5810 (4)	0.3817 (6)	0.2056 (13)	0.061 (5)
N20	0.6922 (3)	0.3276 (6)	0.5768 (11)	0.045 (4)
C20	0.7321 (5)	0.3779 (8)	0.6083 (16)	0.063 (6)
C21	0.7582 (4)	0.3493 (9)	0.7334 (14)	0.052 (5)
N21	0.7638 (4)	0.2629 (6)	0.7181 (12)	0.048 (4)
C22	0.7785 (5)	0.2192 (10)	0.8360 (17)	0.066 (7)
C23	0.7789 (5)	0.1320 (9)	0.7979 (16)	0.058 (6)
N22	0.7339 (3)	0.1158 (6)	0.7204 (12)	0.050 (4)
N1	0.5945 (3)	0.2101 (5)	0.2372 (9)	0.034 (3)
C2	0.5618 (4)	0.1592 (7)	0.2361 (13)	0.040 (4)
N2′	0.5292 (3)	0.1562 (6)	0.1357 (10)	0.046 (4)
N3	0.5594 (3)	0.1108 (6)	0.3279 (10)	0.036 (3)
C4	0.5919 (4)	0.1210 (7)	0.4195 (13)	0.037 (4)
C5	0.6262 (4)	0.1691 (7)	0.4372 (13)	0.037 (4)
C6	0.6281 (3)	0.2178 (7)	0.3351 (13)	0.036 (4)
O6′	0.6574 (2)	0.2678 (5)	0.3354 (9)	0.041 (3)
N7	0.6525 (3)	0.1650 (6)	0.5515 (10)	0.039 (4)
C8	0.6332 (4)	0.1137 (7)	0.6091 (14)	0.044 (5)
N9	0.5968 (3)	0.0845 (6)	0.5317 (12)	0.046 (4)
C9′	0.5669 (6)	0.0255 (11)	0.5642 (20)	0.086 (9)
C110	0.8235 (1)	0.0338 (2)	0.1394 (4)	0.062 (1)
O10	0.7804 (5)	0.0087 (9)	0.1099 (19)	0.126 (9)
O11	0.8358 (6)	0.0521 (12)	0.2601 (15)	0.137 (9)
O12	0.8224 (6)	0.1059 (13)	0.0790 (22)	0.172 (12)
O13	0.8529 (6)	−0.0183 (11)	0.1082 (16)	0.137 (9)
C120	0.9506 (1)	0.8245 (2)	0.0002 (4)	0.061 (1)
O20	0.9075 (4)	0.8424 (9)	−0.0098 (21)	0.140 (10)
O21	0.9674 (6)	0.8749 (10)	−0.0702 (18)	0.130 (9)
O22	0.9556 (6)	0.7461 (9)	−0.0399 (15)	0.127 (9)
O23	0.9732 (6)	0.8322 (15)	0.1182 (16)	0.153 (11)
C130	0.8295 (1)	0.4437 (2)	0.0511 (4)	0.060 (1)
O30	0.8729 (5)	0.4491 (10)	0.1163 (15)	0.122 (8)
O31	0.8127 (5)	0.3709 (9)	0.0673 (17)	0.125 (8)
O32	0.8094 (7)	0.4966 (13)	0.1059 (32)	0.222 (18)
O33	0.8269 (7)	0.4573 (15)	−0.0653 (14)	0.188 (13)
O40	0.4937 (15)	0.8343 (18)	0.1580 (35)	0.306 (29)
O41	1.0000 (0)	0.4813 (11)	0.2500 (0)	0.099 (10)

[a] Equivalent isotropic temperature factors were calculated from U_{ij} values according to $U_{\mathrm{eq}} = {}^1/_3\sum U_{ij}a_i^*a_j^*\mathbf{a}_i\mathbf{a}_j$ (U_{ij} in Å^2).

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Table III. Atomic Coordinates and Equivalent Isotropic Temperature Factors of *cis*-$[(NH_3)_2Pt(U\text{-}N^3)(G\text{-}N^1,N^7)Pt(dien)](ClO_4)_2\cdot 2.5H_2O$ (**5**)

