SYNTHESIS OF ISOMERS OF ORGANOTIN SUBSTITUTED POLYOXOTUNGSTATES AND COMPARISON OF THE ANTITUMOR ACTIVITY OF ISOMERS

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ABSTRACT

A comparison of the antitumor activity against two human tumor cell lines for the isomers of organometallo-substituted polyoxometalates is reported. The polyoxometalate skeletal isomers affect the antitumor activity. It is observed that the order of the antitumor activity of complexes is consistent with the order of the oxidation ability of polyanions among a couple of isomers possessing the same polyanion and organometallic group whether in the series of monosubstituted complexes or trisubstituted complexes as well in the sandwich compounds.

1. INTRODUCTION

Polyoxometalates (POMs) are early transion 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 has expanded significantly, and these derivatives now form a full class of compounds[1]. Organometallic derivatives of POMs are divided into POM-incorporated organometallic complexes, POM-supported organometallic complexes, and organometallic cation salts of polyoxometalates. This class of compounds has attracted much attention because of their variable applications, e.g. as industrial catalysts and as potential antitumor drugs. However, only a few papers involving the biological activity of POMs derivatized with organometallic groups has been reported [2]. In order to develop the application of organo and organometalate polyoxocompounds in medicine, we systematically synthesized organotin, organotitanium, organozirconium and organophosphorus substituted POMs and investigated their antitumor activity [3-10]. This paper reports a comparison of the antitumor activity of the skeletal isomers of organometallo substituted POMs possessing the same composition. It shows that the antitumor activity of the complexes is increasing with the oxidation ability of polyanions[11].

2. EXPERIMENTAL

2.1. Physical measurements

^{1}H NMR spectra were recorded on a Bruker AC-80 spectrometer while ^{183}W and ^{119}Sn NMR were recorded on a Unity-400 spectrometer. Polarograms and cyclic voltamograms were obtained using a BAS-100A electrochemical analyser. W, Si, Sn, Ge were determined by ICP emission spectrometry. The H_2O content was determined by thermogravimetry. C, N and H were determined by using a PE-2400 analyser. K was determined by atomic absorption spectroscopy.

2.2. Materials

The compounds $CH_3COOCH_2CH_2SnCl_3$ ($C_4H_7O_2SnCl_3$) and $CH_3COOCH(CH_3)CH_2SnCl_3$ ($C_5H_9O_2SnCl_3$) were prepared according to [12] while $K_8[\alpha\text{-}SiW_{11}O_{39}]\cdot 13H_2O$, $K_8[\beta_2\text{-}SiW_{11}O_{39}]\cdot 14H_2O$, $\alpha\text{-}Na_{10}GeW_9O_{34}\cdot 18H_2O$ and $\beta\text{-}Na_9HGeW_9O_{34}\cdot 23H_2O$ were prepared following [13] and [14], respectively, and were identified by polarography.

2.3. Preparation of the complexes

2.3.1. α and β_2-$K_3H_2[(CH_3COOCH_2CH_2Sn)SiW_{11}O_{39}]\cdot nH_2O$

$CH_3COOCH_2CH_2SnCl_3$ (0.31g, 1mmol) was dissolved in H_2O 40 mL, the pH of the solution being adjusted to 1.6 by potassium acetate, and 1mmol of powdered α-SiW_{11} or β_2-SiW_{11} was added bit by bit with stirring. The solution turned to clear within several minutes, and solution was kept stirring for 0.5 h. α and β_2-$K_4H_3(CH_3COOCH_2CH_2Sn)SiW_{11}O_{39}]\cdot nH_2O$ were obtained by evaporating the solution to dryness, and the white precipitates was recrystallized from warm water (yield: 1.8 g). Anal. Calc. for $K_3H_2[(C_4H_7O_2Sn)(\beta\text{-}SiW_{11}O_{39})]\cdot 9H_2O$: C, 1.52; K, 3.71; Si, 0.89; Sn, 3.78; W, 63.86; H_2O, 5.14. Found: C, 1.41; K, 3.56; Si, 0.91; Sn, 3.76; W, 63.66; H_2O, 5.00%. Anal. Calc. for $K_3H_2[(C_4H_7O_2Sn)(\beta_2\text{-}SiW_{11}O_{39})]\cdot 11H_2O$: C, 1.51; K, 3.67; Si, 0.88; Sn, 3.73; W, 63.14; H_2O, 6.21. Found: C, 1.69; K, 3.54; Si, 0.91; Sn, 3.69; W, 62.35; H_2O, 6.10%.

