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N7/O6 Chelation in a Complex with an Analogue of Guanine. Preparation, Spectroscopic Study, and Crystal Structure of Bis(η^5-cyclopentadienyl)(theophyllinato)titanium(III)

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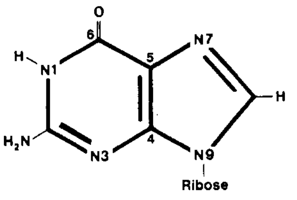
The theophylline–titanium(III) complex $(\eta^5\text{-}C_5H_5)_2$(theophyllinato)Ti was prepared by using either $(\eta^5\text{-}C_5H_5)_2Ti(CO)_2$ or $(\eta^5\text{-}C_5H_5)_2TiCl$ as starting material. The titanocene structure is preserved in the complex. The crystals belong to the monoclinic space group $P2_1/c$, with a = 7.869 (5) Å, b = 7.745 (6) Å, c = 26.86 (2) Å, β = 100.37 (6)°, and Z = 4. The structure was solved for 1737 nonzero Mo Kα reflections (R = 0.041). The unit cell contains discrete $(\eta^5\text{-}C_5H_5)_2$(theophyllinato)Ti molecules. The $(\eta^5\text{-}C_5H_5)_2Ti$ unit has the usual "open-clamshell" arrangement with Ti–centroid distances of 2.054 and 2.073 Å and an angle of 135° between the Ti–centroid directions. The two remaining sites of the approximate tetrahedron are occupied by the N7 and O6 atoms of deprotonated theophylline, with Ti–N7 and Ti–O6 distances of 2.211 (3) and 2.278 (2) Å, respectively. The "bite" of the N7/O6 donors imposes an O6–Ti–N7 angle of 79.6 (1)°, and the Ti–N7 bond lies at a 25° angle from the expected N7 lone-pair direction (Ti–N7–C5 = 104.6 (2)°, Ti–N7–C8 = 154.2 (2)°). This compound affords the first unambiguous example of balanced N7–O6 chelation for an oxopurine. The EPR spectra are consistent with the same structure being retained in toluene–benzene solution.

Introduction

It is widely accepted that N7 is the preferred coordination site in guanosine (I), inosine, and other 6-oxopurines.[2] This site in guanine is believed to be the primary target for Pt antitumor complexes in cellular DNA.[2,3] Several models have been proposed to explain this specificity, one of which assumes that initial metal binding to N7 is followed by ring closure and coordination of O6 with a second coordination position on the metal, leading to an N7/O6 chelate. Although studies on model compounds have conclusively shown that such chelates can form with 6-thiopurines,[4] evidence for chelation in 6-oxo ligands is much less convincing. This problem was examined by Marzilli, Kistenmacher, and coworkers[5,6] by means of a series of copper complexes of theophylline (II). They confirmed N7 as the primary binding site and noticed that O6 is generally hydrogen bonded with other ligands in the metal coordination sphere. The same behavior has also been observed with other metal ions.[7-9] When hydrogen bonding ligands were not available, O6 was found to occupy an apical coordination site around copper, but the Cu–O6 distance (2.92 Å) is much longer than the Cu–N7 distance (~1.95 Å).[6] Thus, even though this molecule can be described as a chelate in the sense that a ring exists, the two bonding interactions are hardly comparable. The present paper provides the first crystallographic evidence for the formation of a balanced N7/O6 chelate with a 6-oxopurine.



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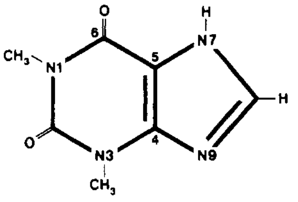

II

The compound discussed here was prepared as part of a research program dealing with the interaction of the titanocene moiety $(\eta^5\text{-}C_5H_5)_2Ti$ with DNA constituents. The dichlorometallocenes of Ti, V, and Nb and the ferrocenium cation belong to one the most important classes of metal agents, after Pt complexes, showing promising antitumor properties. Considerable effort has been devoted by Köpf and Köpf-Maier[10] to shed some light on the mechanism of action of these compounds. From comparisons of their results with those observed with Pt compounds, these authors proposed similar interactions for both types of compounds. In a previous report,[11] we structurally characterized the $(\eta^5\text{-}C_5H_5)_2$(purinato)TiCl complex as a model for a species in which one of the leaving chloride ligands is replaced by a purine base. The present compound provides an example of a species in which both leaving ligands have been displaced by a single bidentate purine base.

Experimental Section

Reagents and Instruments. All manipulations were carried out in Schlenk glassware under an atmosphere of purified nitrogen. Toluene was purified by distillation over Na wire. Tetrahydrofuran (THF) was distilled from a sodium–benzophenone mixture. Bis(η^5-cyclopentadienyl)dichlorotitanium(IV) complex ($(C_5H_5)_2TiCl_2$; Strem Chemicals) and the theophylline ligand (Aldrich Chemicals) were used without further purification. Bis(η^5-cyclopentadienyl)chlorotitanium(III) ($(C_5H_5)_2TiCl$) and bis(η^5-cyclopentadienyl)dicarbonyltitanium(II) ($(C_5H_5)_2Ti(CO)_2$) were prepared by reduction of the dichlorometallocene as described in the literature.[12,13]

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Mass spectra were run on a Hewlitt-Packard 5995A instrument under the following experimental conditions: acceleration voltage, 8 kV; ionization potential, 70 eV; pressure, 10^{-6} torr. The solid samples were introduced in the mass spectrometer in 1-mm glass capillaries supported on a steel rod. The samples were heated from 40 to 180 °C at a rate of 64 deg/min, and spectra were periodically collected over a 10-min period. Infrared spectra were recorded on a Beckman IR4250 spectrometer, and the absorptions of a polystyrene film were used as references. Electron paramagnetic resonance (EPR) spectra were obtained with a JEOL JES-ME X-band spectrometer. Solid polycrystalline and solution samples were introduced in 4-mm quartz tubes. The diphenylpicrylhydrazyl (DPPH) radical was used as frequency reference for the EPR spectra (g = 2.0036). Combustion microanalyses were carried out with a Hewlitt-Packard 185 F&M scientific analyzer at the Département de Chimie, Université Laval.

Preparation of Bis(η^5-cyclopentadienyl)(theophyllinato)titanium(III). This complex was prepared by following two routes, using either the titanium(II) dicarbonyl metallocene (route A) or the titanium(III) monochloro analogue (route B) as the starting material.