atom	*x*	*y*	*z*	U_{eq},[a] Å^2
Pt1	0.1701 (1)	0.2540 (1)	0.3750 (1)	0.039 (1)
Pt2	0.0746 (1)	0.1398 (1)	−0.0609 (1)	0.030 (1)
N10	−0.0443 (14)	0.2479 (9)	0.4091 (7)	0.054 (5)
C10	−0.0520 (20)	0.1736 (14)	0.4664 (12)	0.077 (9)
C11	0.1227 (24)	0.1656 (15)	0.5126 (12)	0.088 (11)
N11	0.2203 (15)	0.1591 (10)	0.4545 (8)	0.064 (6)
C12	0.4030 (26)	0.1749 (20)	0.4870 (14)	0.111 (14)
C13	0.4781 (25)	0.1850 (17)	0.4168 (15)	0.103 (13)
N12	0.4002 (16)	0.2510 (10)	0.3608 (9)	0.069 (6)
N20	0.0785 (14)	0.0192 (7)	−0.1703 (6)	0.045 (4)
N21	−0.1605 (12)	0.0474 (7)	−0.0708 (7)	0.042 (4)
N1a	0.0750 (11)	0.2610 (6)	0.0466 (5)	0.033 (3)
C2a	0.0526 (13)	0.3553 (8)	0.0344 (7)	0.029 (4)
N2a′	0.0137 (13)	0.3604 (7)	−0.0550 (6)	0.041 (4)
N3a	0.0630 (11)	0.4433 (6)	0.1006 (5)	0.031 (3)
C4a	0.0940 (15)	0.4299 (8)	0.1852 (7)	0.035 (4)
C5a	0.1073 (14)	0.3370 (8)	0.2051 (7)	0.032 (4)
C6a	0.1083 (15)	0.2478 (8)	0.1348 (7)	0.034 (4)
O6a′	0.1266 (11)	0.1624 (6)	0.1452 (5)	0.045 (3)
N7a	0.1314 (13)	0.3551 (7)	0.3005 (6)	0.041 (4)
C8a	0.1313 (17)	0.4542 (8)	0.3359 (8)	0.041 (5)
N9a	0.1102 (13)	0.5035 (7)	0.2679 (6)	0.040 (4)
C9a′	0.1059 (24)	0.6143 (9)	0.2805 (9)	0.069 (8)
N1b	0.4665 (14)	0.3593 (8)	−0.0966 (8)	0.055 (5)
C1b′	0.4639 (22)	0.4202 (12)	−0.1642 (13)	0.079 (9)
C2b	0.3058 (18)	0.2855 (9)	−0.1139 (9)	0.045 (6)
O2b′	0.1739 (12)	0.2698 (7)	−0.1853 (6)	0.051 (4)
N3b	0.3082 (12)	0.2317 (7)	−0.0498 (6)	0.040 (4)
C4b	0.4573 (17)	0.2402 (10)	0.0213 (9)	0.049 (6)
O4b′	0.4503 (12)	0.1798 (8)	0.0684 (6)	0.064 (4)
C5b	0.6184 (18)	0.3161 (12)	0.0357 (11)	0.067 (7)
C6b	0.6182 (20)	0.3726 (12)	−0.0227 (12)	0.073 (8)
Cl1	0.4981 (6)	0.1092 (3)	0.7291 (3)	0.077 (2)
O10	0.4732 (36)	0.0826 (20)	0.8036 (17)	0.255 (21)
O11	0.5408 (49)	0.2106 (13)	0.7391 (19)	0.317 (29)
O12	0.3581 (38)	0.0626 (30)	0.6619 (25)	0.413 (29)
O13	0.5926 (54)	0.0662 (27)	0.7064 (32)	0.373 (45)
Cl2	0.2839 (8)	0.5173 (4)	0.6282 (3)	0.099 (2)
O20	0.3258 (41)	0.5847 (13)	0.7179 (10)	0.266 (20)
O21	0.1398 (20)	0.4255 (11)	0.5998 (11)	0.130 (9)
O22	0.2472 (24)	0.5741 (12)	0.5640 (9)	0.145 (10)
O23	0.4231 (24)	0.4860 (19)	0.6288 (17)	0.186 (17)
O30	0.0932 (16)	0.9047 (10)	0.3384 (7)	0.090 (6)
O31	0.3763 (19)	0.8350 (13)	0.7550 (10)	0.142 (9)
O32	0.3697 (32)	0.9603 (25)	0.9476 (21)	0.261 (25)

[a] See footnote in Table II.

in the middle fractions and brought to dryness, and the solid was recrystallized from water. The yield of the colorless cubes of **5** was 30%. Anal. Calcd for $C_{15}H_{35}N_{12}O_{13.5}Cl_2Pt_2$: C, 16.99; H, 3.34; N, 15.85. Found: C, 16.83; H, 3.14; N, 15.64.

Spectra. IR spectra (Perkin-Elmer 783, KBr pellets and Nujol mulls), Raman spectra (Jobin Yvon U 1000, Kr laser, 647.1 nm), and ^1H NMR spectra (Bruker WM 250, D_2O, TSP as internal reference, δ values given relative to TMS) were recorded as reported elsewhere.[22]

Potentiometric titrations were done on a Metrohm E 510 instrument, and UV spectra were recorded on a Perkin-Elmer 555 spectrophotometer (concentrations 5×10^{-5}–1×10^{-4} mol/L). UV spectra used for pK_A determination displayed isosbestic behavior (ip (isosbestic point) at 269 nm for protonation and 237 nm for deprotonation of **1** and at 240 and 273 nm for protonation of **4**).

