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Synthesis and Crystal Structure of Chlorobis(η^5-cyclopentadienyl)purinato titanium(IV), a Model Compound for the Interaction of the Antitumor Titanocene Dichloride Molecule with DNA Bases

ANDRÉ L. BEAUCHAMP*

Département de Chimie, Université de Montréal, C.P. 6210, Succ. A, Montreal, Que. H3C 3V1, Canada

DANIEL COZAK* and ABDELHAKIM MARDHY

Départment de Chimie, Université Laval, Quebec, Que. G1K 7P4, Canada

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$(\eta^5\text{-}C_5H_5)_2TiCl_2$ shows significant antitumor activity and the title compound was investigated as a possible model for a species initially formed between titanocene dichloride and a purine base of DNA. The $(\eta^5\text{-}C_5H_5)_2TiCl(C_5H_3N_4)$ complex was prepared by refluxing the dichloride with purine in the presence of triethylamine in THF. The crystals are monoclinic, space group $P2_1/c$, a = 7.484(2) Å, b = 25.85(1) Å, c = 9.134(3) Å, β = 127.53(3)° and Z = 4 molecules per cell. The structure was refined on 1378 independent nonzero reflections to an R factor of 0.045. The unit cell contains individual molecules in which the basic features of titanocene dichloride are not profoundly affected. The rings show the usual 'open clamshell' arrangement. One of the Cl atoms has been replaced by the N9 atom of deprotonated purine. The purine moiety makes an angle of only 7.2° with the Cl–Ti–N9 plane, thus avoiding steric interference from the cyclopentadienyl rings. The structure is discussed in connection with the possibility of inter- and intra-strand crosslinking of DNA by a $(\eta^5\text{-}C_5H_5)_2Ti$ unit binding to the bases.

Introduction

The transition metal complex *cis*-dichlorodiammineplatinun(II) was the first in a series of Pt(II) compounds to be recognized as an efficient therapeutic agent for the treatment of tumors in living organisms [1]. The antitumor action of Pt in the body was traced to chemical attack by the metal species on DNA molecules [2]. Since these discoveries, the dichlorometallocene complexes $(\eta^5\text{-}C_5H_5)_2MCl_2$ (where M = Ti, V or Nb) are the only other reported group of metal agents of major importance with this property [3–5]. Detailed studies have shown that the metal intracellular distribution in titanocene-treated cells is identical to that reported for the Pt complex [6]. Moreover, inhibition of nucleic acid metabolism is a common effect observed for both groups of agents [7]. These and other considerations have led Köpf and Köpf-Maier to suggest that the mechanisms responsible for the biological actions of titanocene and of Pt-ammine complexes are the same [7, 8], that is, chemical attack of DNA molecules.

To the best of our knowledge, the 1:2 compound formed between uracil and the [bis(η^5-methylcyclopentadienyl)titanium(III)]$^+$ unit is the only reported titanocene compound with a nucleic base [9]. The structure of this compound is not known from X-ray work. Several complexes with heterocyclic nitrogen donors, including pyridine [10], bipyridine [11] and imidazole [12], are also known to exist. As part of a more elaborate scheme to investigate the chemical interactions of titanocene with DNA, we wish to report the synthesis and X-ray structure determination of the title compound with purine. The molecule described here can be regarded as a model for a species initially formed between $(\eta^5\text{-}C_5H_5)TiCl_2$ and a nucleic base. Purine itself is not normally found in DNA and the two purine bases (adenine, guanine) are attached to the backbone through the N9 site used to bind the metal in the present compound. However, this complex was expected to cast some light on geometrical factors governing the interaction of purine bases with the $(\eta^5\text{-}C_5H_5)_2M$ unit.

Purine is a versatile ligand. The neutral molecule contains three lone pairs to coordinate to metal ions. Displacement of the acidic proton on the imidazole ring makes an extra site available in the $(C_5H_3N_4)^-$ ion. At the present time, there are no reliable rules to predict the distribution patterns of protons and metal ions on these sites. The acidic hydrogen is definitely part of the imidazole ring, but it shows no

*Authors to whom all correspondence should be addressed.