Route A. In a 350-mL Schlenk flask, theophylline (1.217 g, 6.76 mmol) was added under a steady flow of N_2 to a toluene solution (50 mL) containing the dicarbonyl complex (1.116 g, 4.77 mmol). The stirred solution was then refluxed for 24 h, during which period the color of the solution changed from red to green. While still hot, the solution was filtered on a fritted-glass disk to remove the unreacted solid theophylline. The filtrate was reheated to its boiling point and left at room temperature. After 24 h, a green solid had crystallized out of the solution and was collected by filtration: yield 1.354 g (79%); mp 246 °C. MS, m/z (relative intensity >13%): 357 (M^+, 33), 293 (21), 292 (100), 291 (15), 180 (24), 178 (13), 139 (16), 129 (18), 113 (14), 68 (14), 65 (22), 64 (17), 39 (21). IR (cm^{-1}, KBr): 3120 w, 3100 w, 3080 w, 2940 br, vs, 1692 br, vs, 1655 br, vs, 1583 w, 1540 sh, 1530 br, vs, 1440 w, 1415 s, 1395 s, 1365 vw, 1347 m, 1310 m, 1250 m, 1212 m, 1158 m, 1150 m, 1115 s, 1050 m, 1017 s, 993 m, 860 vw, 810 vs, 800 vs, 792 vs, 770 vs, 741 vs, 689 m, 640 w, 600 vw, 552 vw, 503 m, 450 m, 420 vw, 405 m, 392 m, 367 w. Anal. Calcd for $C_{17}H_{17}N_4O_2Ti$: C, 57.16; H, 4.80; N, 15.68. Found: C, 57.69; H, 3.38; N, 15.99.

The dicarbonyl complex (0.415 g, 1.77 mmol) and theophylline (0.347 g, 1.93 mmol) were also reacted in THF (50 mL) by following the same procedure. This yielded 0.484 g (76%) of the green theophylline complex after recrystallization in boiling toluene. The spectroscopic data and microanalysis for this sample were as above.

Route B. A suspension of theophylline (1.842 g, 10.23 mmol) and NaH (0.250 g, 10.41 mmol) in THF (30 mL) was magnetically stirred for 15 min under a blanket of N_2. To the stirred mixture was added the starting chlorotitanocene (1.039 g, 4.88 mmol) dissolved in THF (20 mL). The reaction mixture was then refluxed. After 48 h, it was cooled to room temperature and filtered on a fritted-glass disk. The resulting green filtrate was evaporated to dryness under reduced pressure, and the complex was extracted from the solid residue with boiling toluene (50 mL). This solution was decanted and left for 24 h at room temperature, during which time green crystals appeared. The complex was recovered by filtration and dried at room temperature (10^{-2} torr). This procedure gave 0.968 g (56%) of a theophylline complex showing the same spectroscopic properties and microanalysis as the reaction product from route A.

Crystal Data: $C_{17}H_{17}N_4O_2Ti$, fw = 357.25, monoclinic, $P2_1/c$, a = 7.869 (5) Å, b = 7.745 (6) Å; c = 26.86 (2) Å, β = 100.37 (6)°, V = 1610.3 $Å^3$, D_c = 1.473 g cm^{-3}, Z = 4, λ(Mo K$\bar{\alpha}$) = 0.71069 Å (graphite monochromatized), T = 173 K, μ(Mo Kα) = 5.4 cm^{-1}, crystal dimensions 0.17 × 0.22 × 0.20 mm.

Crystallographic Measurements and Structure Determination. The crystalographic work was carried out at 173 K with an Enraf-Nonius CAD-4 diffractometer. The crystal was quickly embedded in Canada balsam, placed on the tip of the glass fiber, and immediately transferred to the diffractometer, where its temperature quickly decreased to 173 K in the cold N_2 stream of the cooling system. Although slight decomposition was visible on the surface, the bulk of the specimen remained intact and no further decomposition occurred during data collection.

A set of 25 randomly distributed reflections was created by the automatic search routine of the CAD-4 software. The reflections were centered, and the indexation procedure yielded a reduced cell of parameters a = 7.745 Å, b = 7.787 Å, c = 26.60 Å, α = 96.5°, β = 90.0°, γ = 90.0°. This cell was checked by taking a long-exposure oscillation photograph about each axis. These films showed the expected layer-line spacings, and a top–bottom mirror was observed for oscillation about the a axis. The Niggli parameters unambiguously indicated that the crystal could not be described with a higher symmetry lattice. Interchange of a and b gave a monoclinic cell with b as the unique axis. Inspection of the $0k0$ and $h0l$ reflection suggested space group $P2_1/n$. The cell was transformed into the more conventional $P2_1/c$ cell given above. The systematic absence of space group $P2_1/c$ ($h0l$, $l \neq 2n$, and $0k0$, $k \neq 2n$) were subsequently checked by inspection of the full data set.

Table I. Refined Coordinates (×10^4, Ti × 10^5, H × 10^3) and Equivalent Temperature Factors (×10^3)