2.3.2. α and β_2-$K_3H_2[(CH_3COOCH(CH_3)CH_2Sn)SiW_{11}O_{39}]\cdot nH_2O$

The α and βcomplexes were prepared analogously. Anal. Calc. for $K_3H_2[(C_5H_9O_2Sn)(\beta\text{-}SiW_{11}O_{39})]\cdot 10H_2O$: C, 1.83; K, 3.69; Si, 0.88; Sn, 3.75; W, 63.38; H_2O, 5.67. Found: C, 1.78; K, 3.51;

Si, 0.93; Sn, 3.62; W, 62.17; H_2O, 5.56%. Anal. Calc. for $K_3H_2[(C_5H_9O_2Sn)(\beta_2\text{-}SiW_{11}O_{39})]\cdot 11H_2O$: C, 1.87; K, 3.65; Si, 0.89; Sn, 3.73; W, 61.84; H_2O, 6.18. Found: C, 1.79; K, 3.48; Si, 0.97; Sn, 3.60; W, 60.27; H_2O, 6.07%.

2.3.3. $K_4H_3[(CH_3COOCH_2CH_2Sn)_3(\alpha\text{-}GeW_9O_{37})]\cdot 10H_2O$

To 40 mL of $CH_3COOCH_2CH_2SnCl_3$ (0.94 g, 3mmol) in H_2O was added sodium acetate to adjust the pH to 1.6. Then 2.7 g (1mmol) of powdered $Na_{10}[\alpha\text{-}GeW_9O_{34}]\cdot nH_2O$ was added in small portions with stirring. The acidity of the mixture was adjusted to pH 4.8 with sodium acetate. Within a few seconds, most of the $\alpha\text{-}GeW_9$ was dissolved and the solution clarified. The solution was stirred for 15 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: 1.5 g). Anal. Calc. for $K_4H_3[(C_4H_7O_2Sn)(\alpha\text{-}GeW_9O_{37})]\cdot 12H_2O$: C, 4.39; H, 0.73; Ge, 2.21; K, 4.72; Sn, 10.80; W, 49.83; H_2O, 6.57. Found: C, 4.38; H, 0.74; Ge, 2.23; K, 4.66; Sn, 11.10; W, 50.91; H_2O, 6.47%.

2.3.4. $K_4H_3[(CH_3COOCH_2CH_2Sn)_3(\beta\text{-}GeW_9O_{37})]\cdot 11H_2O$

The β-isomer was prepared analoguously. Anal. Calc. for $K_4H_3[(C_4H_7O_2Sn)_3(\beta\text{-}GeW_9O_{37})]\cdot 11H_2O$: C, 4.38; H, 0.72; Ge, 2.22; K, 4.75; Sn, 10.86; W, 50.11; H_2O, 6.02. Found: C, 4.40; H, 0.75; Ge, 2.20; K, 4.84; Sn, 11.27; W, 51.12; H_2O, 6.13%.

2.4. In *vitro* antitumoral assay

The antitumor activity of the complexes in *vitro* was determined by the MTT method [8].

3. RESULTS AND DISCUSSION

3.1. ^1H, ^{119}Sn and ^{183}W NMR spectra

^1H, ^{119}Sn and ^{183}W NMR data are listed in Table 1 and the ^{183}W NMR spectra are given in Figure 1.

Most of the studied tungstic heteropolyanions have the Keggin structure, which is based on the arrangement of four groups of three edge shared W_3O_{13} octahedra around the XO_4 central tetrahedron. The overall symmetry is T_d. This Keggin structure is called an α isomer. The β isomer is obtained by rotation of one W_3O_{13} by 60°(overall C_{3v} symmetry). The Keggin polyanions are stable in acid solution. When the pH increases, hydrolytic clevages of W-O bands occur, leading to well-defined lacunary polyanions, with 11,10 or 9 tungsten atoms. The lacunary polyanions can act as ligands with organometallic groups, leading to mono-, di- or tri-nuclear complexes. In the Keggin structure all tungsten atoms are identical, as shown by a single resonance in the ^{183}W NMR spectra. Removal of one W-O group reduces the symmetry of the anion from T_d to C_s and the expected six-line pattern is obtained in the ^{183}W NMR spectrum. When three organic groups occupy the three vacant sites of α- and β-nonatungstosilicates or germanates, tri (organometallo)-substituted polyoxotyngstates with Keggin structure are formed. Since the α- and β-trisubstituted polyanions have C_{3v} symmetry, the ^{183}W NMR spectra should have two line with relative intensity 2:1, corresponding to the belt tungsten atoms (6W) and cap tungsten atoms(3 W), respectively. The ^{183}W NMR spectra of the complexes confirmed that the complexes prepared were mono and tri-organometallo-substituted polyoxotungstates, respectively.