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marked preference for one nitrogen atom in particular. In the solid state, this proton in bonded to N7 in purine [13], but to N9 in a purine–urea complex [14]. Crystal structures have been reported for three metal complexes so far. In $[Cu(H_2O)_4(C_5H_4N_4)]SO_4$, the ligand is formally neutral, but the acidic proton has moved to N1, whereas both N7 and N9 are used to bridge two copper atoms along the infinite chain found in the crystal [15]. Zinc is bound to N7 in $[ZnCl_3(C_5H_5N_4)]$ and the two acidic protons of the purine monocation are located on N1 and N7 [16]. In contrast, copper is bound to N3 in a chloro complex formulated as $[Cu_2Cl_6(C_5H_5N_4)]$ [17], which will be further discussed below.

This appears to be the first crystallographic study on a complex containing purine in the anionic form. From the above discussion, it is clear that the site of attachment of titanium could not be reliably predicted.

Experimental

All manipulations were carried out under a purified nitrogen atmosphere using a Schlenk-type vessel. Tetrahydrofuran (THF) was refluxed over a benzophenone–sodium mixture for 30 min before being distilled. Dichlorotitanocene $(\eta^5\text{-}C_5H_5)_2TiCl_2$ (Strem Chemicals) and purine $C_5H_4N_4$ (Sigma Chemicals) were used as received. Triethylamine was distilled and stored under nitrogen before use. Mass spectra were recorded on a Hewlitt-Packard 5995A apparatus. Infrared spectra were run on a Beckman IR4250 instrument and calibrated against a polystyrene film. Varian EM-360A and Bruker WH-90 instruments were used to record the ^1H NMR data. The C, H and N analyses were carried out on a Hewlitt-Packard 185 F&M Scientific analyzer in our laboratory.

Preparation of $(\eta^5\text{-}C_5H_5)_2TiCl(C_5H_3N_4)$

The product was prepared in a 100 ml Schlenk tube containing 40 ml of freshly distilled THF, to which 1.50 g (6 mmol) of $(\eta^5\text{-}C_5H_5)_2TiCl_2$, 1.45 g (12 mmol) of purine, and 1.68 ml (12 mmol) of $N(C_2H_5)_3$ were successively added. The solution was then refluxed under a positive nitrogen atmosphere for 18 h. After cooling the solution to room temperature, a white precipitate [^1H NMR ($CDCl_3$) δ: 1.36 (t, CH_3), 3.08 (q, CH_2)] appeared at the bottom of the tube and was separated from the dark red solution by filtration. The filtrate was then evaporated to dryness under reduced pressure and redissolved in a minimum quantity of warm THF. This gave 1.65 g of dark red crystals after allowing the solution to cool slowly to room temperature. Yield 82%; mp 155 °C. *Anal.* Calcd. for $C_{15}H_{13}N_4ClTi$: C, 54.16; H, 3.94; N, 16.84. Found: C, 54.68; H, 3.53; N, 16.93. Mass spectroscopy (180 °C, 70 eV), m/e (relative intensity >15%): 332 (M^+, 5), 269 (19), 267 (46), 213 (19), 185 (33), 183 (43), 150 (31), 149 (17), 148 (81), 147 (12), 122 (18), 121 (15), 120 (100), 93 (18), 85 (17), 83 (29), 66 (36), 65 (34), 52 (16). ^1H NMR (DMSO-d_6) δ: 6.73 (s, C_5H_5); 8.70 (s, purine), 9.00 (s, purine) and 9.23 (s, purine). IR (KBr pellet) ν_{max}: 3100 (m, C_5H_5), 1605 (m, C=C), 1595 (s, C=N), 1440 (m, C_5H_5), 1015 (w, C_5H_5), 815 (s, C_5H_5), 570 (w, Ti–N), and 395 (w, Ti–Cl).

