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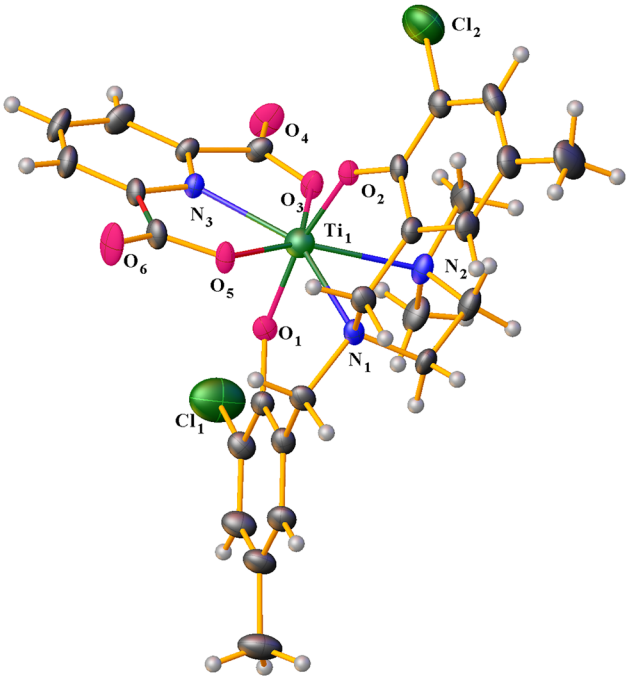
The crystal structure of 6,6′-(((2-(dimethylamino) ethyl)azanediyl)bis(methylene))bis(2-chloro-4-methyl phenolate-κ^4*N,N′,O,O′*)-(pyridine-2,6-dicarboxylato-*N,O,O′*)-titanium(IV), $C_{27}H_{27}Cl_2N_3O_6Ti$



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Abstract

$C_{27}H_{27}Cl_2N_3O_6Ti$, monoclinic, $P2_1/c$ (no. 14), a = 11.609(4) Å, b = 21.476(7) Å, c = 13.504(4) Å, β = 109.881(9)°, V = 3166.2(18) Å^3, Z = 4, $R_{gt}(F)$ = 0.0623, w$R_{ref}(F^2)$ = 0.1945, T = 100(1) K.

CCDC no.: 2112802

Table 1: Data collection and handling.

Crystal:	Red block
Size:	0.3 × 0.2 × 0.2 mm
Wavelength:	Ga *K*α radiation (1.34139 Å)
μ:	2.81 mm^{-1}
Diffractometer, scan mode:	Bruker APEX-II, φ and ω-scans
θ_{max}, completeness:	55°, >99 %
$N(hkl)_{measured}$, $N(hkl)_{unique}$, R_{int}:	23,033, 6002, 0.066
Criterion for I_{obs}, $N(hkl)_{gt}$:	$I_{obs} > 2\sigma(I_{obs})$, 4698
N(param)$_{refined}$:	356
Programs:	Bruker programs [1], SHELX [2]

The crystal structure is shown in the figure. Table 1 contains crystallographic data and Table 2 contains the list of the atoms including atomic coordinates and displacement parameters.

1 Source of materials

The ONON ligand L_1: 6,6′-(((2-(dimethylamino)ethyl)azanediyl) bis(methylene))bis(2-chloro-4-methyl phenol) was prepared according to the general procedure for 24 h as a white solid in a yield of 86 % [3]. The corresponding [ONON]-type $Ti^{(IV)}$ chelate was synthesized according to reported method [4]. Under an N_2 atmosphere, L1 (2.5 mmol, 1000 mg) was dissolved in anhydrous tetrahydrofuran (40 mL), $Ti(O^iPr)_4$ (2.5 mmol, 0.74 mL) was then added to the solution. The reaction was stirring at room temperature for 1 h, 2.6-dipicolinlic acid (Dipic) (2.5 mmol, 417.8 mg) was added and the reaction was continued stirring for 4 h while monitoring the reaction progress by TLC. Upon completion, [$L_1Ti^{(IV)}$(Dipic)] was separated by flash column chromatography (petroleum ether/ethyl acetate = 3/1 and dichloromethane/methanol = 10/1) to obtain a red solid (2.2 mmol, 1352.8 mg, 89 %). Suitable crystals for X-ray diffraction measurements were obtained by slow diffusion of n-hexane to a dichloromethane solution of [$L_1Ti^{(IV)}$(Dipic)] at room temperature.