atom	x	y	z	U_{eq}, $Å^2$
Ti	48785 (7)	21757 (7)	10781 (2)	27
N1	907 (3)	−1741 (3)	877 (1)	31
C1	200 (4)	−2151 (5)	344 (2)	39
C2	181 (4)	−2616 (4)	1253 (1)	31
O2	−960 (3)	−3672 (3)	1109 (1)	41
N3	800 (3)	−2287 (4)	1751 (1)	34
C3	75 (6)	−3171 (6)	2147 (2)	61
C4	2109 (4)	−1078 (4)	1890 (1)	34
C5	2737 (4)	−258 (4)	1510 (1)	28
C6	2201 (4)	−503 (4)	1003 (1)	27
O6	2854 (3)	321 (3)	667 (1)	30
N7	4012 (3)	926 (4)	1729 (1)	30
C8	4025 (4)	665 (5)	2225 (2)	42
N9	2892 (4)	−517 (4)	2349 (1)	43
C11	4911 (4)	5095 (4)	806 (2)	45
C12	4891 (5)	5127 (5)	1327 (2)	63
C13	3315 (6)	4457 (5)	1383 (2)	60
C14	2372 (4)	3944 (5)	910 (2)	52
C15	3394 (5)	4309 (5)	549 (2))	50
C21	7972 (5)	2169 (6)	1318 (2)	63
C22	7608 (5)	2368 (5)	820 (2)	57
C23	6762 (5)	934 (6)	585 (2)	56
C24	6639 (4)	−228 (5)	999 (2)	74
C25	7456 (5)	613 (7)	1438 (2)	67
H1	18 (4)	−340 (4)	30 (1)	37 (9)
H2	−95 (5)	−168 (5)	24 (1)	68 (13)
H3	92 (5)	−169 (5)	12 (2)	73 (13)
H4	−45 (6)	−245 (6)	233 (2)	101 (17)
H5	114 (5)	−369 (5)	241 (1)	68 (13)
H6	−66 (5)	−418 (6)	197 (2)	83 (14)
H8	483 (3)	128 (3)	249 (1)	12 (7)
H11	575 (4)	551 (5)	66 (1)	59 (11)
H12	580 (4)	556 (5)	160 (1)	63 (12)
H13	299 (5)	429 (5)	170 (1)	63 (12)
H14	134 (5)	334 (6)	83 (2)	81 (14)
H15	306 (5)	420 (5)	20 (1)	58 (11)
H21	854 (4)	314 (5)	156 (1)	53 (11)
H22	781 (4)	339 (5)	65 (1)	53 (11)
H23	634 (5)	83 (5)	24 (2)	73 (13)
H24	603 (5)	−135 (5)	97 (1)	64 (12)
H25	764 (4)	30 (5)	174 (1)	54 (11)

The intensity data were collected as reported earlier.[14] Seven standard reflections were monitored during data collection, and their fluctuations remained within ±2.9%. A total of 2275 independent Mo Kα hkl and $hk\bar{l}$ reflections were collected within a sphere limited by 2θ = 45°. After the 190 systematically absent reflections were eliminated, the data set consisted of 2085 unique reflections, of which 1737 with $I/\sigma(I) \geq 3.0$ were retained for structure resolution. These data were corrected for polarization and the Lorentz effect, but not for absorption (expected transmission range: 0.84–0.89).

The structure was solved by the heavy-atom method and refined on $|F_o|$. The Ti atom was positioned from a Patterson map. The remaining non-hydrogen atoms were found in a difference Fourier (ΔF) map phased on Ti. This model was refined isotropically (full matrix) to $R = \sum||F_o| - |F_c||/\sum|F_o|$ = 0.097 and $R_w = [\sum w(|F_o| - |F_c|)^2/\sum w|F_o|^2]^{1/2}$ = 0.101. All the hydrogen atoms were visible in the subsequent ΔF map. They were refined isotropically, whereas the non-hydrogen atoms were refined anisotropically (block diagonal). Convergence was reached for R = 0.041, R_w = 0.050, and a goodness-of-fit ratio of 1.90 for 286 parameters refined. The final ΔF map showed a general background below ±(0.20) e/$Å^{-3}$, and a few peaks in the range ±(0.25–0.40) e/$Å^{-3}$ within 1.1 Å from Ti.

The scattering curves were those of Cromer and Waber,[15] except for

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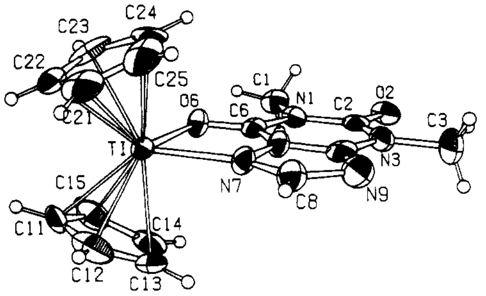

Figure 1. ORTEP drawing of the $(\eta^5\text{-}C_5H_5)_2(C_7H_7N_4O_2)Ti$ molecule, with the numbering scheme used in Table I. The ellipsoids correspond to 50% probability. The hydrogen atoms are shown as small spheres of arbitrary size.

hydrogen.[16] The anomalous dispersion terms f' and f'' of Ti[17] were included in the structure factor calculations. The programs used are listed elsewhere.[18]

The refined coordinates are listed in Table I. The temperature factors and the structure factor table are part of the supplementary material (see paragraph regarding supplementary material at the end of this paper).

Results

Synthesis. The theophilline complex $(\eta^5\text{-}C_5H_5)_2(C_7H_7N_4O_2)Ti^{III}$ was prepared in good yield from either $(\eta^5\text{-}C_5H_5)_2Ti(CO)_2$ or $(\eta^5\text{-}C_5H_5)_2TiCl$ as the starting material. In the first case, MS analysis of the gas over the reaction mixture showed the presence of CO and H_2 in a 3.9:1 ratio. Hence, the overall reaction in this case (route A) is best described by eq 1. The CO ligands are

$$(\eta^5\text{-}C_5H_5)_2Ti(CO)_2 + C_7H_8N_4O_2 \rightarrow (\eta^5\text{-}C_5H_5)_2Ti(C_7H_7N_4O_2) + 2CO + {}^1/_2H_2 \quad (1)$$

easily displaced by other Lewis bases, but simple substitution leading to Ti(II) products is uncommon.[19-21] The low-valent $(\eta^5\text{-}C_5H_5)_2Ti(CO)_2$ complex is often oxidized to a Ti(III) or a Ti(IV) species by the entering ligands, which are themselves reduced (e.g. tetracyanoethylene,[22] 9,10-phenanthroquinone,[23] tetramethylphenanthroline[24]) and sometimes involved in a coupling process (*e.g.* diphenylketene,[25] diphenylacetylene,[21] *N,N'*-di-*p*-tolylcarbodiimide[26]). With molecules containing labile OH or NH groups, the protons are reduced to H_2 and the anionic ligand displaces the CO molecules on the oxidized metal center. For instance, with aliphatic and aromatic carboxylic acids, the corresponding Ti(III) carboxylates are obtained in good yields.[27] Thymine and related heterocyclic molecules also bind to Ti(III) as anions with concomitant liberation of H_2 and CO.[28] The reaction reported here for theophylline clearly belongs to this same class. It has been reported that excess acetic acid favors further oxidation to Ti(IV) and formation of $(\eta^5\text{-}C_5H_5)_2Ti(O_2CCH_3)_2$[23]. No such 2:1 compound was obtained here in presence of a small excess of theophylline. This may be due to the greater steric demand of theophylline and to the formation of a chelate ring efficiently filling both available sites on Ti(III), making the resulting 17-electron molecule less susceptible to further attack than a hypothetical 15-electron unidentate 1:1 complex.[29]