Crystallography. X-ray data were collected on a Phillips-PW 1100 diffractometer with graphite-monochromated Mo Kα radiation (λ = 0.71069 Å). The unit cell dimensions were calculated from 16 (**4**) and 24 (**5**) reflections. Crystal and structure determination data are summarized in Table I. Lp corrections and in a later stage an empirical[36] absorption correction were applied. The positions of the Pt atoms were obtained from a 3-dimensional Patterson map. Subsequent ΔF syntheses provided the positions of the non-hydrogen atoms. Hydrogens were ignored. Final atomic coordinates are given in Tables II (**4**) and III (**5**). The anisotropic thermal parameters are included in the supplementary material. The highest peaks in the final difference maps were 1.5 e Å^{-3} (**4**, 0.9 Å away from Pt1) and 1.4 e Å^{-3} (**5**, 1.1 Å away from Pt2). Complex scattering factors for neutral atoms were taken refs 37 and 38. For the calculations the SHELX program package was used.[39]

The water molecule O32 was regarded as having half-occupancy considering the high thermal motion and the fact that the symmetry-related position ($1 - x$, $2 - y$, $2 - z$) displayed a unreasonably short distance of 2.13 Å.

Results and Discussion

Preparation and Spectroscopic Characterization. $[(dien)Pt(G\text{-}N^7)]^{2+}$ (**1**) exists in (at least) two different modifications, the IR spectra of which display some remarkable differences in particular in the double-bond stretching region, a feature that initially was causing some confusion.[40] In the species that crystallizes as colorless cubes, strong IR bands are observed, for example at 1715 (sh), 1695, 1640, 1600, and 1585 cm^{-1} (Nujol or KBr), while in the form that crystallizes as white needles strong IR bands appear at 1695, 1660, 1600 (sh), and 1585 cm^{-1} (see supplementary material). In a mixture of the two modifications, superpositions of both sets of absorptions are found. In solution (UV, ^1H NMR spectra), both species are identical. It seems possible that different hydrogen-bonding patterns are responsible for the differences in IR spectra.

The deprotonated complex $[(dien)Pt(G\text{-}N^7)]^+$ (**2**), which was isolated, exhibits in the double-bond stretching region of the IR spectrum the expected shift of the ν_{CO} mode from ca. 1700 cm^{-1} (**1**) to 1610 cm^{-1}, consistent with a delocalization of negative charge from N1 into the C6–O bond.[17a,41]

With an excess of Ag$^+$, **1** forms a crystalline adduct of Pt_2Ag stoichiometry, $\{[(dien)Pt(GH)]_2Ag\}(ClO_4)_5\cdot 4H_2O$ (**3**). Reaction with Ag$^+$ was carried out in order to probe the involvement of other potential donor sites of neutral, N7-blocked 9-methylguanine in metal binding. From the IR spectrum of **3** (strong bands at 1685, 1670, 1645 (sh), 1630, and 1590 cm^{-1}; Nujol mull), no definitive conclusions concerning the site of Ag$^+$ attachment (O6 or/and N3) are possible, however. In solution (D_2O, pD $\simeq$ 5), N9–CH_3 and H8 resonances are affected to a different extent by added Ag$^+$: With increasing Ag$^+$ concentration, both resonances are shifted lowfield, but for N9–CH_3 this effect is approximately 5 times as large (e.g. Pt:Ag = 1:10, ΔCH_3 = 0.068 ppm, ΔH8 = 0.012 ppm), which tentatively suggests that N3 rather than O6 is involved in Ag$^+$ binding to neutral, N7-blocked guanine. This conclusion is supported by findings that attachment of $(NH_3)_3Pt^{II}$ to the N3 position of N1,N7-diplatinated 9-ethylguanine causes a strong downfield shift of the methylene protons of the ethyl group at the 9-position.[22] Thus, Ag$^+$ appears to behave like H$^+$, which has been demonstrated by X-ray analysis to bind to N7-platinated, neutral guanine through N3.[42,43]

As far as guanine modes of **4** in the double-bond stretching region of the IR spectra are concerned, they are qualitatively more similar to those of **2** rather than those of **1**. Compound **5** is not considered because of a higher complexity due to the presence of 1-MeU resonances. The most intense cation bands in the spectrum of **4** are at 1600 and 1640 cm^{-1} (overlapping) with less intense modes at either side (1680 and 1565 cm^{-1}). Although the positions of the IR bands at 1695 (**1**), 1640 (**4**), and 1610 cm^{-1} (**2**), if assigned to vibrations of the C6–O group, are consistent with expectations, we share previously expressed reservations[40a] concerning a structural assignment based exclusively on this spectral region. The Raman active guanine modes in the 1700–1300-cm^{-1} region are not really instructive in this respect either:

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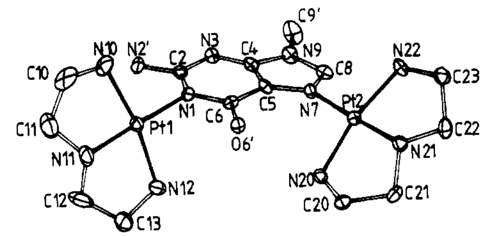

Figure 1. Cation of $\{[(dien)Pt]_2(G\text{-}N^1,N^7)\}(ClO_4)_3 \cdot 2H_2O$ (**4**).

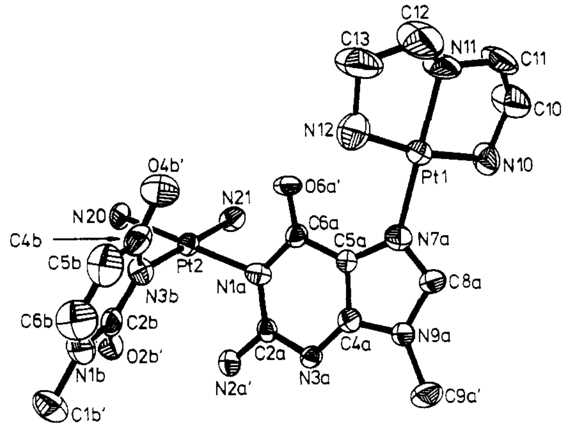

Figure 2. Cation of $cis\text{-}[(NH_3)_2Pt(U\text{-}N^3)(G\text{-}N^1,N^7)Pt(dien)](ClO_4)_2 \cdot 2.5H_2O$ (**5**).

Of the three most intense Raman modes of guanine rings (ca. 1580, 1490, and 1370 cm^{-1}, both in classical[44a,b] and UV resonance spectra[44c]), only the one around 1580 cm^{-1}, which is shifted to 1598 (**4**) and 1605 cm^{-1} (**5**), appears to be potentially useful for diagnostic purposes (supplementary material). However, in N7-platinated, N1-deprotonated guanine ligands, this mode is observed at similar wavenumbers.[17a] Thus, the position of the less intense ν_{C6-O} mode (1688 (free ligand), 1691 (**1**), 1602 (**2**), 1624 cm^{-1} (**4**)) is the most reliable indicator of N7,N1 diplatination at present.

^{1}H NMR chemical shifts of 9-MeG(H) resonances of **1**, **2**, and **4** are consistent with expectations and follow, for H8, the sequence 7.80 (**2**), 7.96 (**4**), and 8.12 ppm (**1**) (shifts at pD values with no acid–base equilibria involved). The 1-MeU ring in **5** has no effect on G-H8 (7.96 ppm as with **4**), indicating that any intracomplex base-stacking interaction does not effect H8.

Acid–base equilibria of **1** and its protonated ($pK_a \simeq 0$) and deprotonated ($pK_a \simeq 8.2$) forms, as determined by UV spectroscopy and potentiometric titration, respectively, are very similar to those of $[(NH_3)_3Pt(GH\text{-}N^7)]^{2+}$.[22] This is also true for compound **4** (pK_a of protonated form $\simeq 1.0$). Formation of the two N7,N1-diplatinated 9-methylguaninato complexes **4** and **5**, which takes place at almost physiological pH conditions, certainly is facilitated by the increase in N1–H acidity of the GH ligand in **1** due to Pt binding at N7.