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Table 2: Fractional atomic coordinates and isotropic or equivalent isotropic displacement parameters (Å^2).

	x	*y*	*z*	U_{iso}*/U_{eq}
C1	0.2589 (2)	0.41131 (14)	0.8174 (2)	0.0413 (7)
C2	0.3402 (3)	0.42048 (14)	0.9208 (2)	0.0435 (7)
C3	0.2926 (3)	0.42919 (16)	1.0017 (2)	0.0532 (8)
H3	0.348018	0.434930	1.071360	0.064*
C4	0.1677 (3)	0.42984 (19)	0.9851 (2)	0.0633 (10)
C5	0.0867 (3)	0.42064 (19)	0.8821 (3)	0.0644 (10)
H5	0.000695	0.420952	0.867787	0.077*
C6	0.1342 (3)	0.41088 (16)	0.7998 (2)	0.0510 (8)
C7	0.1199 (4)	0.4385 (3)	1.0762 (3)	0.0917 (15)
H7A	0.175148	0.417763	1.139073	0.137*
H7B	0.037860	0.420228	1.057589	0.137*
H7C	0.115811	0.483012	1.090507	0.137*
C8	0.4753 (2)	0.42474 (15)	0.94311 (19)	0.0439 (7)
H8A	0.517396	0.421511	1.020145	0.053*
H8B	0.493940	0.466349	0.920889	0.053*
C9	0.6609 (3)	0.39059 (15)	0.9235 (2)	0.0447 (7)
H9A	0.694830	0.388457	1.001366	0.054*
H9B	0.669906	0.434097	0.903057	0.054*
C10	0.7376 (2)	0.34920 (15)	0.8797 (2)	0.0425 (7)
C11	0.7039 (2)	0.33838 (13)	0.7709 (2)	0.0382 (6)
C12	0.7837 (3)	0.30544 (14)	0.7338 (2)	0.0457 (7)
C13	0.8939 (3)	0.28190 (16)	0.8015 (3)	0.0585 (9)
H13	0.947585	0.260027	0.774094	0.070*
C14	0.9249 (3)	0.29054 (17)	0.9091 (3)	0.0623 (9)
C15	0.8474 (3)	0.32472 (16)	0.9473 (2)	0.0538 (8)
H15	0.869725	0.331561	1.020910	0.065*
C16	1.0448 (4)	0.2641 (2)	0.9861 (3)	0.0914 (15)
H16A	1.029690	0.222503	1.009085	0.137*
H16B	1.075312	0.291548	1.047451	0.137*
H16C	1.105818	0.261235	0.950954	0.137*
C17	0.5060 (3)	0.31383 (15)	0.9304 (2)	0.0490 (8)
H17A	0.426916	0.314909	0.943204	0.059*
H17B	0.571451	0.305748	0.998628	0.059*
C18	0.5034 (3)	0.26138 (16)	0.8555 (2)	0.0579 (9)
H18A	0.586964	0.254564	0.853492	0.069*
H18B	0.476780	0.222582	0.880909	0.069*
C19	0.2909 (3)	0.26161 (17)	0.7360 (3)	0.0637 (10)
H19A	0.281298	0.216764	0.744194	0.096*
H19B	0.238271	0.274685	0.665669	0.096*
H19C	0.267481	0.284190	0.789355	0.096*
C20	0.4551 (4)	0.23123 (17)	0.6761 (3)	0.0722 (11)
H20A	0.532782	0.244719	0.669400	0.108*
H20B	0.390922	0.231575	0.606624	0.108*
H20C	0.464224	0.188969	0.705133	0.108*
C21	0.3097 (2)	0.43033 (14)	0.47948 (18)	0.0373 (6)
C22	0.2624 (3)	0.47220 (18)	0.3973 (2)	0.0580 (9)
H22	0.209480	0.458273	0.330581	0.070*
C23	0.2932 (3)	0.53433 (17)	0.4139 (2)	0.0589 (9)
H23	0.261369	0.563687	0.358682	0.071*
C24	0.3712 (3)	0.55361 (15)	0.5122 (2)	0.0527 (8)
H24	0.394618	0.596058	0.524707	0.063*
C25	0.4138 (2)	0.50994 (13)	0.5909 (2)	0.0385 (6)
C26	0.2893 (3)	0.36183 (16)	0.4790 (2)	0.0441 (7)
C27	0.4965 (3)	0.52033 (14)	0.7018 (2)	0.0445 (7)
Cl1	0.03329 (7)	0.39840 (5)	0.67310 (6)	0.0735 (3)
Cl2	0.74555 (7)	0.29269 (4)	0.59838 (6)	0.0579 (3)
N1	0.5277 (2)	0.37574 (11)	0.88961 (16)	0.0377 (6)
N2	0.4201 (2)	0.27546 (11)	0.74950 (17)	0.0466 (6)
N3	0.38382 (19)	0.44974 (10)	0.57411 (15)	0.0348 (5)
O1	0.30213 (16)	0.40155 (9)	0.73775 (13)	0.0406 (5)
O2	0.59491 (15)	0.35878 (9)	0.70494 (13)	0.0371 (4)
O3	0.34693 (19)	0.33679 (9)	0.57077 (13)	0.0460 (5)
O4	0.2265 (2)	0.33369 (12)	0.40193 (15)	0.0704 (7)
O5	0.51578 (18)	0.46968 (9)	0.75692 (14)	0.0449 (5)
O6	0.5372 (3)	0.57168 (11)	0.73191 (19)	0.0760 (8)
Ti1	0.43975 (4)	0.38270 (2)	0.70437 (3)	0.03157 (19)

2 Experimental details

H atoms bonded to C atoms were positioned geometrically with C–H = 0.95 Å (aromatic), 0.99 Å (methylene) and 0.98 Å (methyl) and refined in a riding mode [U_{iso}(H) = 1.2 U_{eq}C (aromatic and methylene)], 1.5 U_{eq}C(methyl).

