Chelation Involving Carbonyl Groups in an Oxopurine: Structure of a 3:1 Titanocene:Xanthine Complex

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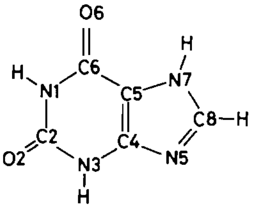
Various dichlorometallocenes recently attracted attention as potential antitumor agents [1]. As part of a research program dealing with the affinity of the titanocene moiety for various biologically interesting molecules, we first reported on the $(\eta^5\text{-}C_5H_5)_2$(purinato)TiCl complex [2]. More recently, the interactions with oxopurines were examined and an unusual trinuclear complex of composition $[(\eta^5\text{-}C_5H_5)_2Ti]_3Cl(HXan)$ was obtained from xanthine (HXan, I). We felt that the high metal-to-ligand ratio could favor the participation of carbonyl groups in coordination, possibly leading to the formation of chelate rings, whose existence was often postulated, but never fully established, for guanine and other oxopurines.



I H_3Xan

Several research teams have indeed investigated the coordination of oxopurines with metal ions [3–5], a major point of interest being the possibility of closing a chelate ring by binding of O6 to a metal atom initially coordinated to the N7 endocyclic site. Such a chelate was considered as an intermediate in a possible mechanism of action for Pt antitumor drugs, which are known to initially bind to N7 of guanine residues in DNA [3]. Model systems showed that carbonyl oxygens of oxopurines usually take part in hydrogen bonding with nearby ligands in the metal coordination sphere. In the absence of hydrogen bond donors, weak coordinating interactions with residual coordination site on the metal may take place. For instance, metal···carbonyl interaction was observed in a Cu(II)–theophylline complex, but the Cu–O6 contact is 2.919 Å, whereas the Cu–N7 distance is 1.956 Å [5]. Therefore, the ring in this compound is unbalanced.

Figure 1 shows that balanced chelate rings can be formed by the titanocene unit at two places on the oxopurine xanthine**. One ring is established via the N7/O6 pair and another one with the N1/O2 pair. The third titanocene unit interacts in a unidentate manner with the N9 site and with a Cl atom. The $(\eta^5\text{-}C_5H_5)_2Ti$ units have the usual 'open clamshell' structure with normal Ti-centroid distances averaging 2.05 Å [2, 6]. The shortest Ti–xanthine bonds are found for O2 (2.170(3) Å and N1 (2.182(3) Å), where the four-membered ring is comparable with those of bidentate carboxylates [6, 7]. The bonds are longer in the five-membered ring including Ti7–O6 and Ti7–N7 (2.247(3) and 2.225(4) Å, respectively). A similar geometry has been found for a $(\eta^5\text{-}C_5H_5)_2Ti$(theophyllinate) compound [8]. In both rings, the Ti–N bonds deviate considerably

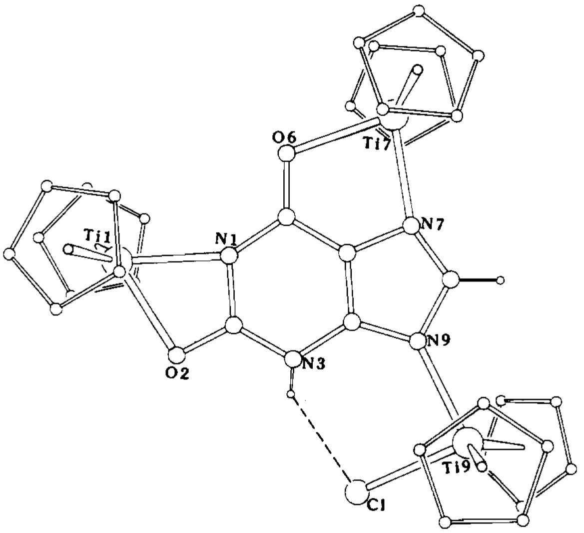


Fig. 1. ORTEP drawing of the $[(\eta^5\text{-}C_5H_5)_2Ti]_3Cl(HXan)$ molecule. Hydrogens on the C_5H_5 rings are omitted for simplicity.