Table II. Interatomic Distances and Bond Angles

	Distances (Å)		
Ti–C11	2.378 (4)	Ti–C21	2.403 (4)
Ti–C12	2.381 (4)	Ti–C22	2.377 (4)
Ti–C13	2.381 (4)	Ti–C23	2.363 (4)
Ti–C14	2.377 (4)	Ti–C24	2.353 (4)
Ti–C15	2.349 (4)	Ti–C25	2.410 (4)
Ti–R1[a]	2.054	Ti–R2[a]	2.073
Ti–N7	2.211 (3)	Ti–O6	2.278 (2)
N1–C2	1.419 (5)	C4–C5	1.368 (5)
N1–C6	1.395 (4)	C4–N9	1.347 (5)
N1–C1	1.474 (5)	C5–C6	1.364 (5)
C2–N3	1.363 (5)	C5–N7	1.408 (4)
C2–O2	1.225 (4)	C6–O6	1.286 (4)
N3–C3	1.464 (6)	N7–C8	1.346 (5)
N3–C4	1.392 (4)	C8–N9	1.360 (5)
C11–C12	1.403 (7)	C21–C22	1.326 (7)
C12–C13	1.377 (6)	C22–C23	1.387 (6)
C13–C14	1.408 (7)	C23–C24	1.447 (7)
C14–C15	1.396 (6)	C24–C25	1.398 (7)
C11–C15	1.405 (6)	C21–C25	1.330 (7)
	Angles (deg)		
R1–Ti–R2	135.0	C12–C11–C15	109.7 (4)
R1–Ti–O6	106.0	C11–C12–C13	105.9 (4)
R1–Ti–N7	107.4	C12–C13–C14	110.3 (4)
R2–Ti–O6	107.6	C13–C14–C15	107.1 (4)
R2–Ti–N7	107.4	C14–C15–C11	106.9 (4)
O6–Ti–N7	79.6 (1)	C22–C21–C25	109.3 (4)
C6–O6–Ti	107.8 (2)	C21–C22–C23	111.4 (4)
C5–N7–Ti	104.6 (2)	C22–C23–C24	104.0 (4)
C8–N7–Ti	154.2 (2)	C23–C24–C25	105.9 (4)
		C24–C25–C21	109.4 (4)

[a] R1 and R2 = centroids of the C11–C12–C13–C14–C15 and C21–C22–C23–C24–C25 rings, respectively.

The same product was isolated by reaction of the Ti(III) compound $(\eta^5\text{-}C_5H_5)_2TiCl$ with sodium theophyllinate generated in situ from NaH (route B, reaction 2). Similar chlorine sub-

$$C_7H_8N_4O_2 + NaH \rightarrow C_7H_7N_4O_2Na + H_2 \quad (2a)$$

$$(\eta^5\text{-}C_5H_5)_2TiCl + C_7H_7N_4O_2Na \rightarrow (\eta^5\text{-}C_5H_5)_2Ti(C_7H_7N_4O_2) + NaCl \quad (2b)$$

stitution has been reported for uracil, pyrazole, biimidazole, bibenzimidazole, and analogous heterocyclic molecules.[30-32] These ligands were first deprotonated with Na metal or *n*-butyllithium and then allowed to react with $(\eta^5\text{-}C_5H_5)_2TiCl$. Our method involving initial deprotonation with NaH and subsequent reaction with $(\eta^5\text{-}C_5H_5)_2TiCl$ seems to be equally efficient and possibly a more accessible synthetic route to the theophylline compound than reaction 1 with the dicarbonyl complex.

Description of the Structure. The crystal contains the monomeric $(\eta^5\text{-}C_5H_5)_2Ti(C_7H_7N_4O_2)$ molecule illustrated in Figure

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Table III. Bond Angles (deg) in Various Theophylline Compounds

angle	present compd	N7–H(R)[44]	N7–M[44]
C1–N1–C2	117.3 (3) (+1.5)[a]	115.8 (12)	116.1 (12) (+0.3)[a]
C1–N1–C6	121.0 (3) (+3.4)	117.6 (10)	117.7 (8) (+0.1)
C2–N1–C6	121.7 (3) (−4.8)	126.5 (6)	126.2 (8) (−0.3)
N1–C2–N3	119.4 (3) (+2.5)	116.9 (15)	117.3 (11) (+0.4)
N1–C2–O2	117.4 (3) (−4.1)	121.5 (7)	121.0 (7) (−0.5)
N3–C2–O2	123.2 (3) (+1.6)	121.6 (9)	121.8 (14) (+0.2)
C2–N3–C3	120.6 (3) (+1.0)	119.6 (7)	119.7 (9) (−0.1)
C2–N3–C4	120.4 (3) (+0.6)	119.8 (9)	119.6 (13) (−0.2)
C4–N3–C3	119.1 (3) (−1.5)	120.6 (7)	121.0 (14) (+0.4)
N3–C4–C5	117.5 (3) (−4.0)	121.5 (3)	122.5 (13) (+1.0)
N3–C4–N9	131.0 (3) (+4.7)	126.3 (7)	125.9 (11) (−0.4)
N9–C4–C5	111.5 (3) (−0.7)	112.2 (7)	111.6 (5) (−0.6)
C4–C5–C6	126.3 (3) (+3.3)	123.0 (10)	121.6 (14) (−1.4)
C4–C5–N7	108.5 (3) (+3.1)	105.4 (8)	107.3 (8) (+1.9)
C6–C5–N7	125.2 (3) (−6.4)	131.6 (8)	131.0 (14) (−0.6)
C5–C6–N1	114.7 (3) (+2.5)	112.2 (11)	112.9 (8) (+0.7)
C5–C6–O6	122.7 (3) (−4.3)	127.0 (7)	127.3 (12) (+0.3)
N1–C6–O6	122.5 (3) (+1.6)	120.9 (9)	119.8 (12) (−1.1)
C5–N7–C8	101.2 (3) (−4.6)	105.8 (8)	103.2 (6) (−2.6)
N7–C8–N9	117.1 (3) (+4.0)	113.1 (8)	116.2 (9) (+3.1)
C4–N9–C8	101.8 (3) (−1.6)	103.4 (8)	101.7 (9) (−1.7)

[a] Difference with respect to the N7–H(R) series.