Crystal Data

$C_{15}H_{13}ClN_4Ti$, fw = 332.66, $F(000) = 170$. Monoclinic, $P2_1/c$, $a = 7.484(2)$, $b = 25.85(1)$, $c = 9.134(3)$ Å, $\beta = 127.53(3)°$, $V = 1402.7$ Å^3, $D_c = 1.575$ g cm^{-3}, $Z = 4$, $\lambda(MoK\bar{\alpha}) = 0.71069$ Å (graphite monochromator), T = 293 K, $\mu(MoK\alpha) = 7.9$ cm^{-1}, crystal dimensions: 0.10 mm (010 – 0$\bar{1}$0) × 0.17 mm (001 – 00$\bar{1}$) × 0.19 mm (100 – $\bar{1}$00).

Crystallographic Measurements

The crystals are somewhat sensitive to moisture and the specimen used was sealed in a Lindemann capillary. The space group was unambiguously determined from precession and cone-axis photographs. Accurate cell parameters and intensity data were obtained with an Enraf-Nonius CAD4 diffractometer, as described elsewhere [18].

A total of 2523 independent hkl and hk$\bar{l}$ reflections within a sphere limited by $2\theta \leq 50°$ were collected, of which 72 were systematically absent reflections. A set of 1378 reflections with intensity significantly above background ($I > 3\sigma(I)$) were retained for subsequent work. The intensity data were corrected for the effects of Lorentz and polarization, but not for absorption (expected transmission range: 0.85–0.93).

The structure was solved by the heavy-atom method and refined on $|F_o|$. Refinement was first carried out isotropically by full-matrix least squares, then anisotropically by block-diagonal least squares. The C–N framework of purine possesses a pseudo-mirror plane through C8 and the midpoints of the C4–C5 and N1–C2 bonds. However, this ambiguity was solved by means of the residual electron densities found for H2 and H6 in the difference Fourier map phased on the nonhydrogen atoms, on the one hand, and from the pattern of bond angles in the six-membered ring (*vide infra*), on the other hand. The hydrogen atoms of the purine and cyclopentadienyl groups were fixed at ideal positions (B = 5.0 Å^2). Their parameters were not refined, but their coordinates were recalculated after each least-squares cycle. The final residuals were $R = \Sigma||F_o| - |F_c||/\Sigma|F_o| = 0.045$ and $R_w = [\Sigma w(|F_o| - |F_c|)^2/\Sigma w|F_o|^2)]^{1/2} = 0.054$. The goodness-of-fit ratio was 2.06 for 191 parameters refined. The final difference

Fourier map showed a general background below ±0.25 e/Å^3, except for a few peaks in the range ±|0.25–0.40| e/Å^3 within 1.1 Å from Ti or Cl. The final coordinates are listed in Table I. The temperature factors and structure factor amplitudes are available upon request.

TABLE I. Refined Coordinates of $(\eta^5\text{-}C_5H_5)_2TiCl(C_5H_3N_5)$ ($\times 10^4$, Ti $\times 10^5$).

Atom	*X*	*Y*	*Z*
Ti	45166(15)	15738(3)	13810(11)
Cl	5726(3)	2369(1)	2915(2)
N1	1576(9)	−55(2)	3809(6)
C2	1592(11)	22(3)	2380(8)
N3	2320(9)	432(2)	1997(6)
C4	3147(8)	802(2)	3259(6)
C5	3271(9)	768(2)	4852(7)
C6	2419(11)	326(2)	5053(8)
N7	4274(8)	1204(2)	5892(6)
C8	4658(9)	1481(2)	4902(7)
N9	4037(7)	1265(2)	3283(5)
C10	2247(9)	1705(2)	−1822(7)
C11	1892(9)	2132(2)	−1101(8)
C12	884(10)	1967(2)	−315(8)
C13	534(9)	1434(2)	−585(7)
C14	1384(9)	1267(2)	−1503(7)
C15	8491(9)	1455(3)	3302(8)
C16	7785(11)	1576(3)	1565(10)
C17	6437(10)	1170(3)	416(8)
C18	6302(12)	816(3)	1472(11)
C19	7584(11)	994(3)	3242(9)

The scattering curves were those of Cromer and Waber [19], except for hydrogen [20]. The anomalous dispersion terms f′ and f″ of Ti and Cl [21] were used in structure-factor calculations. The programs used are listed elsewhere [22].

