Synthesis, Spectroscopic Characterization and Antitumor Activity *in vitro* of Organometallo Substituted Polyoxotungstates $(RM)_3P_2W_{15}O_{59}^{n-}$ (RM = CpTi, CpZr, $C_4H_7O_2Sn$ or $C_5H_9O_2Sn$)

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Tetrabutylammonium or potassium salts of organometalllic derivatives of lacunary polyanion $(RM)_3P_2W_{15}O_{59}^{n-}$ (RM = CpTi, CpZr, $C_4H_7O_2Sn$ or $C_5H_9O_2Sn$) have been prepared and structurally characterized by elemental analysis, IR, UV-vis, ^1H NMR and ^{183}W NMR spectroscopies. The title complexes exhibit antitumor activity *in vitro*.

Keywords organometallic derivative of polyoxometalate, Dawson structure, antitumor activity

Introduction

Polyoxometalates (POMs) are early transition metal oxygen anion clusters. Since the initial reports of the synthesis of $[PW_{11}O_{39}\{Ti(\eta^5\text{-}C_5H_5)\}]^{4-}$ 20 years ago, the fields of organometallic derivatives of POMs have expanded significantly, and these derivatives now form a full class of compounds.[1] This class of compounds has attracted much attention because of their variable applications, *e.g.* as industrial catalysts and potential antitumor drugs. There are only two or three papers involving the biological properties of organometalllic derivatives of POMs. In order to develop this uncharted territory, the synthesis of organotin, organotitanium, organozirconium and organophosphory polyoxometalates, and their antitumor activity were investigated.[2-11] The reactivity of lacunary polyoxoanions with organometallic groups has also been summarized.[1] While the reaction of the trivacant lacunary polyoxoanion $P_2W_{15}O_{56}^{12-}$ with organometallic groups has rarely been reported, except for $[(PhSn)_3P_2W_{15}O_{59}]^{9-}$ and $[(BuSn)_3P_2W_{15}O_{59}]$.[9-12] Herein, the synthesis, spectroscopic characterization and antitumor activity *in vitro* of cyclopentadienyltitanium, cyclopentadienylzirconium and estertin derivatives of $[\alpha\text{-}P_2W_{15}O_{56}]^{12-}$ polyanion have been reported.

Experimental

Preparation of the title compounds

Cp_2TiCl_2, Cp_2ZrCl_2, $\beta\text{-}CH_3OOCCH_2CH_2SnCl_3$ ($C_4H_7O_2SnCl_3$), $\beta\text{-}CH_3OOCCH(CH_3)CH_2SnCl_3$ ($C_5H_9O_2SnCl_3$) and $Na_{12}[\alpha\text{-}P_2W_{15}O_{56}]\cdot 24H_2O$ were prepared following the reported procedures.[13-15] Their purity was checked by IR or ^1H NMR spectroscopies.

$K_7H_2[(CpTi)_3P_2W_{15}O_{59}]\cdot 5H_2O$ (1) A solution containing Cp_2TiCl_2 (1.245 g, 5 mmol), acetylacetone (6 mmol) and water (30 mL) was stirred for 4 h to give a clear scarlet solution. Powdered $Na_{12}[\alpha\text{-}P_2W_{15}O_{56}]\cdot 24H_2O$ (1.7 mmol) was then added, and after vigorous stirring for 5 min the solution turned from red to yellow. The undissolved residue was filtered off and KCl was added to the filtrate in small portions until no more precipitation was observed. The resulting yellow solid was recrystallized from warm water and dried under suction. Yield 2.0 g (32%). Anal. calcd for $K_7H_2[(CpTi)_3P_2W_{15}O_{59}]\cdot 5H_2O$: C 3.96, H 0.38, K 6.11, P 1.38, Ti 3.21, W 61.73, H_2O 2.42; found C 4.00, H 0.37, K 6.29, P 1.36, Ti 3.11, W 61.39, H_2O 2.56.

$(Bu_4N)_9[(CpZr)_3P_2W_{15}O_{59}]$ (2) $(Bu_4N)_8Na_4[\alpha\text{-}P_2W_{15}O_{56}]$ (1.0 g, 0.22 mmol) and $(\eta^5\text{-}C_5H_5)_2ZrCl_2$ (0.194 g, 0.66 mmol) were dissolved in the mixture of 15 mL of CH_3CN and 70 mL of $1,2\text{-}C_2H_4Cl_2$ to form a yellow solution. 2.0 g of anhydrous Na_2CO_3 was added. The resulting mixture was stirred vigorously until the yellow color disappeared. It was then filtered, and 200 mL of anhydrous ether were added to the filtrate to precipitate out the product. After pouring off the solvent, the product was redissolved in 100 mL of $1,2\text{-}C_2H_4Cl_2$, reprecipitated by addition of ether and dried *in vacuo*. The crude product (1.93 g) was crystallized from $(CH_3)_2COC_6H_5CH_3$ to yield 1.45 g (33%) of product. Anal. calcd for $(Bu_4N)_9[(CpZr)_3P_2W_{15}O_{59}]$: C 29.79, H 5.24, N 1.97, P 0.97, W 43.02, Zr 4.27; found C 29.79, H 5.44, N 1.87, P 0.98, W 43.01, Zr 4.57.