1. Selected interatomic distances and bond angles are listed in Table II.

The titanocene unit has the common "open-clamshell" structure,[11] with a normal average Ti–C distance of 2.377 Å. The Ti–centroid distances are 2.054 and 2.073 Å for rings 1 and 2, respectively, whereas the Ti–centroid vectors make an angle of 135°. The two coordination positions in the "mouth of the clamshell" are occupied by the N7 and O6 atoms of a theophyllinate anion forming a chelate ring. In contrast with the complexes of the same ligand with copper, where the Cu–O6 distance was found to be ~1.0 Å longer than Cu–N7[6], the distances from Ti to the donor atoms (Ti–N7 = 2.211 (3) Å; Ti–O6 = 2.278 (2) Å) indicate binding of similar magnitude with both. To our knowledge, this is the first example of balanced N7/O6 chelation with 6-oxopurines. These bonds are nevertheless somewhat longer than those for similar systems with unidentate ligands. For instance, the Ti–O6 bond reported here is the longest known for a titanocene derivative. The bond length ranges found for various classes of complexes with oxygen ligands are 1.85–1.93 (phenoxides[33] and alkoxides[34]), 1.99–2.13 (water),[35] 2.06–2.15 (monodentate nitrate),[36] 1.92–2.00 (monodentate carboxylates),[37] 2.13–2.18 (bidentate carboxylates),[38] and 2.11–2.20 Å (ethers)[39]. Even in the bridging tetradentate oxalate complex, the Ti–O bonds are in the range 2.15–2.18 Å.[40] Ti–O distances of 2.26 Å with THF[41] and 2.25 Å with diethyl diazomalonate[42] have been found. Our Ti–O6 bond is relatively long, despite the fact that binding is taking place with an Ti–O6–C6 angle of 107.9 (2)°, a direction theoretically predicted to provide large charge density about O6.[43] The Ti–N7 bond is also relatively long. In the $(\eta^5\text{-}C_5H_5)_2$(purinato)TiCl complex with the monodenate purine monoanion, the Ti–N9 bond was found to be 2.131 (5) Å.[11] We do not believe that the weakening of this bond is due to the small O6–Ti–N7 angle (79.6 (1)°) imposed by the "bite" of the bidentate theophyllinate ion, since stronger bonds have been found for angles much smaller, namely in bidentate carboxylate[38] and aquo[35] complexes. This is more likely due to the fact that the Ti–N7 bond lies far from the expected lone-pair direction of N7. Binding along this direction would require equal C5–N7–Ti and C8–N7–Ti angles, as found in the monodentate purinate complex,[11] while the C8–N7–Ti angle here (154.2 (2)°) differs from the C5–N7–Ti angle (104.6 (2)°) by 50°. In other words, the Ti–N7 bond lies at a 25° angle from the anticipated lone-pair direction. Therefore, chelation by formation of the Ti–O6 bond is achieved at the expense of some Ti–N7 bonding.

The nine atoms of the purine system are coplanar within 4.5σ, the largest departure being found for C2 (0.013 Å). The exocyclic atoms O2 and C3 are distant from this plane by 0.013 (2) and 0.021 (4) Å, respectively. This plane makes an angle of 1.1° with the plane through Ti, O6, and N7.

In Table III are compared the bond angles of theophylline in the present compound with average results for theophylline derivatives and for N7-bonded complexes. Besides uncoordinated neutral theophylline, the N7–H(R) series given in the table includes N7-substituted derivatives with C-bonded substituents, which exhibit the same pattern of angles as theophylline itself (see Table VII, supplementary material). In the N7–M compounds, a theophylline monoanion is bonded to the metal atom via N7 in a unidentate manner. Structure for which weak metal···O6 interactions have also been found are included in this series, since this extra interaction does not perceptibly affect the ligand geometry.

The C5–N7–C8 angle in the Ti compound is 4.6° less than in free theophylline (N7–H(R) series), whereas the angles at the immediate neighbors are increased by 3.1 (N7–C5–C4) and 4.0° (N7–C8–N9). These changes are somewhat larger than those found for the N7–M complexes but are qualitatively similar. In both cases, the more remote angles undergo the same changes: −1.6° for C8–N9–C4 and −0.7° for C5–C4–N9. Similar patterns of structural changes have been observed for other purine systems upon deprotonation (or dealkylation) of an endocyclic N–H (or N–R) group.[45] The smaller C–N–C angle at the deprotonation site can be ascribed to the greater repulsion experienced by the adjacent N–C bonds from the nitrogen lone pair no longer retained along the N–H covalent bond. The remaining ring angles react to this change in such a way that planarity is retained (i.e., a net change on all angles of ~0°). Most of the balancing changes occur at the next neighbors, whereas the more remote apices are affected much less and in an unpredictable manner. It has been noted[11] that proton substitution by a metal ion affects ring geometry in a manner similar to proton dissociation. This generalization is supported by the series of N7–M compounds in Table III, with which the five-membered ring of the present Ti complex compares well. The variations on the angles at N7, C5, and C8 are somewhat greater here. Our value of the C4–N9–C8 angle (101.8 (3)°), equal to that of the N7–M series and 1.6° smaller

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(44) N7–H(R) = average values for 14 structures of neutral theophylline compounds containing an N7–H or N7–C bond; N7–M = average values for 12 structures of complexes in which a metal is bound to N7 of a theophylline monoanion. For details, see Table VI in the supplementary material.

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than for the N7–H(R) compounds, confirms that N9 is not protonated in this Ti compound, since it should otherwise be $\geqslant 103^\circ$.[46]

When compared with the N7–H(R) average values listed in Table III, the N7–M data indicate that the six-membered ring is not appreciably affected upon substitution of the N7–H proton by a metal atom. However, O6 coordination (present compound) introduces large variations in this ring, most of which can be correlated with a reduction of the N7/O6 "bite". The first effect is a simple in-plane motion of O6 toward N7, which decreases the C5–C6–O6 angle by 4.3°. The two adjoining angles undergo an equivalent overall change in the other direction (N1–C6–O6, +1.6°; N1–C6–C5, +2.5°), thereby maintaining the planar environment of C6. Reduction of the other angle in the chelate ring (N7–C5–C6) from 131.6 to 125.2° implies a motion of the C6–O6 group as a whole and some reorganization in the N1–C2–N3 portion. The positive variations at C6 (+2.5°) and C5 (+3.3°) are balanced by opposite variations at the adjacent apices (–4.8° at N1, –4.0° at C4), whereas smaller changes at C2 (+2.5°) and N3 (+0.6°) reduce the overall variation on the internal angles to ~0° and keep the ring planar.