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**Two molecules of $[(\eta^5\text{-}C_5H_5)_2]_3TiCl(C_5H_2N_4O_2)$ crystallize in the triclinic $P\bar{1}$ group with three molecules of toluene trapped in the lattice. The cell parameters are: a = 10.857, b = 13.043, c = 16.400 Å, α = 67.18, β = 75.05, γ = 86.02°. The structure was solved refined on 4679 unique non-zero reflections measured at 173 K to R = 0.047. There are two-fold disorders for one of the toluene and four of the C_5H_5 rings. The rest of the structure is perfectly ordered and well defined. Details on structure determination along with the preparative and spectroscopic work will be presented later.

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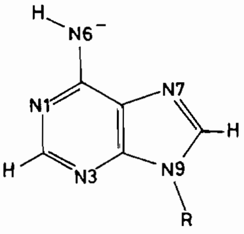
from the expected lone pair directions, as evidenced from the large differences between the Ti–N–C angles at N1 (Ti1–N1–Cl = 90.5(3)° *vs.* Ti1–N1–C6 = 149.1(3)°) and at N7 (Ti7–N7–C5 = 104.0(3) *vs.* Ti7–N7–C8 = 152.8(3)°). The third $(\eta^5\text{-}C_5H_5)_2$-Ti group is bound in a more symmetric manner (Ti9–N9–C4 = 131.2(3)° *vs.* Ti9–N9–C8 = 125.6-(3)°), with a Ti9–N9 distance (2.216(3) Å) lengthened by 0.09 Å compared with the similar bond in the complex with the purine anion [2]. The Ti9–Cl bond (2.515(1) Å) is also 0.17 Å longer than in the purinate compound. An intramolecular hydrogen bond is established between this Cl atom and the N3–H proton (N3•••Cl = 3.030(4) Å).

The present trinuclear complex contains both four- and five-membered balanced rings involving carbonyl groups of xanthine, despite the unfavorable overlap with the nitrogen lone pairs pointed out by previous workers [9]. Therefore, it is very likely that chelate rings could also form, at least for the $(\eta^5\text{-}C_5H_5)_2Ti$ unit, with other nucleic bases containing similar arrangements of donor atoms. The N7/O6 pattern exists for guanine, whereas N1/O2-type rings could form with cytosine (N3/O2) or uracil and thymine (N3/O2 and N3/O4). On the other hand, we have previously shown that the NH_2 groups of adenine and cytosine can be deprotonated under mild conditions in the presence of CH_3Hg^+ cations [10]. Therefore, it can be anticipated that the resulting deprotonated group (**II**), whose electron distribution probably approaches that of an imide (**IIb**), could participate in chelate formations just as carbonyl groups do. Pairs of imide/endocyclic nitrogen pairs can be found in various purines and pyrimidines, possibly leading to chelate with five-membered rings via N6/N7 in adenine (**II**), or four-membered rings via N3/N4 for cytosine (**III**), N1/N6 for adenine and N1/N2 for guanine. Some of these donor pairs are known to bridge Pt atoms [11] or CH_3Hg^+ groups [10]. Very recently, Lippert and coworkers [13] reported a Pt(IV) complex of 1-methylcytosine in which the deprotonated ligand forms a N3/N4 chelate. The present work suggests that chelation of N/O of N/N donor pairs of nucleobases to a single metal atom is sterically feasible.



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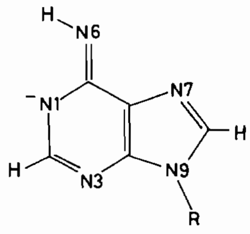

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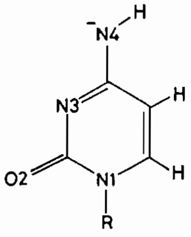

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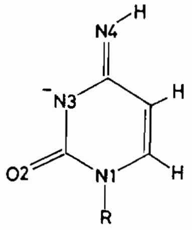

IIIb

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