Results

The present 1:1 complex was prepared from a reaction mixture containing $(\eta^5\text{-}C_5H_5)_2TiCl_2$, purine and $N(C_2H_5)_3$ in a 1:2:2 ratio. On several occasions during the reaction, aliquots were taken from the solution and evaporated. The residue was redissolved in $CDCl_3$ and product formation was monitored by following the cyclopentadienyl proton NMR signals of the dichloride (δ = 6.60 ppm) and of the product (δ = 6.70 ppm). Moreover, the proton NMR spectrum of the white precipitate formed during the reaction coincides with that of the protonated amine $[HN(C_2H_5)_3]Cl$. These observations are consistent with the reaction proposed in eqn. 1:

$$(\eta^5\text{-}C_5H_5)_2TiCl_2 + C_5H_4N_4 + N(C_2H_5)_3 \longrightarrow (\eta^5\text{-}C_5H_5)_2TiCl(C_5H_3N_4) + [HN(C_2H_5)_3]Cl \quad (1)$$

Thus the second chlorine atom failed to be displaced by a purinate group; even a sixfold excess of purine and triethylamine yielded the same compound.

The dark red crystals were found to contain the $[(\eta^5\text{-}C_5H_5)_2TiCl(C_5H_3N_4)]$ molecule shown in Fig. 1.

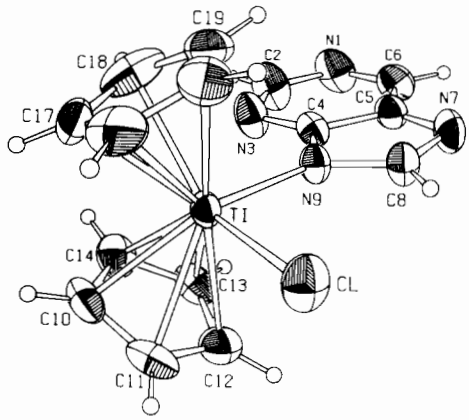


Fig. 1. ORTEP drawing of the $[(\eta^5\text{-}C_5H_5)_2TiCl(C_5H_3N_4)]$ molecule. The ellipsoids correspond to 50% probability. Hydrogens are shown as small spheres of arbitrary sizes.

The pair of π-bonded cyclopentadienyl rings adopt the 'open clamshell' arrangement found for the dichloride [23] and a number of $(\eta^5\text{-}C_5H_5)_2TiXY$ compounds [24–33]. The centroids of the cyclopentadienyl rings, the Cl atom and the N9 site of deprotonated purine define a distorted tetrahedron about titanium. Interatomic distances and bond angles are listed in Table II. The steric demand of the C_5H_5 rings produces a R–Ti–R angle (132.3°, R = ring centroid) much greater than that of Cl–Ti–N (92.1(1)°). Typical ranges for these angles in similar compounds are 128–133° and 87–98°, respectively [23–31]. The Ti–Cl distance, 2.338(2) Å, lies in the range 2.32–2.37 Å observed for Cp_2TiCl_2 compounds (Cp = $\eta^5\text{-}C_5H_5$ or substituted cyclopentadienyl) [23, 33, 35], but it is significantly shorter than those reported for several $(\eta^5\text{-}C_5H_5)_2$-TiClY molecules: Y = OEt, 2.405(1) Å [24]; Y = O, 2.409(1) Å [25]; Y = CH_3CO, 2.494(6) Å [26]; Y = substituted phenoxy ions, 2.38–2.40 Å [28]. Only in $Cp_2TiCl(SiMe_3)$ is the Ti–Cl distance (2.31(1) Å [27]) shorter than ours. The Ti–N distance of 2.131-(5) Å is similar to those found for N donor sites in complexes with deprotonated pyrrole (2.085(5) Å) [29] and diphenylurea (2.14(2) Å) [30].

