# Chemistry and antioxidant properties of titanium(IV) complexes

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**Abstract** The synthesis of titanium(IV) complexes with biologically active hydrazide ligands has been carried out. The complexes were characterized by spectroscopic methods (IR, <sup>1</sup>H NMR and <sup>13</sup>C NMR), elemental analysis and conductivity studies. These studies suggest bidentate coordination of the ligands through carbonyl oxygen and primary amine nitrogen, resulting in octahedral geometries. Hydrazides with pyridyl substituents displayed 1:2 metalto-ligand ratio, and hydrazides with imino substituents exhibited 1:3 metal-to-ligand ratio resulting in an outer sphere complex. The remaining complexes displayed inner sphere coordination with 1:1 metal-to-ligand ratio. These complexes exhibit varying degrees of radical scavenging properties against DPPH, superoxide and nitric oxide free radicals. The free ligands showed inhibition against DPPH but were inactive against superoxide and nitric oxide free radicals. The structure-activity relationships of the complexes are discussed.

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## Introduction

Titanium complexes show a range of biological properties, including promising activity toward a number of tumor cell types [1-3] as well as anticancer, antifungal and antibacterial activities [4]. The antitumor activity of titanocene dichloride has been established against various animal and xenografted human tumors and found to be more efficient than cisplatin [5]. Similarly, a number of biological activities have been determined for hydrazides and their complexes [6–10]. Hydrazides may behave as a bidentate ligand to give a five-membered ring, using their carbonyl oxygen and amino nitrogen as donor atoms to the metal [11, 12], or may act as monodentate ligands using one of these donor atoms [12].

A number of reactive oxygen species (ROS) including free radicals and non-radicals are generated by a variety of metabolic processes [13]. Low levels of ROS are important for protecting the host from microorganisms, but their excessive production is associated with adverse effects on the body. ROS attack biomolecules, leading to local injury, oxygen dysfunction and diseases such as cancer, inflammation, premature aging, Parkinson's disease and neurodegeneration [14]. The diffusion-limited reaction of nitric oxide (NO) and superoxide (SO) is associated with the production of the toxic oxidant peroxynitrite. Superoxide dismutases, a family of metalloenzymes, are known for their crucial role in body defense mechanisms against the unfavorable effects of oxygen free radicals. They catalyze the conversion of  $\mathrm{O_2}^-$  to  $\mathrm{H_2O_2}$  and  $\mathrm{O_2}$  at the diffusion limit [15]. The free radical scavenging properties of metal complexes may also make them useful for the treatment of these diseases.

In spite of its interesting structural and biological activities, little has been reported in this context for



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titanium. In this paper, we report the synthesis and chemistry of hydrazide complexes of Ti(IV). The DPPH, superoxide and nitric oxide radical scavenging potentials of these complexes are also presented.

# **Experimental**

#### Materials and methods

TiCl<sub>4</sub> and chemicals for antioxidant activities were of reagent grade, purchased from Merck or Sigma-Aldrich and used without further purification. Organic solvents were purified and dried before use by standard methods [16]. Conductance was measured with a Hanna (HI-8633) conductivity meter (Romania). Infrared spectra were recorded on a Shimadzu 460 IR spectrometer in the range of 4000–400  $\mbox{cm}^{-1}$  using KBr disks.  $^1\mbox{H}$  NMR and  $^{13}\mbox{C}$ NMR spectra were recorded in DMSO solvent at 600 MHz on a Bruker AVANCE AV 600 spectrophotometer. Carbon, hydrogen and nitrogen analyses were performed on a PerkinElmer 2400 series II CHN/S analyzer. Chloride contents were determined volumetrically using AgNO<sub>3</sub> [17]. Complexometric EDTA back-titration was performed for the analysis of titanium contents in which sodium potassium tartrate was used as a masking agent in the presence of indicator xylenol orange (1 g in 100 g KNO<sub>3</sub>) [18].