Crystal Structures of 4 and 5. Figures 1 and 2 depict the cations of compounds **4** and **5**, respectively. Selected interatomic distances and angles are given in Table IV. Details of the anion geometries are deposited in the supplementary material. In **4**, two (dien)Pt^{II} entities are coordinated to the anionic 9-methylguanine ligand via N7 and N1, while in **5**, a (dien)Pt^{II} residue is bound to N7 and a $cis\text{-}(NH_3)_2Pt(1\text{-}MeU)$ residue is bound to N1. The geometries of the (dien)Pt^{II} groups in both compounds are normal,[45] including the deviations of some of the angles from ideal square-planar coordination geometry of the Pt due to the strain exercised by the tridentate ligand. Carbon atoms of the ethylene groups of the dien ligands do not display a uniform pattern as far as positions relative to the N_4Pt plane are concerned (supplementary material). The 9-MeG planes are slightly nonplanar in both compounds, with exocyclic groups and Pt deviating substantially. With **4**, largest deviations occur with Pt1 (−0.36 Å) and N2′ (−0.12 Å); with **5** they are −0.13 Å (N2a′), +0.12 Å (Pt2), and +0.10 Å (C9a′). There are no significant differences in bond lengths and bond angles in the 9-MeG ligands of **4** and **5**, and a comparison with N7-platinated, neutral 9-ethylguanine[6] does not reveal significant differences either. Compared with the triply platinated 9-ethylguanine anion $\{[(NH_3)_3Pt]_3(G\text{-}N^7,N^1,N^3)\}^{5+}$,[22] the only significant difference occurring both in **4** and **5** is the increase in the internal ring angle N3–C4–C5 (132 (1)° in **4**, 127 (1)° in **5**, 120 (1)° in Pt_3G). Considering **4** only, additional differences in ring angles C4–C5–C6 (115 (1)° in **4**, 125 (1)° in Pt_3G), C4–C5–N7 (114 (1)° in **4**, 106 (1)° in Pt_3G), and N9–C4–C5 (103 (1)° in **4**, 109 (1)° in Pt_3G) are to be seen. Thus, the changes observed in guanine geometry on 3-fold metal coordination (N7,N1,N3)[22] essentially are a consequence of the third Pt entity binding to the heterocyclic ring, whereas binding of two Pt(II) entities to N7 and N1 are causing much smaller perturbations.

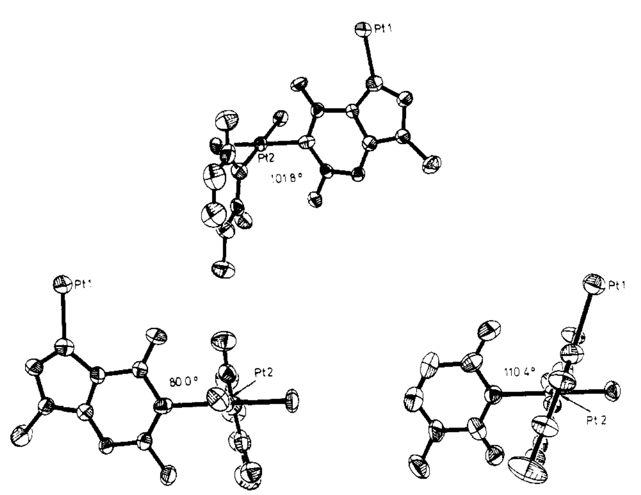

Figure 3. Conformational drawings of the cation **5** for determination of dihedral angles according to the convention of Kistenmacher et al.[30]

The 1-methyluracil ligand in **5** does not display any unusual features. Structural data are well within those of related compounds[31,46] as is the 0.25-Å deviation of Pt2 from the heterocyclic plane.

Angles between Pt coordination planes and the guanine ligand are 65.9° (Pt1, **4**), 41.4° (Pt2, **4**), 61.7° (Pt1, **5**), and 69.6° (Pt28 **5**). (For a complete list of planes and angles between planes, see the supplementary material.) Thus, the dihedral angle between the coordination plane of the Pt binding to N7 is somewhat variable, ranging from ca. 62–65° in $[(dien)Pt(guanosine)]^{2+}$,[43] Pt_3G,[22] and **5** to 41.4° in **4**. The O6′ of **4** is within a reasonable distance of N20 (2.91 Å) to permit hydrogen-bond formation, but the Pt2–N20–O6′ angle of 89° is somewhat unfavorable for an intramolecular hydrogen bond. However, an intermolecular hydrogen bond between O6′ and N21 (2.83 Å; 125° at N21) is likely to occur. The only intramolecular hydrogen bond in cation **5** is between the exocyclic NH_2 group of G and the exocyclic O2 of U (N2a′···O2b′ = 2.97 Å, C2a–N2a′–O2b′ = 124°). O6a′ is involved in an intermolecular hydrogen bond (2.89 Å) with N21 of an adjacent cation. A complete list of close contacts is given in the supplementary material.

Relevance of 5. Figure 3 gives conformational drawings of complex **5** with dihedral angles determined according to the convention proposed by Kistenmacher et al.[30] The dien ligand is omitted for clarity. Dihedral angles are 101.8° between the 1-MeU and 9-MeG plane, 80.0° between 1-MeU and the Pt2

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Table IV. Selected Distances (Å) and Angles (deg) in Cations of **4** and **5**