The bond lengths are less sensitive to deprotonation and/or complexation. However, a few significant changes are detected. Coordination to O6 reduces the double bond character of C6=O6, as evidenced from the C–O distance (1.286 (4) Å) being greater than that in molecules with O6 free (1.229 (12) Å for N7–H(R), 1.238 (6) Å for N7–M). The lengthening is greater than found in $CuCl_2(1,3\text{-}Me_2uracil)_2$, where binding of Cu to a carbonyl oxygen increased the C–O distance by only 0.02 Å.[47] The C2=O2 distance in the titanium complex (1.225 (4) Å) is not modified as expected. Electron redistribution in the N7–C5–C6 portion of the chelate ring is probably responsible for rather large variations of 0.023 and –0.051 Å in the C5–N7 and C5–C6 bond lengths after chelate formation. The N7–C8–N9 region is also slightly affected, in the same manner as for the series of N7–M compounds. The N7–C8 and C8–N9 distances, which are respectively 1.346 (18) and 1.337 (12) Å in the N7–H(R) compounds, are in the opposite order for the present titanium complex (1.346 (5) and 1.360 (5) Å, respectively) and for the N7–M compounds in general. This indicates that the double bond, localized between C8 and N9 in the N7–H(R) compounds, is more delocalized over the N7–C8–N9 region after deprotonation.

Infrared Spectrocopy. The IR spectrum of the complex was recorded (see Experimental Section) and compared with that of uncomplexed theophylline (Figure 4, supplementary material). One of the three bands at ca. 3100 cm^{-1} and the absorptions at 1440, 1115, 1017 and 800 cm^{-1} are attributable to the π-bonded C_5H_5 rings.[48] Most of the remaining bands originate from vibrations in the theophylline unit. Although a number of bands are significantly affected by complexation, they will not be discussed since no detailed assignments are available for theophylline.

The broad ν(N–H) band at 2600–2850 cm^{-1} and the γ(N–H) band at 852 cm^{-1} [49] are both absent from the spectrum of the complex, as expected. The 1500–1750-cm^{-1} portion containing the C=O, C=C, and C=N stretching vibrations is where evidence for N7/O6 chelation has generally been looked for. The intense ν(C=O) absorptions at 1720 and 1670 cm^{-1} (1715 and 1675 cm^{-1} in THF solution) for free theophylline are shifted to 1692 and 1655 cm^{-1} (1700 and 1662 cm^{-1} in THF), respectively, for the complex. Also, substantial shifts from 1615 and 1570 cm^{-1} (1610 and 1560 cm^{-1} in THF) to 1583 and 1530 cm^{-1} (1592 and 1545 cm^{-1} in THF), respectively, are observed for the purine ring modes. Although these changes clearly show that theophylline unit is perturbed, they are primarily sensitive to the loss of the imidazole proton. In a previous report on Hg–theophylline complexes,[50] it was shown that this spectral region is not greatly modified when theophylline forms compounds like $[CH_3Hg(C_7H_8N_4O_2)]NO_3$, where the ligand remains formally neutral and retains its imidazole proton. Salas-Peregrin and co-workers[51] arrived at the same conclusion for the $PdCl_2(C_7H_8N_4O_2)_2$ compound, where the metal is bonded to the free imidazole nitrogen of neutral theophylline. On the other hand, for compounds such as $CH_3Hg(C_7H_7N_4O_2)$, where the imidazole proton is replaced by the metal, the IR bands in the 1500–1750-cm^{-1} region occur virtually at the same positions as for the present titanocene compound, in spite of the fact that the CH_3Hg^+ group is bonded to N7 only, without participation of O6.[8b] Therefore, we feel that balanced N7/O6 chelation compared with unidentate N7 binding introduces no drastic changes in the 1500–1750-cm^{-1} region of the IR spectrum.

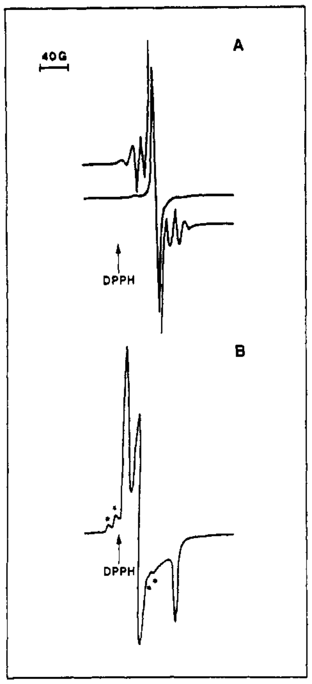

Figure 2. EPR spectra: (A) $(\eta^5\text{-}C_5H_5)_2(C_7H_7N_4O_2)Ti$ complex in toluene–benzene (4:1) solution at ambient temperature; (B) Same sample in a glass at 77 K. The asterisks indicate the hyperfine splitting with titanium.

EPR Spectroscopy. The X-band EPR spectra are consistent ith the structure found in the crystal being retained in toluene–benzene (4:1) solution. The powder spectrum (Figure 2, curve A) shows a single resonance (g = 1.971), as does the solution spectrum at room temperature (g = 1.979). At high recorder gain, hyperfine spin-metal coupling with ^{47}Ti ($I = {}^5/_2$, 7.28% natural abundance) and ^{49}Ti ($I = {}^7/_2$, 5.51%) nuclei is observed in the solution spectrum. The line intensities are consistent with superimposed octet and sextet splittings of the degenerate spin states expected with these nuclei, though not all of the eight lines could be observed due to the very intense single derivative resonance signal originating from the more abundant ^{46}Ti, ^{48}Ti, and ^{50}Ti (I = 0, 86.74%) nuclei[52] (Figure 2). The average hyperfine splitting measured (A = 13.45 G), is among the strongest values reported so far for a mononuclear titanocene derivative.[22,24,30,52]

The liquid-nitrogen-temperature spectrum of the complex in toluene–benzene (4:1) glass is also shown in Figure 2 (curve B). The spectrum is characteristic of a rhombic tensor with g values of 2.000, 1.987, and 1.952. This type of spectra has been reported

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for several paramagnetic mononuclear titanocene complexes of the type (η^5-C_5H_5)$_2$Ti(XL) (XL = bidentate ligand).[27] The four weak signals depicted by an asterisk in the glass spectrum are attributable to the hyperfine spin-metal coupling. The interline splitting measured in the glass spectrum at 77 K is identical with that observed in the room-temperature spectrum.

