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A model compound for the interaction of thallium(I) with nucleobases: crystal and molecular structure of (nitrato)(1-methylcytosine)thallium(I)

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Abstract

The reaction of 1-methylcytosine with $TlNO_3$ in variable ratios gave crystals of the 1:1 complex, $Tl(C_5H_7N_3O)NO_3$. The crystal structure of the title compound, which represents the first example of a nucleobase complex with Tl(I), has been performed. $C_5H_7N_4O_4Tl$ crystallizes in the triclinic system, space group $P\bar{1}$, with cell dimensions $a=3.786(2)$, $b=10.804(5)$, $c=11.508(5)$ Å, $\alpha=105.02(3)$, $\beta=92.37(4)$, $\gamma=98.24(4)°$, $U=448.4(4)$ Å^3, $Z=2$.

Introduction

Metal salts of the main Group III elements display interesting features in biological system [1]. Although toxic, several salts of Al^{3+}, Ga^{3+}, In^{3+} and Tl^{3+} as well as the chloride of Tl^+ have been demonstrated to be active against certain animal tumors, with $Ga(NO_3)_3$ being particularly effective [2]. Surprisingly, TlCl shows the highest activity of all these salts against a particular tumor, the ascitic form of the Walker 256 carcinosarcoma, while it is inactive against a series of other tumors [2, 3]. ^{67}Ga citrate has been found to accumulate in tumor tissue and sites of inflammation [4] and is now widely used as a radioimaging agent.

As to the toxic effects of Al^{3+}, they have, among others, been attributed to binding to ATP and subsequent interference with ATP dependent processes [5]. Binding of Al^{3+} to ATP has been demonstrated by use of multinuclear NMR spectroscopy [6], and preferential binding of Al^{3+}, Ga^{3+} and In^{3+} to DNA and RNA as opposed to proteins has been observed [7]. Several possibilities such as interference with cell membrane transport of ions [8], interference with the metabolism of S-containing species [9], and coordination to non-protein biomolecules [10] have been discussed as possible reasons for thallium toxicity. Considering the mutagenic properties of thallium salts [11], binding to nucleic acids and in particular to DNA, seems to be likely as well.

As part of our continuous interest in the structural chemistry of metal nucleobase complexes, we have begun to also study interactions of main group elements with model nucleobases [12]. Here we report the first example of a thallium(I) compound with a model nucleobase, 1-methylcytosine (1-MeC). The coordination chemistry of cytosine nucleobases has been the subject of numerous studies. Crystal structure analyses up to *c.* 1987 have been reviewed [13]. They show an astonishing variety in metal binding patterns, including the following ones: N3; O2; N4; N3,O2 (chelating, semichelating or bridging); N3,N4 (chelating or bridging); N3,N4,N4 and phosphate-O. In addition, metal binding to C5 [14] and in a π fashion to C5,C6 [15] has been established using spectroscopic techniques. On the basis of the chemical similarity between Tl^+ and Ag^+, a structure of the title compound $Tl(1\text{-}MeC)NO_3$ similar to that of the corresponding Ag^+ complex [16] might have been expected. On the other hand, we were aware of the variability of Tl coordination numbers, ranging from 2 to 12 [17].

Experimental

The title compound was obtained as long, colourless needles by cocrystallization (4 °C, slow evaporation) of equal amounts of $TlNO_3$ and 1-methylcytosine in water. The yield was 89%. Elemental analysis data were satisfactory for C,H and N. Variation of the metal:nucleobase ratio from 1:4 to 3:1 did not yield another product. For the structure determination,

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a crystal of size 0.14×0.36×0.08 mm was used. Details of the X-ray data collection and structure determination are as follows: triclinic space group $P\bar{1}$, $a=3.786(2)$, $b=10.804(5)$, $c=11.508(5)$ Å, $\alpha=105.02(3)$, $\beta=92.37(4)$, $\gamma=98.24(4)°$, $U=448.4(4)$ Å^3, $Z=2$, $D_c=2.899$ g cm^{-3}; Nicolet R3m/V diffractometer with graphite-monochromated Mo Kα radiation; 5393 reflections with $3.0\leqslant 2\theta \leqslant 60.0°$; data correction for Lorentz–polarization and absorption effects (Ψ-scans); 2644 unique reflections, 2507 of which with $F \geqslant 3.0\sigma(F)$ were used during the final structure refinement.