(a) Coordination Spheres of Pt Atoms of **4**

Pt1–N10	2.08 (1)	Pt2–N20	2.05 (1)	C10–C11	1.51 (4)	C20–C21	1.55 (2)
Pt1–N11	2.03 (2)	Pt2–N21	1.99 (1)	C11–N11	1.44 (3)	C21–N21	1.50 (2)
Pt1–N12	2.06 (1)	Pt2–N22	2.04 (1)	N11–C12	1.43 (3)	N21–C22	1.52 (2)
Pt1–N1	2.06 (1)	Pt2–N7	2.02 (1)	C12–C13	1.50 (4)	C22–C23	1.55 (2)
N10–C10	1.52 (3)	N20–C20	1.52 (2)	C13–N12	1.53 (2)	C23–N22	1.53 (2)
N10–Pt1–N11	83.6 (6)	N20–Pt2–N21	84.5 (4)	C10–C11–N11	109.9 (18)	C23–C22–N21	104.0 (14)
N10–Pt1–N12	169.4 (5)	N20–Pt2–N22	167.2 (5)	C11–N11–Pt1	110.7 (14)	C22–N21–Pt2	106.3 (10)
N10–Pt1–N1	97.5 (5)	N20–Pt2–N7	97.0 (4)	Pt1–N11–C12	107.1 (15)	C22–N21–C21	113.4 (13)
N11–Pt1–N12	86.7 (6)	N21–Pt2–N22	83.8 (5)	C11–N11–C12	122.1 (18)	Pt2–N21–C21	109.7 (9)
N11–Pt1–N1	178.7 (5)	N21–Pt2–N7	178.1 (5)	N11–C12–C13	115.0 (19)	N21–C21–C20	104.6 (12)
N12–Pt1–N1	92.3 (5)	N22–Pt2–N7	94.5 (4)	C12–C13–N12	112.0 (15)	C21–C20–N20	106.2 (13)
Pt1–N10–C10	108.4 (12)	Pt2–N22–C23	110.2 (9)	C13–N12–Pt1	107.5 (12)	C20–N20–Pt2	108.4 (8)
N10–C10–C11	110.3 (23)	N22–C23–C22	105.1 (12)				

(b) Coordination Spheres of Pt Atoms of **5**

Pt1–N10	2.05 (1)	Pt2–N20	2.07 (1)	N10–C10	1.51 (2)	N11–C12	1.42 (2)
Pt1–N11	2.02 (1)	Pt2–N21	2.05 (1)	C10–C11	1.47 (2)	C12–C13	1.46 (2)
Pt1–N12	2.05 (1)	Pt2–N1a	2.04 (1)	C11–N11	1.42 (2)	C13–N12	1.51 (2)
Pt1–N7a	2.02 (1)	Pt2–N3b	2.03 (1)				
N10–Pt1–N11	85.1 (4)	N20–Pt2–N21	92.2 (4)	Pt1–N10–C10	108.4 (8)	C11–N11–C12	125.6 (14)
N10–Pt1–N12	169.9 (4)	N20–Pt2–N1a	178.7 (4)	N10–C10–C11	110.5 (11)	N11–C12–C13	114.7 (15)
N10–Pt1–N7a	96.1 (4)	N20–Pt2–N3b	88.2 (4)	C10–C11–N11	114.3 (12)	C12–C13–N12	111.0 (13)
N11–Pt1–N12	85.3 (5)	N21–Pt2–N1a	89.0 (4)	C11–N11–Pt1	108.6 (8)	C13–N12–Pt1	108.4 (9)
N11–Pt1–N7a	177.0 (5)	N21–Pt2–N3b	179.5 (3)	Pt1–N11–C12	107.2 (10)		
N12–Pt1–N7a	93.4 (4)	N1a–Pt2–N3b	90.6 (4)				

(c) 9-MeG Ligand (Designated a in Figure 2)

	4	**5**		**4**	**5**
N1–C2	1.37 (2)	1.37 (1)	C6–N1	1.36 (1)	1.39 (1)
C2–N2′	1.36 (2)	1.36 (1)	C5–N7	1.38 (2)	1.40 (1)
C2–N3	1.36 (2)	1.34 (1)	N7–C8	1.34 (2)	1.31 (1)
N3–C4	1.30 (2)	1.34 (1)	C8–N9	1.38 (2)	1.38 (1)
C4–C5	1.36 (2)	1.38 (1)	N9–C4	1.41 (2)	1.37 (1)
C5–C6	1.45 (2)	1.42 (1)	N9–C9′	1.51 (3)	1.47 (1)
C6–O6′	1.28 (2)	1.24 (1)			
Pt–N1–C2[a]	120.7 (8)	121.5 (7)	C4–C5–C6	115.2 (12)	119.9 (9)
Pt–N1–C6[a]	117.0 (9)	117.8 (7)	O6′–C6–C5	124.3 (11)	126.0 (10)
C6–N1–C2	121.8 (12)	120.6 (9)	O6′–C6–N1	120.6 (12)	120.5 (9)
N2′–C2–N1	117.9 (13)	117.2 (9)	C5–C6–N1	115.1 (11)	113.4 (9)
N2′–C2–N3	117.0 (12)	115.6 (9)	Pt–N7–C5[b]	133.7 (10)	128.1 (7)
N1–C2–N3	125.1 (11)	127.3 (9)	Pt–N7–C8[b]	121.7 (9)	124.9 (8)
C2–N3–C4	110.8 (11)	111.8 (8)	C5–N7–C8	104.5 (11)	107.0 (9)
N9–C4–N3	124.4 (13)	126.9 (9)	N7–C8–N9	110.3 (13)	110.5 (10)
N9–C4–C5	103.4 (11)	106.5 (9)	C9′–N9–C8	125.4 (14)	126.8 (9)
N3–C4–C5	132.1 (14)	126.5 (10)	C9′–N9–C4	126.4 (12)	125.6 (9)
N7–C5–C4	113.6 (13)	108.4 (9)	C8–N9–C4	108.1 (12)	107.6 (8)
N7–C5–C6	131.2 (12)	131.5 (9)			