Mass Spectrometry. The electron-impact spectrum (see Experimental Section) suggests that Ti-theophyllinate chelation is relatively strong. It shows a strong parent ionic peak at m/z 357 attributable to the molecular ion $[C_{17}H_{17}N_4O_2Ti]^+$. The presence of the base peak at m/z 292 is due to $[C_{12}H_{12}N_4O_2Ti]^+$, resulting from the loss of a neutral cyclopentadienyl ring from the parent ion, without loss of theophylline. Similar fragmentation behavior producing high concentrations of the molecular and metallocyclic fragments in the mass spectra have been reported for titanocene compounds containing strong chelating ligands, such as deprotonated uracil, cyanuric acid, thymine, biimidazole, and bibenzimidazole.[28,30,32] The peaks at m/z 178 and 113 are typical of the titanocene moiety and correspond to molecular ions having lost the theophylline unit to give $[C_{10}H_{10}Ti]^+$ and one cyclopentadienyl ring to give $[C_5H_5Ti]^+$, respectively. The rest of the peaks are due to ionized ligand fragments.

Discussion

To our knowledge, the present work affords the first unambiguous proof for the formation of a "balanced" N7/O6 chelate with a 6-oxopurine. This type of interaction has attracted considerable attention in recent years, since it has been proposed as a critical step in the mechanism responsible for the antitumor activity of $PtCl_2(NH_3)_2$ and other *cis*-diammineplatinum(II) complexes.[2,3] According to this model, the incoming Pt(II) species would first bind to the available N7 site of guanine; in a subsequent step, the second leaving group would be displaced by O6 with closure of a chelate ring on Pt. As pointed out by other authors,[4] the presence of N7 in a five-membered ring fused with a six-membered ring would impose a large N7-C5-C6 angle of 125-130° in the chelate ring. Furhtermore, the N7 lone pair would be oriented somewhat outward from O6; indeed, if a metal atom is placed at 2.0 Å from N7 along the expected direction of the lone pair (equal C5-N7-M and C8-N7-M angles), this metal would be 3.0 Å away from O6 and would see the O6 lone pair with a C6-O6-M angle of 98°. Therefore, metal-O6 bonding can only take place at the expense of some efficiency in metal-N7 overlap. We have mentioned above that the Ti-O and Ti-N bonds are not found to be individually very strong, which means that some bonding with N7 has probably been sacrificed to render Ti-O6 bonding possible. Regardless of this, the strong intensity of titanium-theophylline-related fragments in the EI-MS spectra suggests that the overall bonding effect of theophylline is stronger than that encountered in other analogous titanium complexes with monodentate-bonded ligands. In fact, this observation applies strictly to the gas-phase cationic species of titanium complexes. However, in practice, as pointed out by several workers,[53] qualitative comparisons of this type can safely be made with the corresponding neutral transition-metal complex or with fragments of analogous molecules.

Although this structure shows that balanced N7/O6 chelates can exist with 6-oxopurines, it does not prove that a similar chelate necessarily exists for the Pt-guanine system. Indeed, chelation in the present system is helped by two factors.

First, theophylline is present as the monoanion, in which charge delocalization makes O6 more electron-rich than in the neutral form. This probably holds true even after Ti coordination to N7, as the metal is less electron-attracting than the expelled proton. On the other hand, metal coordination to the N7 position of guanosine or a guanine residue in DNA takes place without displacing an imidazolic proton, with the result that N7 coordination should make O6 *less* electron-rich, thereby reducing its affinity for the metal.

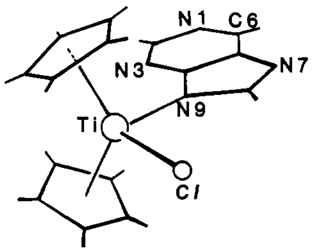

Figure 3. Structure of the (η^5-C_5H_5)$_2$(purinato)TiCl molecule.[11]

Secondly, chelate formation may depend on the particular van der Waals envelope of the titanocene unit. In a previous paper reporting the structure of (η^5-C_5H_5)$_2$TiCl(purinato), the intramolecular nonbonded contacts between the C_5H_5 rings and the N9-coordinated purine anion were examined in detail.[11] As shown in Figure 3, the purine anion lies close to the Cl-Ti-N9 plane; it is roughly parallel to the "mouth of the clamshell", and the six-membered ring is oriented outward. Intramolecular contacts were calculated for hypothetical molecules in which the purine ligand would be rotated to various positions about the Ti-N9 bond. It was noted that rotation can take place only in a narrow ±30° range about the parallel orientation. Beyond these limits, steric hindrance between the C_5H_5 hydrogens and either H8 or N3 becomes increasingly important. Rotation of 180° would remove steric hindrance with the C_5H_5 hydrogens but would lead to unacceptably short contacts with the Cl atom. Consequently, the six-membered ring must be oriented outward. This complex shows the other interesting characteristic of being bonded along the expected lone-pair direction of N9 (Ti-N9-C8 = 127.7 (4)°; Ti-N9-C4 = 129.7 (4)°). If the same purine anion were bonded via N7, there would be short H···H contacts between the C6-H hydrogen and those of the C_5H_5 rings. We proposed the presence of this repulsive effect in a hypothetical N7-bonded complex as a factor favoring the N9-bonded species, where the corresponding N3 site is devoid of a substituent. If analogous considerations are applied to the case of theophylline, it can be predicted that, in a titanocene complex with a unidentate N7- or N9-bonded theophylline anion, significant steric hindrance would exist. Indeed, this time, a bulky methyl group is attached to N3, whereas the C6 position is occupied by an oxygen, where a smaller hydrogen was present in purine. There is no obvious way to overcome these repulsions for an N9-bonded complex, since steric hindrance would arise from a methyl group. On the other hand, for an N7-bonded species, the repulsive O6···C_5H_5 interaction can be changed into Ti-O6 binding, if the theophylline is rotated by 180° while the other ligand inside the clamshell is displaced.