The structure was solved via Patterson function and $\Delta\rho$ maps. It was refined (on F) using full-matrix least-squares with anisotropic displacement parameters for all non-H atoms and a common isotropic one for the H atoms, which were placed in geometrically calculated positions (C–H, 0.96; N–H, 0.90 Å). A total of 128 parameters was refined; 15 reflections were omitted because of suspected extinction. Weights $w=1.0/(\sigma^2(F)+(0.004F^2))$ led to a featureless analysis of variance in terms of $\sin\theta$ and F_o. The refinement converged to $S=0.90$, $R=0.042$, $R_w=0.048$, $(\Delta/\sigma)_{max}=0.08$. The largest peaks in the final $\Delta\rho$ map were $\pm 2.4(4)$ e Å^{-3} and were close to the Pt atoms. Atomic scattering factors were from ref. 18. Other programs used are given in refs. 19–23.

Atomic coordinates and equivalent isotropic temperature factors are given in Table 1.

TABLE 1. Atomic coordinates and equivalent isotropic or isotropic displacement parameters (Å^2×10^4)

	x	y	z	U_{eq}/U^a
Tl(1)	0.14059(5)	0.42671(2)	0.13951(2)	367
N(1)	0.7661(9)	0.8429(4)	0.1889(4)	331
C(1)	0.701(1)	0.9146(6)	0.1013(6)	475
H(11)	0.814(1)	1.0036(6)	0.1305(6)	480
H(12)	0.796(1)	0.8751(6)	0.0271(6)	480
H(13)	0.447(1)	0.9110(6)	0.0875(6)	480
C(2)	0.6269(9)	0.7126(5)	0.1639(5)	299
O(2)	0.449(1)	0.6587(5)	0.0653(4)	440
N(3)	0.6876(9)	0.6454(5)	0.2450(4)	329
C(4)	0.877(1)	0.7062(5)	0.3500(4)	307
N(4)	0.929(1)	0.6375(6)	0.4270(5)	450
H(41)	1.058(1)	0.6759(6)	0.4979(5)	480
H(42)	0.837(1)	0.5526(6)	0.4088(5)	480
C(5)	1.029(1)	0.8415(5)	0.3779(5)	370
H(5)	1.164(1)	0.8849(5)	0.4534(5)	480
C(6)	0.964(1)	0.9044(5)	0.2955(5)	377
H(6)	1.059(1)	0.9949(5)	0.3115(5)	480
N(11)	0.509(1)	0.2444(5)	0.2956(4)	384
O(11)	0.612(1)	0.3635(5)	0.3227(6)	651
O(12)	0.332(1)	0.1917(6)	0.1979(5)	726
O(13)	0.584(1)	0.1787(6)	0.3633(5)	662