(d) 1-MeU Ligand of **5** (Designated b in Figure 2)

N1–C1′	1.49 (2)	C2–N3	1.38 (1)	C4–O4′	1.23 (2)	C5–C6	1.33 (2)
N1–C2	1.40 (2)	N3–C4	1.36 (2)	C4–C5	1.43 (2)	C6–N1	1.37 (2)
C2–O2′	1.24 (2)						
N3–C2–N1	116.1 (12)	C2–N3–Pt2	117.6 (8)	O4′–C4–C5	122.6 (13)	C2–N1–C1′	116.4 (12)
N3–C2–O2′	124.1 (12)	C4–N3–Pt2	119.1 (8)	N1–C6–C5	121.2 (14)	C1′–N1–C6	122.1 (12)
N1–C2–O2′	119.8 (11)	N3–C4–C5	118.4 (12)	C6–C5–C4	119.3 (14)	C2–N1–C6	121.5 (12)
C2–N3–C4	123.3 (11)	N3–C4–O4′	119.0 (12)				

[a] Pt denotes Pt1 in **4** and Pt2 in **5**. [b] Pt denotes Pt2 in **4** and Pt1 in **5**.

coordination plane, and 110.4° between 9-MeG and the Pt2 coordination plane. The dihedral angle of almost 102° between the two nucleobase planes is among the largest observed in *cis*-$(NH_3)_2Pt^{II}$ complexes and virtually the same as in *cis*-$[(NH_3)_2Pt(1\text{-}MeC)_2]^{2+}$[47,48] and in the *cis*-$[(NH_3)_2Pt(1\text{-}MeC)(1\text{-}MeU)]^+$ entities of heteronuclear Pt_2Cu[16] and PtAg[49] derivatives. Pt2 in **5** exhibits a similar environment as does Pt in the Pt_2Cu and PtAg complexes in that the Pt binding sites are flanked by identical sets of exocyclic groups (three keto oxygens, one amino group), which suggests that the coordination of a heterometal to two of these oxygens in the Pt_2Cu and PtAg compounds influences the dihedral angle only slightly. In all five compounds, intracomplex hydrogen bonding between amino and oxo groups is observed.

The magnitude of the dihedral base–base angle confirms previous predictions[30] concerning the geometry of a hypothetical core–core cross-link of cisplatin between purine-N^1 and pyrimidine-N^3 and speculations concerning the expected drastic deformation of the DNA duplex. While the unprotonated N3 position of cytosine might appear a more likely coordination site for Pt(II) than the protonated N3 position of thymine, any Pt(II)–OH group,

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which exists at neutral or even acidic pH, in principle is capable of binding to a thymine N3 (or uracil N3) position,[50] even in a dinucleotide containing also guanine.[51]

A crucial question is the likelyhood of a T-N^3,G-N^1 cross-link from a steric point of view. In **5**, the C1b′ and C9a′ positions, which in DNA would correspond to the separations of the two C1′ positions in the glycosidic bonds, are separated by 9.50 Å. This value is to be compared with C1′⋯C1′ separations of 6.05–6.79 Å in *cis*-[Pt$(NH_3)_2${d(pGpG)}] molecules[3] and ca. 8 Å in partially unwound DNA containing an intercalator between two bases,[52] for example. From model building it would seem that a 9.50-Å separation between the C1′ positions of two adjacent bases in one strand represents the upper limit for backbone unwinding and that, for this reason, a 1,3-linkage with an intervening base probably would be accomplished more easily than a 1,2-linkage. 1,3-Cross-linkes within a DNA strand have been observed before, albeit between other bases.[53]

Like in other Pt(II) compounds containing N3-bound uracil or thymine ligands,[9] the 1-MeU ligand in **5** has a protective effect on all three ligands. Treatment with excess CN^- quickly and selectively displaces the N7-bound (dien)Pt^{II} entity while leaving the N1-bound entity unaffected. We have not been able to get crystals suitable for X-ray analysis yet, but we expect the complex formed, *cis*-$(NH_3)_2$Pt(1-MeU-N^3)(9-MeG-N^1), to display a similarly large dihedral angle between the two nucleobases as has been found with **5**.