## Synthesis of the hydrazide ligands

Hydrazides were synthesized by reported methods [6, 9, 10]. The appropriate hydrated hydrazine (2 mL, 40 mmol) was added to a solution of the ester (1 mmol) in ethanol (50 ml). The mixture was refluxed for 2–3 h to get a solid product. This was filtered off, washed with hexane and dried. The hydrazides were recrystallized from methanol. Analytical data for all the free ligands have been reported previously [19, 20].

#### Synthesis of the complexes

All the experimental manipulations were carried out under dry nitrogen using Schlenk techniques to avoid the hydrolysis of TiCl<sub>4</sub>. Complexes were synthesized by slow addition of a solution of the hydrazide (10 mmol) in methanol (10 ml) to an orange solution of TiCl<sub>4</sub> (5 mmol) in toluene (10 ml) with constant stirring at 0 °C. The mixture was stirred for 4 h. The solid product so obtained was filtered off, washed with a 1:1 mixture of toluene and methanol and dried under vacuum. Elemental, physical and analytical data are provided in Table 1.

#### **Radical scavenging activities**

Reported methods were used for measuring antioxidant properties for the test compounds. The change in absorbance of DPPH was examined at 515 nm by the spectrophotometric method described by Lee [21]. Superoxide scavenging activities of the compounds were determined using the modified method described by Gaulejac et al. [22]. Sodium nitroprusside in aqueous solution at physiological pH spontaneously generates nitric oxide to produce nitrite ion, which can be estimated using the Griess Illosvoy reaction [23].

 $IC_{50}$  values were calculated by observing the results of different concentrations of the test compounds at 1–1000  $\mu M.$  The EZ-Fit Enzyme kinetics program was used to calculate  $IC_{50}$  values of the compounds.

#### **Results and discussion**

#### Synthesis and physicochemical properties

Hydrazide ligands (1–7) were synthesized in reasonable yields as depicted in Scheme 1. The synthesized hydrazide ligands were characterized using spectroscopic and microanalytical techniques. Their <sup>1</sup>HNMR spectra displayed the appropriate splitting patterns for the benzene rings. The parent peak of correct m/z ratio was observed in their mass spectra. Elemental, physical and analytical data of complexes (1c–7c) are summarized in Table 1. Based upon these spectral data, the Ti(IV) complexes are tentatively assigned octahedral geometries as depicted in Fig. 1. These studies indicate that Ti(IV) complexes with ligands 1 and 2 exhibit 1:2 metal-to-ligand ratio, while ligands 3–6 show 1:1 ratio and ligand 7 displays 1:3 ratio, as detailed below.

All the complexes obtained were non-hygroscopic and stable at room temperature, having light brown colors, and soluble in polar organic solvents like DMSO and DMF. Complexes **1c** and **2c** have the conductivity values 103 and 123  $\Omega^{-1}$  cm<sup>2</sup> mol<sup>-1</sup>, respectively, indicating 1:2 electrolytic ratio with two chloride ions outside the coordination sphere, whereas complex **7c** exhibits 1:4 electrolytic ratio with four Cl<sup>-</sup> ions outside the sphere ( $\Lambda_{\rm M} = 213.0 \ \Omega^{-1} \ {\rm cm}^2 \ {\rm mol}^{-1}$ ) [24] as shown in Fig. 1. Formation of white precipitates upon addition of AgNO<sub>3</sub> to solutions of the complexes confirmed outer sphere complexes. Molar conductivity values of **3c–6c** were found to be in the range of 17–21  $\Omega^{-1} \ {\rm cm}^2 \ {\rm mol}^{-1}$ , indicating non-electrolytic natures for these complexes [25].