$U_{eq}=(1/3)\Sigma_i\Sigma_j U_{ij}a_i^* a_j^* \mathbf{a}_i \cdot \mathbf{a}_j$

Discussion

Superficially, the crystal structure of Tl(1-Mec)NO$_3$ bears a close resemblance to the corresponding Ag compound [16]. Like in the latter, the basic structural feature of the Tl compound is the formation of infinite stacks of pairs of cytosine rings, occurring along the x axis, with the metal ions linking the nucleobases through N(3) and O(2) and the nitrate anions shielding the metals from the outside. This situation is best visualized in the stereodiagram given in Fig. 1. The existence of centrosymmetric, eight-membered macrochelates involving N(3), C(2) and O(2) positions of two 1-MeC rings as well as two metal ions is also retained in the Tl structure. However, the differences in size between Ag$^+$ (1.26 Å) and Tl$^+$ (1.47 Å) and preferred coordination numbers between the two metal ions also leads to distinct differences. While Ag$^+$ in Ag(1-MeC)NO$_3$ has a coordination number of four in an approximately trigonal pyramidal environment, Tl$^+$ forms eight bonds to two N(3), three O(2) as well as three nitrate oxygen atoms, ranging from 2.872(3) to 3.138(3) Å and averaging at 2.993 Å. Both Tl–O [24] and Tl–N [25] distances are comparable with reported data. As shown in Fig. 2 and listed in Table 2, the two shortest metal–nucleobase interactions occur to N(3) and O(2a), but a third bond, to O(2), is only slightly longer than the former. Thus the binding situation is to be considered a combination of a N(3),O(2) chelate *and* monofunctional binding to O(2) of the symmetry related cytosine ring *a*. A similar binding pattern has previously been observed for a Ca^{2+} complex of unsubstituted cytosine [26]. Expectedly, the N(3)–Tl(1)–O(2) angle (45.8(1)°) is still smaller than the angles (52–54°) in two chelates of Cd(II) with cytosine nucleobases [27]. Tl(1) forms two additional, weaker bonds to symmetry-related cytosines, to O(2) of ring *b* and N(3) of ring *c*. Both Tl(1), O(2), Tl(1a) and O(2a) as well as Tl(1), O(2), Tl(1b) and O(2b) form planar, four-membered rings, thereby giving rise to a staircase arrangement of Tl$_2$O$_2$ entities. As depicted in Fig. 3, all contacts to cytosine rings are such that Tl(1) is substantially out of the nucleobase plane. This is in marked contrast to the situation in Ag(1-MeC)NO$_3$, where Ag$^+$ is essentially within the plane of 1-MeC. The coordination sphere of each Tl is completed by three nitrate oxygens, with two (O(11),O(12)) acting in a chelating fashion and one (O(11c)) in a monodentate one. Although the coordination sphere of Tl(1) is irregular, there is no indication for a stereoactive lone electron pair at the metal, consistent with predictions [24a].

The geometry of the nitrate anion is normal. As can be seen from Figs. 1 and 3, the nitrates are stacked in a similar fashion as are the cytosine rings,

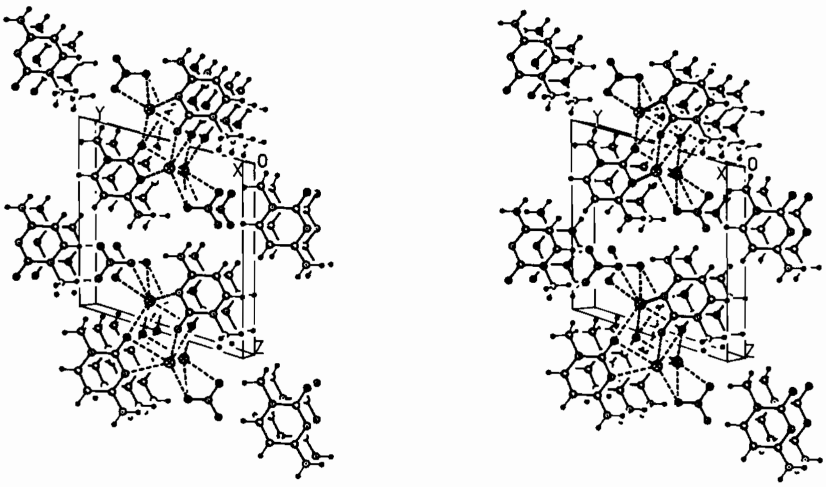

Fig. 1. Stereoview of the crystal packing of $Tl(1\text{-}MeC)NO_3$.