The C–C distances in the cyclopentadienyl rings (mean = 1.384 Å) are normal. The relative orientation of the rings is 9.5° away from the eclipsed conformation. Ring 1 is planar within 1.6 σ (0.010 Å) and ring 2 within 1.0 σ (0.009 Å). The Ti–Centroid distances (2.054 and 2.050 Å) are typical of this type of molecule [24–33]. The individual Ti–C distances to carbon atoms on the same side as Cl and N9 tend to

TABLE II. Selected Interatomic Distances and Bond Angles in $(\eta^5\text{-}C_5H_5)_2TiCl(C_5H_3N_4)$[a].

Distance (Å)			
Ti–Cl	2.338(2)	Ti–R1[b]	2.054
Ti–N9	2.131(5)	Ti–R2[b]	2.050
Ti–C10	2.348(5)	C10–C11	1.391(9)
Ti–C11	2.380(6)	C11–C12	1.388(11)
Ti–C12	2.388(7)	C12–C13	1.396(8)
Ti–C13	2.393(7)	C13–C14	1.394(10)
Ti–C14	2.356(6)	C14–C10	1.419(9)
Ti–C15	2.382(8)	C15–C16	1.369(10)
Ti–C16	2.348(10)	C16–C17	1.390(11)
Ti–C17	2.339(9)	C17–C18	1.377(11)
Ti–C18	2.344(8)	C18–C19	1.364(10)
Ti–C19	2.379(7)	C19–C15	1.356(10)
Angles (deg)			
Cl–Ti–N9	92.1(1)	C10–C11–C12	108.7(6)
Cl–Ti–R1	106.3	C11–C12–C13	108.3(6)
Cl–Ti–R2	106.8	C12–C13–C14	107.9(6)
N9–Ti–R1	107.5	C10–C14–C13	107.9(6)
N9–Ti–R2	104.6	C16–C15–C19	108.8(7)
R1–Ti–R2	132.3	C15–C16–C17	107.1(7)
C4–N9–Ti	129.7(4)	C16–C17–C18	107.6(7)
C8–N9–Ti	127.7(4)	C17–C18–C19	107.9(7)
C11–C10–C14	107.1(6)	C18–C19–C15	108.6(7)

[a]Values for the purine ligand are given in Table III. [b]R1 and R2 are the centroids of (C10, C11, C12, C13, C14) and (C15, C16, C17, C18, C19), respectively.

be slightly greater (2.38–2.39 Å) than those on the opposite side of the molecule (2.34–2.35 Å).

If only atomic positions were considered, the purine framework would possess a mirror plane through C8 and the midpoints of the N1–C2 and C4–C5 bonds. Although carbon and nitrogen are sometimes difficult to distinguish from X-ray data, the pattern of angles clearly supports the atom labeling used here. For instance, C2–N1–C6 and N1–C2–N3 differ by 8–11° in uncoordinated purine (Table III). The same angles in the titanium complex show a difference of 11.5° in the same direction. Wrong labeling, which would interchange these two angles, would imply unrealistic changes on these angles. A similar difference between C2–N3–C4 and N1–C6–C5 reinforces this conclusion. Thus, the site of attachment for titanium in this molecule is N9, not N7.

The purine ligand is best described as two individual planar rings, with a slight bent of 1.2° about the C4–C5 bond. The mean plane through purine as a whole makes an angle of only 7.2° with the N9–Ti–Cl plane. The six-membered ring is pointing away from Cl, with which it would sterically interfere in the opposite orientation. Roughly equal Ti–N9–C4 and Ti–N9–C8 angles (129.7(4) and 127.7(4)°, respectively) indicate that coordination takes place along the anticipated lone-pair direction, with only minimal distortion. However, rotating the purine about the Ti–N9 bond toward a perpendicular orientation with respect to the Cl–Ti–N9 plane would introduce increasing steric hindrance with the C_5H_5 rings.