#### Infrared spectroscopy

The infrared spectral data and assignments for the free hydrazides (1-7) and their complexes (1c-7c) are

Table 1 Physical and elemental data of complexes (1c-7c)

Compound	Molecular mass (g)	Molecular formula	Elemental analysis: % cal (found)					$\Lambda_{\rm M}$ (DMSO) ohm <sup>-1</sup>
			C	Н	Ν	Ti	Cl	$cm^2 mol^{-1}$
1c	463.95	$C_{12}H_{14}N_6O_2Cl_4Ti$	31.1	3.0	18.1	10.3	30.6	103
			(31.6)	(3.2)	(18.5)	(10.6)	(30.7)	
2c	463.95	$C_{12}H_{14}N_6O_2Cl_4Ti$	31.1	3.0	18.1	10.3	30.6	123
			(30.9)	(3.1)	(18.4)	(10.4)	(30.1)	
3c	325.82	C7H8N2OCl4Ti	25.8	2.5	8.6	14.7	-	18
			(25.3)	(2.8)	(8.0)	(14.6)		
4c	343.83	C7H7N2OFCl4Ti	24.5	2.1	8.1	13.9	-	17
			(24.8)	(2.3)	(7.8)	(13.8)		
5c	451.88	C7H7N2OICl4Ti	18.6	1.5	6.2	10.6	-	21
			(18.5)	(1.7)	(6.2)	(10.7)		
6c	360.38	C7H7N2OCl5Ti	23.3	1.9	7.8	13.3	_	20
			(23.6)	(2.1)	(8.0)	(13.3)		
7c	643.19	$C_{21}H_{27}N_9O_3Cl_4Ti$	39.2	4.2	19.6	7.4	22.1	213
			(40.0)	(4.5)	(18.9)	(7.8)	(21.4)	



Scheme 1 Synthesis of hydrazide ligands (1–7). 1. R = 4-Pyridyl; 2. R = 3-Pyridyl; 3.  $R = C_6H_5$ ; 4. R = 2-F-C<sub>6</sub>H<sub>4</sub>; 5. R = 4-I-C<sub>6</sub>H<sub>4</sub>; 6. R = 4-Cl-C<sub>6</sub>H<sub>4</sub>; 7. R = NH-C<sub>6</sub>H<sub>5</sub>

summarized in Table 2. The hydrazide ligands have more than one potential coordination site, and IR spectral data help in determining the bonding modes of the ligands. The free hydrazides all exhibit a sharp C=O stretching frequency at  $1654 \pm 35$  cm<sup>-1</sup>, which is in agreement with the earlier reported values of 1670–1640  $\text{cm}^{-1}$  [10, 19, 20]. The considerable increase in C=O frequency upon complexation  $(1670 \pm 35 \text{ cm}^{-1})$  indicates coordination of the carbonyl oxygen to the Ti(IV) center, resulting in a decrease in the double bond character of C=O and an increase in C-N double bond character. This is also supported by a negative shift in C-N frequency in all the complexes except 7c [26]. In complex 7c, there is no significant shift in the C=O peak which is an indication that carbonyl oxygen takes no part in coordination. The possibility of coordination through both the pyridyl nitrogen and carbonyl oxygen is probably ruled out by steric considerations [27].

A pair of fairly intense bands around  $3207-3322 \text{ cm}^{-1}$  is characteristic of the N–H stretching frequencies of the hydrazinic group. Upon complexation with Ti(IV), this band broadens (2927–3447 cm<sup>-1</sup>) and shows positive or negative shift, suggesting involvement of the primary nitrogen in coordination with Ti. This results in bidentate coordination of the ligands via coordination through

primary amine nitrogen and carbonyl oxygen [26]. Bands due to aromatic C=C stretching, NH<sub>2</sub> bending and NH stretching are also identified in the spectra of both the free ligands and their complexes.

#### <sup>1</sup>H NMR spectroscopy

<sup>1</sup>H NMR spectral data of the free hydrazides and their complexes in DMSO are summarized in Table 3. The free ligands all displayed a singlet assigned to the NH group in the range of 9.49–10.07 ppm. This peak does not show any significant shift upon complexation, indicating non-coordination of this group. The free ligands also exhibit a singlet at about 4.47-4.61 ppm attributed to the NH<sub>2</sub> protons, which shifts to 10.37-13.54 ppm in the spectra of the complexes. This indicates bonding of the hydrazinic NH<sub>2</sub> to the metal center, supporting the IR results. Earlier studies with divalent cations of Pt, Zn, Hg and Cd also supported this conclusion [28]. The imino (NH) group which is directly attached to the aromatic ring displayed a singlet at 7.32 ppm for ligand 7. Upon complexation (7c), this peak shifts to 9.69 ppm, indicating coordination of this group to the metal. Hence, this ligand forms a five-membered chelate ring with Ti by using its hydrazinic and imino