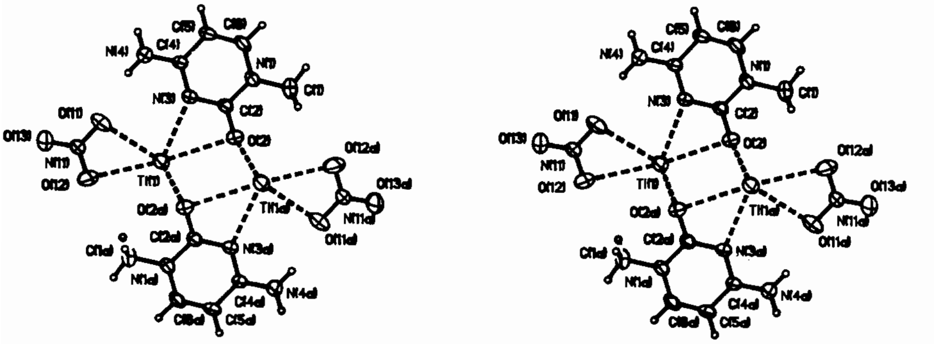

Fig. 2. Stereoview of section of the polymeric stack of a pair of $Tl(1\text{-}MeC)\ NO_3$ indicating the combination of N(3), O(2) chelating and O(2) binding.

having a slight (5.8(2)°) dihedral angle with the latter. O(11) forms a hydrogen bond with the exocyclic amino group of 1-MeC (N(4)...O(11), 2.943(7) Å; H(42)...O(11), 2.064(7) Å; N(4)–H(42)–O(11), 165.2(6)°).

A comparison with structural data of free 1-methylcytosine [28] displays no significant changes.

The structure contains three different Tl–Tl contacts shorter than 5.0 Å: 3.786(1) (Tl(1)...Tl(1c)), 4.097(1) (Tl(1)...Tl(1b)) and 4.727(2) Å (Tl(1)...Tl(1a)). Considering the generally shorter contacts observed in a large number of solid-state Tl(I) compounds [29], none of these contacts seem to imply metal–metal interactions.

^1H and ^{13}C NMR spectra (D_2O) of 1-MeC are hardly affected by the presence of Tl(I) in solution. Likewise, the vibrational spectra (IR, Raman) of the title compound are, as far as 1-MeC modes are concerned, virtually unchanged and therefore of little diagnostic value. These findings are consistent with the results of the crystal structure determination, which indicate several relatively weak contacts to the nucleobase rather than one or two strong ones as typically observed in nucleobase complexes of transition metal ions. Even without any additional examples of Tl(I) nucleobase complexes available at present, based on the structural features of the $Tl(1\text{-}MeC)NO_3$ compound, it would seem likely that any effect of Tl(I) on DNA structure should be very subtle. A major steric distortion of DNA, as observed for binding of bifunctional Pt electrophiles, is probably not to be expected.

Supplementary material

Positional parameters and anisotropic temperature factors of the title compound, short contacts and a listing of observed and calculated structure factors can be obtained from the Fachinformationszentrum Karlsruhe, D-7514 Eggenstein-Leopoldshafen 2, under CSD 55731 on request. Requests should be accompanied by the complete literature citation.