The ^1H and ^{119}Sn NMR spectra of complexes indicate that the $[RSn]^{3+}$ groups incorporated in the lacunary polyanions, forming the corresponding substituted complexes, respectively.

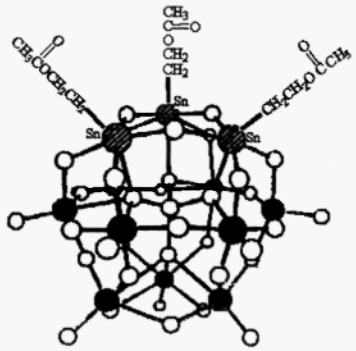

Fig.2 Structure of $K_4H_3[(CH_3COOCH_2CH_2Sn)_3(\alpha\text{-}GeW_9O_{37})]\cdot 10H_2O$

3.2. Electrochemistry

The redox properties of α- and $\beta_2\text{-}RSnSiW_{11}$ and α- and β-$(RSn)_3GeW_9$ were investigated by the

polarographic and cyclic voltammetric methods. Half-wave potentials for the complexes are listed in Table2. The cyclic voltamogram of $(C_4H_7O_2Sn)(\alpha\text{-}SiW_{11})$(a) and $(C_4H_7O_2Sn)(\beta_2\text{-}SiW_{11})$(b) are given in Fig.2.

Table 1 ^1H, ^{119}Sn and ^{183}W NMR data (ppm)

Anion	δ (^1H)			δ (^{119}Sn)	δ(^{183}W)
	OCH_3	CH(β)	CH (α)		
α-$(C_4H_7O_2Sn)SiW_{11}$	3.89(s)	3.09(t)	1.96(t)	-567.2	-64.4(2) , -108.7(2), -134.7(2), -140.2(2), -153.2(1), -193.1(2)
β_2-$(C_4H_7O_2Sn)SiW_{11}$	3.78(s)	3.05(t)	1.97(t)	-569.3	-97.5(2), -104.6(2), -110.0(1), -118.1(2), -132.7(2), -155.0(3)
α-$(C_4H_7O_2Sn)_3GeW_9$	4.23(s)	3.52(t)	1.99(t)	-494.0	-49.2(2), -122.8(1)
β-$(C_4H_7O_2Sn)_3GeW_9$	4.27(s)	3.59(t)	1.99(t)	-491.3	-84.5(2), -114.7(1)
$CH_3COOCH_2CH_2SnCl_3$	3.94(s)	2.94(t)	2.22(t)		

*Relative intensity in parentheses

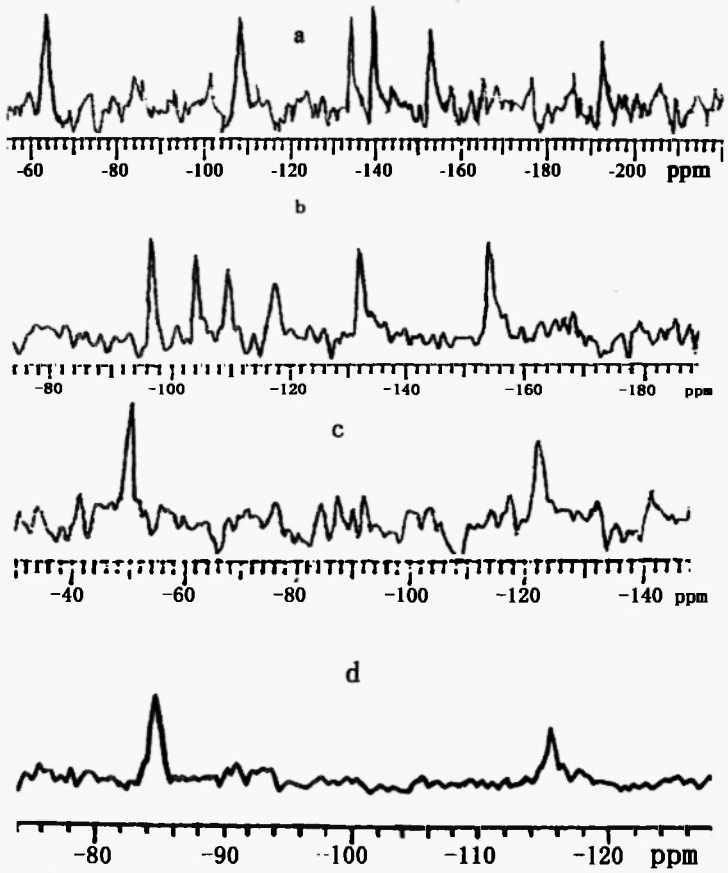

Fig.1 ^{183}W NMR spectra of (RSn)(α-SiW_{11}) (a), (RSn)(β-SiW_{11})(b), (RSn)(α-GeW_9)(c), (RSn)(β-GeW_9)(d)