Results from crystallographic studies on free and coordinated purine compounds are compared in Table III. In general, protonation, deprotonation and complexation affect the bond lengths only to a very limited extent. On the other hand, bond angles respond much more significantly. For instance, in the $[ZnCl_3(C_5H_5N_4)]$ complex [16], the purine ligand is protonated at N1, whereas free purine is not. As a result, C2–N1–C6 is increased by 4.2°, while the adjacent angles are decreased by 2.8 and 3.4° with respect to free purine as the N9–H tautomer. This pattern of angle changes upon protonation is well documented for purines [34] and it can be related to reduced steric activity of the nitrogen lone pair when forming an N–H bond in the protonated species. Complexation of zinc at N7 introduces changes in the same direction, but much smaller, on the angles at N7 (+1.7°), C5 (−1.6°) and C8 (−1.4°). The C5–C4–N9 and C4–N9–C8 angles differ very little from those found in the N9–H tautomeric form of purine, since the N9–H bond is present in both cases. The N7–H

TABLE III. Distances and Angles in Various Purine Moieties.[a]

	PuH		PuH-Urea	$[ZnCl_3(PuH_2)]$	$[Cu_2Cl_6(PuH_3)]$	$[Cu(H_2O)_4(PuH)]SO_4$	$[(\eta^5\text{-}C_5H_5)_2TiCl(Pu)]$
	(N7–H) ref. 13		(N9–H) ref. 14	N1–H, N9–H, N7–Zn ref. 16	N1–H, N7–H, N9–H, N3–Cu ref. 17	N1–H, N7–Cu, N9–Cu ref. 15	N9–Ti this work
N1–C2	1.349(10)	1.349(6)	1.345(4)	1.348(5)	1.351(8)	1.381(22)	1.328(9)
N1–C6	1.330(10)	1.330(6)	1.342(4)	1.345(4)	1.333(8)	1.257(22)	1.337(8)
C2–N3	1.339(10)	1.324(6)	1.337(4)	1.313(5)	1.324(8)	1.364(22)	1.332(9)
N3–C4	1.337(10)	1.336(6)	1.326(4)	1.336(4)	1.330(7)	1.348(22)	1.326(7)
C4–C5	1.407(10)	1.398(6)	1.400(4)	1.393(4)	1.390(7)	1.425(22)	1.403(8)
C5–C6	1.393(10)	1.385(6)	1.383(4)	1.362(4)	1.388(9)	1.379(22)	1.374(9)
C5–N7	1.373(10)	1.375(6)	1.386(4)	1.382(4)	1.364(8)	1.377(22)	1.367(7)
N7–C8	1.327(10)	1.337(6)	1.386(4)	1.317(5)	1.318(8)	1.412(22)	1.315(9)
C8–N9	1.311(10)	1.313(6)	1.363(4)	1.353(4)	1.350(9)	1.317(22)	1.371(7)
C4–N9	1.379(10)	1.369(6)	1.367(4)	1.358(4)	1.370(8)	1.361(22)	1.363(7)
	(N7–H)		(N9–H)	N1–H, N9–H, N7–Zn	N1–H, N7–H, N9–H, N3–Cu	N1–H, N7–Cu, N9–Cu	N9–Ti
C2–N1–C6	118.4(8)	117.5(5)	118.9(3)	123.1(3)	124.3(5)	126.1(10)	116.3(6)
N1–C2–N3	127.9(8)	128.5(5)	127.0(3)	124.2(3)	123.4(6)	120.9(10)	128.8(7)
C2–N3–C4	113.0(8)	113.4(5)	112.3(3)	112.8(3)	113.3(5)	115.1(10)	113.2(6)
N3–C4–C5	123.9(8)	123.1(5)	126.5(3)	126.6(3)	126.4(5)	121.3(10)	123.9(6)
C4–C5–C6	117.9(8)	118.5(5)	116.1(3)	117.4(3)	117.8(5)	120.6(10)	116.6(6)
C5–C6–N1	118.9(8)	119.1(5)	119.2(3)	115.8(3)	114.8(5)	115.4(10)	121.1(6)
C4–C5–N7	105.1(8)	105.5(5)	110.7(3)	109.1(3)	108.0(5)	108.0(10)	109.3(5)
C5–N7–C8	106.5(8)	106.3(5)	103.2(3)	104.9(3)	107.6(5)	102.9(10)	103.2(5)
N7–C8–N9	115.1(8)	114.1(5)	114.3(3)	112.9(3)	110.7(6)	114.3(10)	116.6(5)
C8–N9–C4	103.8(8)	104.6(5)	106.2(3)	106.9(3)	107.4(5)	105.7(10)	102.5(5)
C5–C4–N9	109.6(8)	109.6(5)	105.6(3)	106.2(3)	106.3(5)	108.8(10)	108.3(5)