TABLE 2. Bond distances (Å) and bond angles (°) of Tl(1-MeC)NO_3

Tl(1)–N(3)	2.872(3)	N(1)–C(6)	1.365(7)
Tl(1)–O(2a)	2.900(4)	C(2)–O(2)	1.250(6)
Tl(1)–O(2)	2.954(4)	C(2)–N(3)	1.354(8)
Tl(1)–O(12)	2.965(5)	N(3)–C(4)	1.337(6)
Tl(1)–O(11)	2.980(5)	C(4)–N(4)	1.321(9)
Tl(1)–O(2b)	3.039(4)	C(4)–C(5)	1.438(7)
Tl(1)–O(11c)	3.100(5)	C(5)–C(6)	1.336(9)
Tl(1)–N(3c)	3.138(3)	N(11)–O(11)	1.243(7)
N(1)–C(1)	1.455(9)	N(11)–O(12)	1.239(6)
N(1)–C(2)	1.381(7)	N(11)–O(13)	1.232(9)
N(3)–Tl(1)–O(2a)	91.5(1)	O(11)–Tl(1)–O(2b)	150.1(1)
N(3)–Tl(1)–O(2)	45.8(1)	O(11)–Tl(1)–O(11c)	77.0(1)
N(3)–Tl(1)–O(12)	109.8(1)	O(11)–Tl(1)–N(3c)	114.7(1)
N(3)–Tl(1)–O(11)	70.2(1)	O(2b)–Tl(1)–O(11c)	91.7(1)
N(3)–Tl(1)–O(2b)	139.0(1)	O(2b)–Tl(1)–N(3c)	84.0(1)
N(3)–Tl(1)–O(11c)	113.0(1)	O(11c)–Tl(1)–N(3c)	65.3(1)
N(3)–Tl(1)–N(3c)	78.0(1)	C(2)–N(1)–C(6)	120.2(5)
O(2a)–Tl(1)–O(2)	72.3(1)	C(1)–N(1)–C(6)	120.1(5)
O(2a)–Tl(1)–O(12)	82.1(1)	C(1)–N(1)–C(2)	119.7(5)
O(2a)–Tl(1)–O(11)	97.0(1)	N(1)–C(2)–N(3)	119.9(5)
O(2a)–Tl(1)–O(2b)	79.2(1)	N(1)–C(2)–O(2)	118.9(5)
O(2a)–Tl(1)–O(11c)	150.2(1)	O(2)–C(2)–N(3)	121.2(5)
O(2a)–Tl(1)–N(3c)	140.0(1)	C(2)–N(3)–C(4)	119.8(5)
O(2)–Tl(1)–O(12)	142.3(1)	N(3)–C(4)–C(5)	121.5(5)
O(2)–Tl(1)–O(11)	113.5(1)	N(3)–C(4)–N(4)	117.9(5)
O(2)–Tl(1)–O(2b)	93.7(1)	N(4)–C(4)–C(5)	120.6(5)
O(2)–Tl(1)–O(11c)	137.1(1)	C(4)–C(5)–C(6)	117.0(5)
O(2)–Tl(1)–N(3c)	72.9(1)	N(1)–C(6)–C(5)	121.6(5)
O(12)–Tl(1)–O(11)	42.1(1)	O(12)–N(11)–O(13)	120.1(6)
O(12)–Tl(1)–O(2b)	108.3(1)	O(11)–N(11)–O(13)	121.1(6)
O(12)–Tl(1)–O(11c)	73.9(1)	O(11)–N(11)–O(12)	118.8(6)
O(12)–Tl(1)–N(3c)	137.8(1)		

Symmetry codes: (a) $1-x, 1-y, -z$; (b) $-x, 1-y, -z$; (c) $x-1, y, z$.

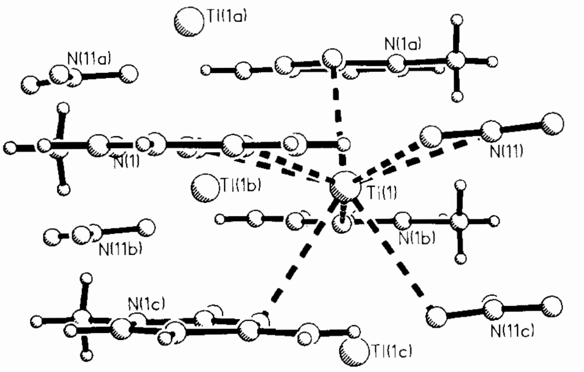

Fig. 3. View along planes of 1-MeC rings and nitrate anions with eight shortest contacts of Tl(1) to four different 1-MeC molecules and two different nitrates.

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