Table 2IR spectral data ofhydrazide ligands 1–7 and theircomplexes 1c-7c

Compound	$-NH_2$	C=O	NH bending	C–N	Others v
1	3304, 3113	1668	1633	1335	1136, 995, 845, 675, 436
1c	3447, 3163	1688	1607	1313	1219, 996, 846, 755, 674
2	3322, 3207	1672	1595	1338	1121, 953, 708, 631, 525
2c	3174, 3061	1696	1628	1309	1201, 1106, 1014, 840, 730, 647
3	3230, 3198	1661	1616	1348	1119, 989, 882, 803, 685, 516, 412
3c	3190, 2931	1671	1640	1306	1004, 826, 842, 724, 558
4	3288, 3207	1615	1568	1343	993, 744, 653, 508
4c	3190, 3169	1641	1617	1324	862, 815, 781, 754, 698, 658, 575
5	3295, 3188	1630	1583	1328	1169, 1057, 1005, 963, 845
5c	3205, 2927	1672	1587	1306	1306, 1277, 1170, 1143, 1003
6	3309, 3217	1661	1557	1345	1095, 999, 839, 729, 674, 533
6c	3232, 2958	1686	1597	1311	1278, 1094, 846, 746, 681, 528
7	3260, 3303	1687	1593	1303	1225, 1145, 925, 753, 696, 643, 509
7c	3285, 2984	1689	1615	1319	1245, 981, 752, 691, 633, 502

N as donor atoms. The aromatic protons show their signals at 6.88–8.94 ppm for the free hydrazides; these peaks are shifted to 6.98–9.46 ppm in the spectra of the complexes.

# <sup>13</sup>C NMR spectroscopy

<sup>13</sup>C NMR spectral data for the free hydrazides and their complexes are summarized in Table 3. The expected

numbers of carbon signals were observed in the spectra of both the free ligands and complexes. The free ligands gave a singlet in the range of 163.23–157.33 ppm which is characteristic of a C=O carbon atom [29]. Upon complexation, the position of this signal shifted upfield or downfield in **1c– 6c** [30, 31], indicating coordination of the C=O oxygen to the metal center, in agreement with the IR assignments. The position of the C=O peak for ligand 7 remains unchanged

Compound	<sup>1</sup> H NMR	. (δ ppm)	<sup>13</sup> C NMR ( $\delta$ ppm)		
	NH <sub>2</sub>	NH	Aromatic protons	C=O	Aromatic carbons
1	4.61	10.07	7.71-8.68	163.86	120.95-150.16
1c	13.54	11.23	8.10-8.94	159.10	122.87-147.53
2	4.54	9.93	7.45-8.95	164.26	123.37-151.67
2c	13.53	10.02	7.73–9.46	158.36	126.57-152.75
3	4.47	9.74	7.40-7.81	163.09	120.65-151.20
3c	11.03	10.93	7.62-7.91	165.32	129.24-137.48
4	4.51	9.49	7.23-7.56	163.23	115.88-132.21
4c	10.40	10.13	7.27-7.61	157.3	115.99-132.61
5	4.47	9.81	7.75-7.83	165.09	128.87-137.14
5c	10.37	11.65	7.66–7.94	160.35	129.45-137.61
6	4.49	9.84	7.45-7.83	164.72	128.35-135.80
6c	12.36	11.59	7.60-7.94	161.56	128.81-137.54
7	4.30	8.57, 7.32	6.88-7.49	157.33	118.08-139.92
7c	10.10	9.09, 9.69	6.98–7.44	157.25	118.33-138.68

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even after complexation, confirming the non-coordination of this group. The signals for the aromatic carbons were observed in the range of 115.88-151.67 ppm in the spectra of the free hydrazides (1–7) and were shifted by 1–2 ppm for the complexes (1c–7c).