[a] Pu = $(C_5H_3N_4)^-$, PuH = $(C_5H_4N_4)$, PuH_2 = $(C_5H_5N_4)^+$, PuH_3 = $(C_5H_6N_4)^{2+}$.

and N9-H forms of uncoordinated purine show significant differences on bond angles in the 5-membered rings (Table III). These differences can be rationalized along the same lines as above.

The angles around N1 and N3 in the $[(\eta^5\text{-}C_5H_5)_2\text{-}TiCl(C_5H_3N_4)]$ complex are similar to those of free purine in either form, in good agreement with the absence of protons on these sites in the complex. However, the angles in the imidazole ring differ considerably. Deprotonation of the N9–H tautomeric form of purine is expected to decrease the C4–N9–C8 angle by ~4.5° (to ~101.5°), and to increase C5–C4–N9 and N9–C8–C7 by ~1.5° (to ~107 and ~116°, respectively). Complexation at N9 then reduces these changes, but only to a small extent. Thus, our values of 102.5(5), 108.3(5) and 116.6(5)° for C4–N9–C8, C5–C4–N9 and N9–C8–N7, respectively, follow the general trends for purines.

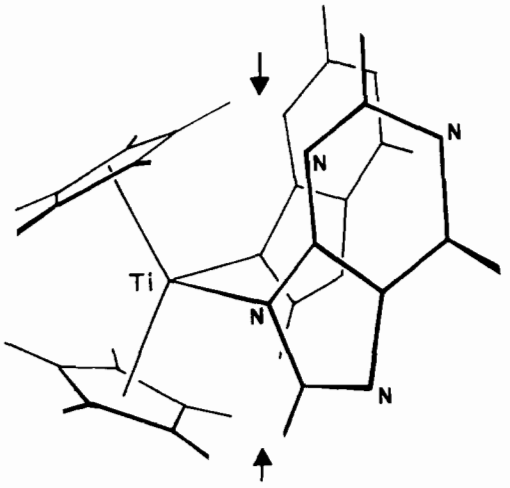
The structure of a purine–copper compound formulated as $[Cu_2Cl_6(C_5H_5N_4)]$ was recently described [17]. Copper is bound to N3 and protons occupy the N9 and N1 sites. Since copper is presumably divalent, the charge balance requires the purine unit to be dicationic, but only two N-bonded protons were located in the electron-density map. Inspection of Table III clearly shows that an extra proton must be present on N7 and that the purine moiety is $(C_5H_6N_4)^{2+}$. Indeed, the C5–N7–C8 angle in the copper complex is 4.4° greater than in uncoordinated purine (N9–H tautomer), whereas the C4–C5–N7 and N7–C8–N9 angles are respectively 2.7 and 3.4° smaller. This is a clear indication for N7-protonation. The large angles at N1 and N9 in the copper complex support the presence of protons at these positions, as deduced from the electron-density map.