In summary, the van der Waals profile of the titanocene unit makes it difficult for a theophylline ligand to coordinate in a unidentate manner, because of steric hindrances with the groups attached to C6 or N3. On the other hand, the theophylline ion possesses a highly basic imidazole ring, which could lead to strong bonding with the metal center, if the steric problem can be overcome. Binding via N9 would not eliminate steric hindrance, whereas bidentate via N7/O6 does. It appears to us that the overall environment of the coordination sites plays a determining role in the formation of the chelate ring, by assembling two sterically complementary fragments.

The fact that chelation has not been observed so far suggests that N7/O6 may be disfavored under less restricted conditions. However, the possibility of such a ring being formed should not be dismissed lightly, even for Pt, since Lippert and co-workers[54] recently showed that Pt forms a four-membered chelate ring via N3/N4 with deprotonated 1-methylcytosine, a binding mode which has not been considered so far as a likely possibility.

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(53) Generally, the excess kinetic and excitation energies involved in the MS fragmentation are not determinant factors for comparisons such as those made here. See: Müller, J. *Angew. Chem., Int. Ed. Engl.* **1972**, *11*, 653-665. Efraty, A.; Huang, M. H. A.; Weston, C. A. *Inorg. Chem.* **1975**, *14*, 2796-2799.

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Registry No. $(\eta^5\text{-}C_5H_5)_2(C_7H_7N_4O_2)Ti$, 102342-11-0; $(\eta^5\text{-}C_5H_5)_2Ti(CO)_2$, 12129-51-0; $(\eta^5\text{-}C_5H_5)_2TiCl$, 60955-54-6.

Supplementary Material Available: Infrared spectra of theophylline and $(\eta^5\text{-}C_5H_5)_2(C_7H_7N_4O_2)Ti^{III}$ (Figure 4), listings of refined temperature factors (Table IV), distances and angles involving the hydrogen atoms (Table V), and weighted least-squares planes (Table VI), and a survey of interatomic distances and bond angles in crystal structures of theophylline derivatives (Table VII) (16 pages). Ordering information is given on any current masthead page.

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Electrochemistry of Nitrite Reductase Model Compounds. 2. Formation of an Iron Bis-Nitro Porphyrin Complex

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The reaction of $Fe^{III}(P)Cl$ and $Fe^{III}(P)(NO_3)$ (where P = tetraphenylporphyrin (TPP), tetraphenylchlorin (TPC), and octaethylporphyrin (OEP)) with nitrite was studied by UV/visible, proton NMR, and infrared spectroscopy and by electrochemistry. Quantitative analysis of the visible spectra generated by the titration of ferric–porphyrin complexes with nitrite showed the appearance of mono- and bis-nitrite complexes. The red shift of the Soret band for the bis-nitrite complexes of Fe^{III}TPP and -TPC is consistent with an anionic porphyrin complex. If a stronger axial ligand such as chloride was present, it was difficult to observe the mono-nitrite intermediate. Proton NMR of the titration of $Fe(TPP)(NO_3)$ with nitrite in DMF showed that both the mono and bis complexes were low spin, while the infrared spectrum was consistent with a Fe–N-bonded nitro complex. The cyclic voltammograms at slow scan rates of $Fe(TPP)(NO_3)$ in DMF and Me_2SO in the presence of nitrite showed reversible waves, and the shift in the $E_{1/2}$ values was consistent with the formation of mono- and bis-nitro complexes, with no coordination of the ferrous complex with nitrite. The formation constants calculated voltammetrically were consistent with the spectroscopically obtained values. The presence of the mono- and bis-nitro complexes was also seen for high concentrations of nitrite (about 20 mM) where, at high scan rates, a second reduction wave, which grew at the expense of the wave seen at low scan rates, was observed to be about 150 mV more negative than the original ferric/ferrous wave. Thus, the reduction must proceed by dissociation of the bis-nitrite complex to the mono-nitrite complex prior to reduction. At high scan rates, the dissociation of the bis-nitrite complex is too slow for the reduction to proceed exclusively through that mechanism, and a new wave is seen for the direct reduction of the bis-nitrite complex. A single oxidation wave was observed at all scan rates. For $Fe(OEP)(NO_3)$, there is evidence that one of the nitrite ligands remains coordinated in the ferrous oxidation state. In methylene chloride, the ferric/ferrous wave was irreversible, and the details of the electrochemistry are still under investigation. For all porphyrins and solvents studied, a new wave was seen at about −0.9 V vs. Ag/AgCl when nitrite was present. At this potential, one expects either NO or Fe(L)(NO) to reduce. At this time, the evidence points to the origin of this wave being due to NO and not Fe(L)(NO) when the solvent is DMF. During prolonged electrolysis, as in coulometry, though, a significant amount of Fe(L)(NO) was eventually formed.

Introduction

The enzymatic reduction of nitrite to ammonia (assimilatory nitrite reduction) is catalyzed by a class of enzymes with the same prosthetic groups: one siroheme (an iron isobacteriochlorin)[1,2] and an Fe_4S_4 cluster.[3,4] While the details of the enzymatic reduction have not been elucidated yet, work thus far has shown that nitrite reacts with the siroheme to form a nitrite complex that is reduced to an iron nitrosyl,[5] hydroxylamine, and then ammonia.[2] There is a second class of enzymes, the dissimilatory nitrite reductases, that reduce nitrite to nitric oxide, nitrous oxide, or dinitrogen. This enzyme contains two hemes *c* and two hemes d_1. For heme d_1, both a chlorin[6,7] structure and a dioxoisobacteriochlorin[8] structure have been proposed. As with the assimilatory enzymes, a nitrite complex is formed[9] that is reduced to nitric oxide,[10,11] nitrous oxide, or dinitrogen. The exact structure of the nitric oxide intermediate is still unclear and recent work has shown that labeled nitric oxide will not reduce to nitrous oxide, while labeled nitrite will.[12,13] An "HNO" species is thought to be involved.

The importance of the chlorin and isobacteriochlorin groups in the functioning of the enzymes is still an open question. The electrochemistry of iron porphyrins, chlorins, and isobacteriochlorins has been examined by several workers,[14,15] including ourselves.[16] An equally important question for the functioning of nitrite reductases is the redox chemistry and properties of iron–nitrosyl and iron–nitrite complexes. There are several reports on the electrochemistry of iron porphyrin nitrosyls,[17] as well as

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