$K_4H_5[(CH_3OOCCH_2CH_2Sn)_3P_2W_{15}O_{59}]\cdot 10H_2O$ (3) To a solution of $CH_3COOCH_2CH_2SnCl_3$ (0.94 g, 3 mmol) in H_2O (40 mL) was added solid $Na_{12}P_2W_{15}O_{56}\cdot 24H_2O$ (4.5 g, 1 mmol) in small portions with stirring. The acidity of the mixture was adjusted to pH 4.5 with solid sodium of acetate.

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The solution turned clear within several minutes, and was kept stirring for 10 min and filtered. KCl was added to the filtrate until there was no more precipitate formed. The white precipitate was filtered and recrystallized from hot water. Yield 2.6 g (*ca.* 54%). Anal. calcd for $K_4H_5[(CH_3OOC\text{-}CH_2CH_2Sn)_3P_2W_{15}O_{59}]\cdot 10H_2O$: C 3.85, H 0.55, K 3.31, P1.32, Sn 7.58, W 58.28, H_2O 3.82; found C 3.60, H 0.53, K 3.34, P 1.30, Sn 7.57, W 58.20, H_2O 3.34.

$K_4H_5[(CH_3OOCCH(CH_3)CH_2Sn)_3P_2W_{15}O_{59}]\cdot 10H_2O$ (**4**) This complex was prepared analogously as compound **3**. Anal. calcd for $K_4H_5[(CH_3OOCCH(CH_3)CH_2Sn)_3P_2\text{-}W_{15}O_{59}]\cdot 10H_2O$: C 3.78, H 0.38, K 3.28, P 1.66, Sn 7.53, W 56.77, H_2O 3.79; found C 3.72, H 0.37, K 3.31, P 1.38, Sn 7.52, W 56.21, H_2O 3.77.

Analytical methods and apparatus

P, W, Ti, Zr and Sn were determined by an ICP emission spectrometer. C, H and N were determined using a PE-2400 analyser. K was determined by atomic absorption spectroscopy. Water was estimated by thermogravimetry. The thermogravimetric analysis (TA) measurements were carried under nitrogen atmosphere with a heating rate of 10 ℃·min^{-1} in the temperature 25—400 ℃ on a PE TA apparatus.

^{183}W NMR spectra were recorded at 16.64 MHz on a Unity-400 spectrometer at room temperature. Chemical shifts referred to 2 mol·L^{-1} Na_2WO_4 in D_2O. ^1H NMR spectra were recorded on a Bruker AC-80 spectrometer (solvent D_2O). IR spectra were recorded on an Alpha Centauri FTIR spectrometer (4000—200 cm^{-1} range) with KBr pellets. UV-vis spectra were recorded on a 756MC spectrometer.

Antitumor activity studies in vitro

The antitumor activity of these compounds was tested by the MTT (3-[4,5-dimethylthiazol-2-yl]-2,5-diphenyltetrazolium bromide, also named thiazolyl blue) experiment as previously described.[2]

Results and discussion

IR *and* UV-vis *spectra*

The observed IR and UV-vis frequencies and tentative assignments of the main bands of the complexes are given in Table 1. Compared with $P_2W_{18}O_{62}^{6-}$, the IR spectra of the organometallo substituted polyoxoanions still have the four characteristic peaks of ν_{as}(W—Od) (Od, terminal oxygen), ν_{as}(W—Ob—W), ν_{as}(W—Oc—W) (Ob, Oc, bridging oxygen) and ν_{as}(X—Oa) (Oa, central oxygen), indicating that the novel complexes still retain the basic frame of the Dawson structure. However, as a consquence of the incorporation of the organometallic groups, the ν(W—Od), ν(W—Ob—W) and ν(W—Oc—W) are decreased relative to those of $P_2W_{18}O_{62}^{6-}$. This is due to an increase of negative charge on the polyanion. The IR spectra display a single, sharp absorption at 1468 and 1469 cm^{-1} in the 1300—1500 cm^{-1} region. This feature is characteristic of the C—C stretch for a η^5-C_5H_5 ligand bonded to Ti or Zr,[16] which shows the existence of cyclopentadienyl ligand. The IR spectra of compound **3** and **4** show the ν(C = O) vibrational peak at 1736 and 1738 cm^{-1}, respectively, indicating that the estertin group exists in the polyoxoanions. When β-methoxycarbonylethyltin reacts with P_2W_{15}, the intramolecular carbonyl coordination to Sn is broken, and Sn is bonded to the oxygen atom of P_2W_{15}, so the C = O vibration frequency shifts to 1736 and 1738 cm^{-1} from 1648 cm^{-1} of the $C_4H_7O_2SnCl_3$, respectively.