Discussion

The acidic proton of purine, although involved in a tautomeric equilibrium between N9 and N7 [35], remains on the five-membered ring [13, 14]. Therefore, titanium binding to this part of the ligand is consistent with the basic properties of the purinate anion with respect to the proton. The N7 and N9 donors are also more accessible than N3 and N1, as the smaller internal C–N–C angles in the five-membered ring (~108° *vs.* ~120°) result in greater Ti–N–C angles and reduced repulsions between the atoms bonded to the α carbons (*i.e.* H8 and N3) and the rest of the coordination sphere.

The preference for N9 over N7 is still unclear. Metal binding to the N9 position of purine derivatives has been observed in 1:1 complexes with the anions of xanthine [36] and adenine [37], but theophylline reacts through N7 [38]. The relative basicities of N7 and N9 are probably a subtle function of the substituents present in the other ring. However, steric effects from the groups attached to C6 and N3 are also likely to play a role. In the present case, it can be shown that in a hypothetical $(\eta^5\text{-}C_5H_5)_2TiCl(C_5H_3N_4)$ species where purine would be bonded through N7, there would exist contacts shorter than 2.2 Å between H6 and cyclopentadienyl hydrogens. Thus, the absence of steric hindrance in the region of N3, which is devoid of a substituent, could promote binding to N9.

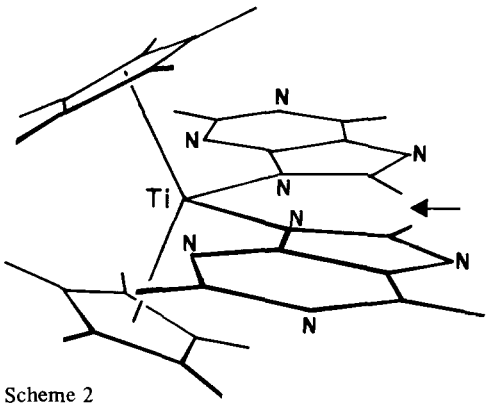
The overall geometry of the present complex provides a basis to speculate on possible modes of interaction of the $(\eta^5\text{-}C_5H_5)_2Ti$ moiety with bases in DNA. A determining factor is the fact that the purine lies close to the N9–Ti–Cl plane and that rotation about the Ti–N9 bond is restricted to a narrow ~30° range. A purine ring standing at 90° from the observed orientation would experience unreasonable steric repulsion due to contacts of N3 or H8 with cyclopentadienyl hydrogens at less than 1.3 Å. In this respect, the pyrimidines (cytosine, uracil and thymine) bound through their endocyclic N3 sites would represent a worse situation, as the substituents on the α carbon are still bulkier. Therefore, *intra*-strand crosslinking, one of the mechanisms retained for the Pt antitumor compounds, has to be discarded, since the positions occupied here by Cl and N9 would have to be occupied by donors of two consecutive bases of DNA having the most unfavorable orientation with respect to the $(\eta^5\text{-}C_5H_5)_2Ti$ unit (Scheme I).



Scheme 1

*Inter*strand crosslinking could take place provided the two roughly coplanar bases on different strands can be introduced into the 'mouth of the clamshell' without producing excessive steric hindrance on each other. This appears to be possible if at least one of the sites of attachment to the metal is an exocyclic group on the base. However, introduction of two bases bound through endocyclic groups would require some distortion. Indeed, we have generated a

hypothetical $[(\eta^5\text{-}C_5H_5)_2Ti(C_5H_3N_4)_2]$ unit by substituting Cl by a second N9-bonded purinate ion oriented outward (Scheme II). The distance between the H8 atoms on these ligands is only 1.1 Å and cannot be appreciably reduced by simply rotating the ligands about Ti–N9 bonds in the narrow range allowed. These steric effects could explain why the 2:1 complex was not isolated here in spite of the large excess of purine used in the preparation. However, it would be premature to rule out the possibility of obtaining a 2:1 compound, because the H8···H8 repulsion could presumably be relieved by increasing the N9–Ti–N9′ and the Ti–N9–C8 angles.



Scheme 2

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