On the basis of the IR, NMR and elemental data discussed above, the geometry of these Ti complexes is tentatively assigned as octahedral. All the ligands are bidentate, coordinating through their primary amine nitrogen and carbonyl oxygen, except **7c** in which coordination is through the imino N atom instead of carbonyl O atom.

#### **Radical scavenging activities**

#### DPPH radical scavenging activity

The antioxidant potential of the free hydrazides, their titanium complexes, and titanium tetrachloride solution was determined using DPPH. All tested compounds showed varying degrees of scavenging potential. Their  $IC_{50}$  values against DPPH are presented in Fig. 2. Butyl hydroxyanisole (BHA) and propyl gallate (PG) were used as standards.

DPPH is a stable free radical that can accept an electron or hydrogen radical to become a diamagnetic molecule [32]. The hydrogen-donating ability of antioxidants is responsible for the reduction of DPPH radical to DPPHH [32, 33]. In hydrazides and their metal complexes,  $\alpha$ - or  $\beta$ hydrazinic nitrogen could be the site for removal of hydrogen radical required for the reduction of DPPH.

#### $DPPH\cdot + AH \rightarrow DPPHH + A\cdot$

The reduced form of DPPH can be assayed by the decrease in absorbance at 517 nm induced by an



Fig. 2 DPPH radical scavenging of the free hydrazides, their Ti complexes and  $TiCl_4$  solution

antioxidant. It is visually observed by a change in color from purple to yellow [34].

The results reveal that the nature and position of substituent on the benzene ring of the hydrazide have considerable effect on the activity of these compounds against DPPH. The IC<sub>50</sub> value exhibited by unsubstituted ligand **3** was 133.3  $\mu$ M, while substitution of iodo (39  $\mu$ M) and chloro (87  $\mu$ M) groups at the *para* position of the benzene ring of hydrazide increased activity, and substitution of fluoro at the *ortho* (650  $\mu$ M) position decreased the activity, indicating that electronic and steric factors both play an important role in their radical scavenging potential. Ligand **4** with an *ortho*-fluoro substituent exhibits lowest radical scavenging potential, indicating that electron withdrawing substituents have a negative effect on their antioxidant potential. It is interesting to note that free ligand **7** exhibits the highest IC<sub>50</sub> value; however, after complexation with the metal center, it shows the lowest IC<sub>50</sub> value. This may be attributed to the coordination with two N atoms instead of one N and one O as exhibited by the other compounds. Based upon these results, it is concluded that the electronic properties of the ligands play a crucial role in their antioxidant potential, since Ti(IV) is an electron-deficient system and cannot itself facilitate the reduction of DPPH. The Ti(IV) salt solution showed very weak radical scavenging activity (IC<sub>50</sub> = 407  $\mu$ M) against DPPH. It is hypothesized that  $\alpha$ - or  $\beta$ -hydrazinic nitrogen is responsible for the reduction of DPPH.

#### Superoxide radical scavenging activity

SOD catalyzes the dismutation of superoxide radical  $(O_2^{-})$ to molecular oxygen and hydrogen peroxide by redox reactions involving electron-proton coupling [35]. The free hydrazide ligands and their complexes were investigated for their scavenging potential against superoxide using a nonenzymatic radical generating system. In this system, reduction of PM<sup>+</sup> (phenazine methosulphate) to PMH is carried out by NADH with the generation of  $O_2^{-}$  which in turn reduces NBT (nitroblue tetrazolium) to formazan dye. Any antioxidant present in the system scavenges the superoxide and hinders the formation of formazan, which is measured by the decrease in absorbance at 560 nm. Propyl gallate (PG) and butyl hydroxyanisole were used as standard superoxide radical scavengers. IC50 values for all of the compounds are shown in Fig. 3. The free hydrazide ligands are inactive against  $O_2^-$ , whereas their Ti complexes give IC<sub>50</sub> values in the range of 17–243 µM. Four of the Ti complexes (1c, 2c, 6c, and 7c) showed better or similar scavenging of superoxide compared to the standard PG (IC<sub>50</sub> = 106  $\mu$ M). Complex 7c exhibits the lowest IC<sub>50</sub> value of 17  $\mu$ M. It is interesting to note that the same complex also displayed the highest antioxidation potential against DPPH. The presence of the imino group in this complex may be responsible for its potent antioxidant behavior because of its electron-donating potential to the metal center. Complex 2c also shows a notable scavenging activity with an IC<sub>50</sub> value of 40  $\mu$ M. This observation supports our conclusion that electron-donating substituents help in scavenging free radicals, due to the pyridyl group with N at the *para* position [21].