The UV-vis spectra of the title anions show two peaks at *ca.* (198 ± 3) and (269 ± 3) nm. The first is assigned to the Od→W charge transfer band and the second is attributed to the Ob/Oc→W charge transfer band.

^1H NMR *and* ^{183}W NMR *spectra*

^1H NMR and ^{183}W NMR data are listed in Table 2, and the ^{183}W NMR spectra of complexes **1** and **3** are shown in Fig. 1.

Table 1 IR and UV-vis data of the title complexes

Anion	IR (cm^{-1})						UV-vis (nm)	
	ν_{as}(W—Od)	ν_{as}(P—Oa)	ν_{as}(W—Ob—W)	ν_{as}(W—Oc—W)	ν(C=O)/ν(C—C)		Od—W	Ob/c—W
1	957	1082	1018	906	773	1468	201	272
2	956	1081	1018	910	768	1469	202	273
3	951	1093	1014	908	781	1736	195	266
4	952	1093	1014	908	781	1738	195	266
α-P_2W_{18}	966	1090	1022	916	792		210	325
$C_4H_7O_2SnCl_3$							1648	
$C_5H_9O_2SnCl_3$							1660	

Table 2 ^{1}H NMR and ^{183}W NMR data

Complex	^{1}H NMR δ					^{183}W NMR δ^{a}		
	OMe	Me	β-H	α-H	Cp	"cap" W	"belt" W	"belt" W
1					6.53	-144.2(1)	-184.6(2)	-231.5(2)
2					6.57	-150.6(1)	-183.2(2)	-224.5(2)
3	3.74 (s)		3.00 (t)	1.72 (t)		-153.9(1)	-224.7(2)	-264.6(2)
4	5.22 (s)	4.20 (s)	3.31 (t)	1.83 (t)		-155.2(1)	-225.4(2)	-265.6(2)
$C_4H_7O_2SnCl_3$	3.94 (s)		2.94 (t)	2.22 (t)				

[a] Relative intensity in parentheses.

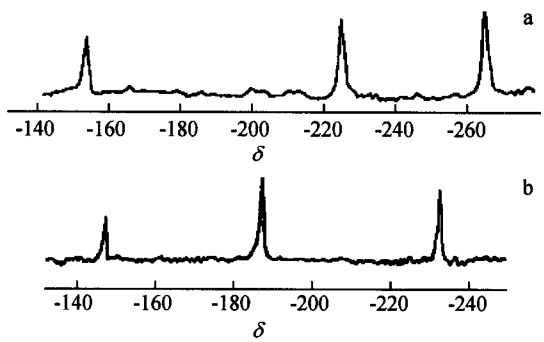

Fig. 1 ^{183}W NMR spectra of complex **3** (a) and complex **1** (b).

The ^{1}H NMR spectra of compounds **1** and **2** display a η^5-C_5H_5 resonance at δ 6.53 and 6.57, respectively. The ^{1}H NMR spectra of estertin substituted polycomplexes are similar to those of $C_4H_7O_2SnCl_3$ and $C_5H_9O_2SnCl_3$, respectively. Only the chemical shifts changed, being affected by the polyanion. These results showed that the (CpTi), (CpZr) or $(RSn)^{3+}$ group incorporated with the trivacant $P_2W_{15}O_{56}^{12-}$. The ^{183}W NMR spectra of the title complexes show three peaks with relative intensities 1:2:2, indicating that the title polyanions have the anticipated C_{3v} Dawson structure with three cap[WO] replaced by [RM], that is, the three substituted organometallic groups occupy the three polar vacant sites of $P_2W_{15}O_{56}^{12-}$ anion, forming $(RM)_3$-$P_2W_{15}O_{59}^{9-}$ polyanions with Dawson structure.

Antitumor activity in vitro

The inhibitory effect and median inhibitory concentration (IC_{50}) against SSMC-7721 (liver cancer) and Hela (cervix cancer) for the title complexes are given in Table 3.

The data summarized in Table 3 show that the title complexes display inhibitory action to two human cancer cells, and the degree of inhibitory of the polyoxometalate containing $[CpTi]^{3+}$ group is higher than those of others. This result was observed for the different lacunary heteropolyanions.[4,17]

Table 3 Inhibitory effect and IC_{50} of the title complexes on two human tumor cells *in vitro*

Complex	Dose (μg/mL)	SSMC-7721		Hela	
		Inhibitory effect (%)	IC_{50}[a] (μg/mL)	Inhibitory effect (%)	IC_{50} (μg/mL)
1	100	100	20.8	79.6	47.2
	10	24.7		109	
	1	2.5		0.8	
2	100	97.1	40.6	78.2	63.3
	10	13.8		12.6	
	1	1		0.8	
3	100	100	30.6	100	50.1
	10	16.9		9.6	
4	100	100	30.1	100	48.3
	10	17.1		11.3	

[a] The 50% inhibitory concentration (IC_{50}) is defined as the concentration which suppresses tumor cell by 50%.

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