Conclusions. Two complexes **4** and **5** have been isolated and characterized by X-ray methods that involve a guanine binding pattern of Pt(II) entities (N7,N1 bridging), previously observed in solution both for *cis*-$(NH_3)_2Pt^{II}$ (on reaction with 9-EtGH, guanosine, and 5′-GMP) and for $(NH_3)_3Pt^{II}$. **5** is special in that it represents a novel model for a cross-link of *cis*-$(NH_3)_2Pt^{II}$ with two nucleobase donor atoms present in double-helical DNA in the interior only. Provided it were to be formed, it would cause a major perturbation of DNA structure due to the large dihedral angle of 101.8° between the base planes, irrespective of a possible intra- or interstrand fashion. Compared to it, the kinking of DNA, as induced by G-N^7,G-N^7 cross-linking at the periphery, is considerably smaller.

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Supplementary Material Available: Tables of atomic and thermal parameters, anion geometry parameters, close contact parameters, equations of planes, and deviations of atoms from planes and figures showing IR and Raman spectra (14 pages); tables of observed and calculated structure factors (50 pages). Ordering information is given on any current masthead page.

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Reaction of Hydroxide Ion with Manganese(III) Tetramesitylporphyrin and the Oxidation States of Manganese Tetramesitylporphyrins[†]

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The autoreduction reaction of the non-μ-oxo-dimer-forming chloromanganese(III) tetramesitylporphyrin, (TMP)Mn^{III}(Cl), with methanolic tetra-*n*-butylammonium hydroxide (YO^- species = OH^- or CH_3O^-) in acetonitrile and dimethyl sulfoxide under anaerobic conditions has been examined by UV/visible and ^2H NMR spectroscopies, where the spectral changes accompanying the reaction could be associated with changes in the oxidation and ligation states of the manganese porphyrin. Two intermediates, (TMP)Mn^{II} and [(TMP)Mn^{II}(OY)]$^-$, may be directly observed to form during the reaction by a mechanism thought to involve homolytic bond cleavage, which in a slower reaction convert to a product whose structure is suggested to be that of a [(TMP)-$Mn^{III}(OY)_2]^-$ species. Exposure to air at any time during the reaction leads to the formation of the manganese(III) peroxo complex, [(TMP)$Mn^{III}(O_2)]^-$. The [(TMP)Mn^{II}(OY)]$^-$ species may be prepared independently from the reaction of (TMP)Mn^{II} with YO^-, and ^2H NMR spectral studies on the titration of a toluene solution of (TMP-d_8)Mn^{II} with YO^- indicate only one YO^- ligation. The pyrrole β-deuterium chemical shift for the [(TMP-d_8)Mn^{II}(OY)]$^-$ complex in toluene at 25 °C is 37 ppm. The various oxidation states of the manganese tetramesitylporphyrins were examined in order to identify the intermediates and products of the reaction. Thin-layer spectroelectrochemical oxidation of the chloromanganese(III) tetramesitylporphyrin in methylene chloride shows the first 1e oxidation to be porphyrin centered, providing the manganese(III) porphyrin π cation radical, ($^{\bullet+}$TMP)Mn^{III}(Cl). Exchange of the chloro ligand for the hydroxy ligand shows that the first 1e oxidation of the hydroxymanganese(III) tetramesitylporphyrin at low temperature is metal centered, providing the (TMP)Mn^{IV}(O) species. Further 1e oxidation of the latter produces a species identified as the oxidized porphyrin radical cation, ($^{\bullet+}$TMP)Mn^{IV}(O). Spectroscopic data for the (TMP)-$Mn^{IV}(OY)_2$ and [($^{\bullet+}$TMP)Mn^{III}(Cl)]($SbCl_6^-$) species (UV/vis and ^2H NMR) and the ($^{\bullet-}$TMP)Mn^{II} and ($^{2-}$TMP)Mn^{II} species (UV/vis) are reported.

Introduction

Manganese constitutes an essential metal in several biological systems that are involved in electron-transfer reactions. By variations in its oxidation and ligation states it mediates such diverse biological functions as the oxidation of water to molecular oxygen in green plant photosynthesis,[1] disproportionation of hydrogen peroxide in several microorganisms (catalase activity),[2] and decomposition of $O_2^{\bullet-}$ in bacterial superoxide dismutase.[3] Among these functions the oxidation of water to yield oxygen is

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[†] Abbreviations used: TMP, dianion of tetramesitylporphyrin; TPP, dianion of tetraphenylporphyrin.

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