The lowest scavenging potential was exhibited by complex **4c** which has a fluoro substituent with hydrazide. This compound also showed the lowest DPPH radical scavenging potential. As described above, it may be due to the high electronegativity of the fluoro group which may hinder the removal of hydrogen from the  $\alpha$ - or  $\beta$ -hydrazinic nitrogen. The precursor titanium tetrachloride was also found to be a potent scavenger of superoxide and displayed the lowest IC<sub>50</sub> value of 14 µM. The reaction may be



Fig. 3 Superoxide radical scavenging of  $TiCl_4$  and its complexes with hydrazide ligands. All free ligands are inactive

facilitated due to a change in oxidation state of Ti(IV) mediated by superoxide; however, complexation of metal ions is crucial for their medicinal value because of their potential to enter the cell.

### Nitric oxide scavenging activity

The nitric oxide scavenging abilities of the free hydrazides and their complexes were investigated by using the SNP (sodium nitroprusside)–SNA (sulphanilic acid)–NBT system. In this system, NO derived from sodium nitroprusside produces nitrite ion. On reacting with SNA, the nitrite ion forms a *p*-diazonium salt. This salt reacts with NED to give an azo dye, a pink-colored complex with an absorbance at 540 nm. Antioxidants inhibit formation of the azo dye, resulting in a decrease in absorbance at the same wavelength. The IC<sub>50</sub> values of the compounds are shown in Fig. 4.



Fig. 4 Nitric oxide radical scavenging of  $TiCl_4$  and the hydrazide complexes

The free hydrazides were all inactive against NO. whereas their corresponding complexes exhibit promising antioxidant potentials. TiCl<sub>4</sub> solution was found to possess poor scavenging ability against NO. Four of the complexes (1c, 2c, 6c, and 7c) showed inhibitory values lower than the standard ascorbic acid (AA). The chloro- and iodo-substituted hydrazide complexes (5c, 6c) exhibit better scavenging abilities compared to the fluoro-substituted complex (4c). Complexes 1 and 2 possess pyridyl rings with nitrogen at the *meta* and *para* position, respectively; they were observed to be good antioxidants, but complex 2c exhibited a lower  $IC_{50}$  value of 177  $\mu M$  compared to 1c  $(IC_{50} = 283 \ \mu M)$ . Both complexes have similar steric hindrance but different electronic effects; therefore, electronic factors may play an important role in their NO scavenging properties.

#### Conclusion

Titanium(IV) complexes with substituted hydrazide ligands were synthesized and characterized by chemical and physical measurements. The complexes have octahedral geometries in which the hydrazide ligands are coordinated by the primary amine nitrogen and carbonyl oxygen donor atoms for complexes 1c-6c, while the imino nitrogen is coordinated in complex 7c. These complexes were more potent antioxidants against DPPH than their respective free ligands. The free hydrazide ligands are inactive against superoxide and nitric oxide, whereas their complexes showed promising scavenging potential. The electronic and steric properties of the ligands affect the antioxidative behavior of their complexes. For nitric oxide, scavenging ability seems to be dependent upon electronic effects. Complex 2c exhibited the lowest IC<sub>50</sub> values for DPPH and superoxide and is therefore worthy of further research.

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#### **Compliance with Ethical Standards**

**Conflict of interest** No potential conflict of interest was reported by the author(s).

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