3 Comment

Titanocene dichloride ([$Cp_2Ti^{(IV)}Cl_2$], TDC) [5] and Budotitane ((bis-(1-phenyl-1,3-butanedione)$Ti^{(IV)}$) [6] entered clinical trials as antitumor drugs, but eventually failed due to their insufficient aqueous stability. In recent years, Salan $Ti^{(IV)}$ alkoxyl complexes have been widely studied as alkene polymerization catalysts and antitumor drugs [7, 8]. As a second chelating ligand, [Salan$Ti^{(IV)}$(Dipic)] formed by Dipic not only has excellent anti-tumor activity *in vitro* and *in vivo*, but also significantly improves its aqueous stability [9]. Based on its excellent stability, its radioisotopic complex [^{45}Ti][Salan$Ti^{(IV)}$Dipic] is allowed to be used as a PET probe [10] and could *via* sonogashira reaction introduced alkynyl to enhance antitumor activity [11]. The [ONON]-type ligand is similar with Salan but has a flexible pendant donor side arm having O, N, O atoms on the backbone with a N atom from the pending arm. Studies on the antitumor activity of [ONON] Ti *bis*-chelates are relatively limited, to the best of our knowledge only one study has reported its antitumor activity [4]. Reported in this article [$L_1Ti^{(IV)}$(Dipic)] showed excellent antitumor activity against Hep G2 and Hela S3 cell lines.

As shown in the Figure, the central Ti cation is seven-coordinated by three nitrogen atoms and four carboxylate oxygen atoms, forming a distorted penta-dentated bipyramidal geometry. The bond lengths of four Ti–O and three Ti–N are ranging from 1.847(2) to 2.085(2) Å and from 2.194(2) to 2.363(2) Å, respectively.

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Conflict of interest statement: The authors declare no conflicts of interest regarding this article.

References

1. Bruker. *SMART and SAINT for Windows NT Software Reference Manuals*, (version 5.0); Bruker Analytical X-Ray Systems: Madison, WI, 1997.
2. Sheldrick G. A short history of SHELX. *Acta Crystallogr. A* 2008, *64*, 112–122.
3. Peri D., Manna C. M., Shavit M., Tshuva E. Y. $Ti^{(IV)}$ Complexes of branched diamine bis(phenolato) ligands: hydrolysis and cytotoxicity. *Eur. J. Inorg. Chem.* 2011, *2011*, 4896–4900.
4. Zhao T., Wang P., Liu N., Li S., Yang M., Yang Z. Facile synthesis of [ONON] type titanium$^{(IV)}$ *bis*-chelated complexes in alcoholic solvents and evaluation of anti-tumor activity. *J. Inorg. Biochem.* 2022, *235*, 111925.
5. Köpf H., Köpf-Maier P. Titanocene dichloride-the first metallocene with cancerostatic activity. *Angew. Chem. Int. Ed. Engl.* 1979, *18*, 477–478.
6. Keller H. J., Keppler B., Schmähl D. Antitumor activity of cis-dihalogenobis(1-phenyl-1,3-butanedionato)titanium$^{(IV)}$ compounds. *J. Cancer Res. Clin.* 1983, *105*, 109–110.
7. Jones M. D., Brady L., McKeown P., Buchard A., Schäfer P. M., Thomas L. H., Mahon M. F., Woodman T. J., Lowe J. P. Metal influence on the iso-and hetero-selectivity of complexes of bipyrrolidine derived salan ligands for the polymerisation of rac-lactide. *Chem. Sci.* 2015, *6*, 5034–5039.
8. Shavit M., Peri D., Manna C. M., Alexander J. S., Tshuva E. Y. Active cytotoxic reagents based on non-metallocene non-diketonato well-defined C2-symmetrical titanium complexes of tetradentate bis(phenolato) ligands. *J. Am. Chem. Soc.* 2007, *129*, 12098–12099.
9. Grützke M., Zhao T., Immel T. A., Huhn T. Heptacoordinate heteroleptic salan (ONNO) and thiosalan (OSSO) titanium$^{(IV)}$ complexes: investigation of stability and cytotoxicity. *Inorg. Chem.* 2015, *54*, 6697–6706.
10. Severin G. W., Nielsen C. H., Jensen A. I., Fonslet J., Kjar A., Zhuravlev F. Bringing radiotracing to titanium-based antineoplastics: solid phase radiosynthesis, PET and ex vivo evaluation of antitumor agent [(45) Ti](salan)Ti(dipic). *J. Med. Chem.* 2015, *58*, 7591–7595.
11. Zhao T., Wang P., Ji M., Li S., Yang M., Pu X. Post-synthetic modification research of salan titanium bis-chelates *via* sonogashira reaction. *Acta Chim. Sin.* 2021, *79*, 1385–1393.