Table2. Polarographic half-wave potential (V) for the complexes [a]

Compound	–	–
α–$(C_4H_7O_2Sn)SiW_{11}$	-0.576(2)	-0.812(2)
β_2–$(C_4H_7O_2Sn)SiW_{11}$	-0.636(2)	-0.932(2)
α–$(C_5H_9O_2Sn)SiW_{11}$	-0.556(2)	-0.720(2)
β_2–$(C_5H_9O_2Sn)SiW_{11}$	-0.692(2)	-0.820(2)
α–$(C_4H_7O_2Sn)_3GeW_9$	-0.816(2)	-0.988(2)
β–$(C_4H_7O_2Sn)_3GeW_9$	-0.753(2)	-0.933(2)

a All polarography in 1.0 mol·dm^{-3} (pH = 4.7) acetate buffer solution with 5.10^{-4} mol·dm^{-3} heteropolycompound.

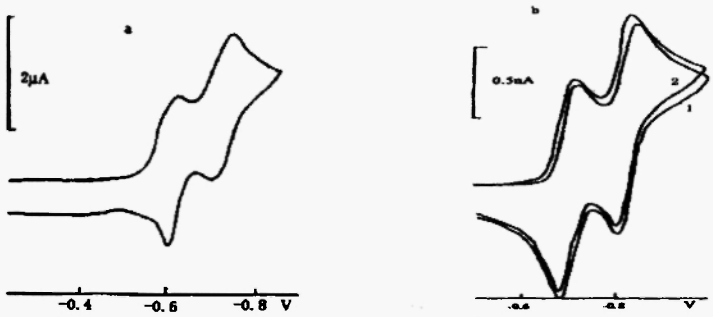

Fig.2 Cyclic voltamogram of (a) with E^I_{pc}=-668mv, E^I_{pa}=-592mv, at pH=4.7, sweep rate of 50 mv·s^{-1}, and (b) with E^I_{pc}=-722mv, E^I_{pa}=-684mv, at pH=4.7, sweep rate of 50(1) and 100mv·s^{-1}(2).

3.3. Antitumor activity of complexes *in vitro*

The inhibitory effect and effective cell 50% lethal concentration (IC_{50}) against SSMC-7721 (liver) and Hela (cervix) two human cancer cells as well the $E_{1/2}$ values for the complexes are given in Table 3.

Table 3 Inhibitory effect on two human tumor cell lines in *vitro* and half-wave potentials of the title complexes

Compound	Dose/ μg·mL^{-1}	SSMC-7721		Hela		$E_{1/2}$/V[b]	
		Inhibitory effect (%)	IC^a_{50}/ μg·mL^{-1}	Inhibitory effect (%)	IC_{50}/ μg·mL^{-1}	E_I	E_{II}
α-($C_4H_7O_2Sn$)SiW_{11}	100	93.6		100			
	10	9.1	53.3	10.5	49.6	-0.576	-0.812
$β_2$-($C_4H_7O_2Sn$)SiW_{11}	100	68.9		66.9			
	10	6.5	76.2	6.4	77.1	-0.636	-0.932
α-($C_5H_9O_2Sn$)SiW_{11}	100	100		100			
	10	10.2	49.9	11.1	47.5	-0.556	-0.720
$β_2$-($C_5H_9O_2Sn$)SiW_{11}	100	69.1		67.2			
	10	6.4	76.8	6.6	75.6	-0.692	-0.820
α-($C_4H_7O_2Sn$)$_3GeW_9$	100	40.4		30.6			
	10	2.7	122.6	1.4	163.6	-0.816	-0.988
β-($C_4H_7O_2Sn$)$_3GeW_9$	100	51.1		49.9			
	10	5.3	97.7	5.3	100.4	-0.753	-0.933

a The 50% inhibitory concentration (IC_{50}) is defined as the concentration which suppresses tumor cells by 50%.
b All polarography in 1.0 mol·dm^{-3} (pH=4.7) acetate buffer solution with 5-10 mol·dm^{-3} heteropolycompound.

It can be seen from Table 3 that all the complexes exhibit the antitumor activity in *vitro*. The inhibitory effect of α-($C_4H_7O_2Sn$)SiW_{11} and α-($C_5H_9O_2Sn$)SiW_{11} is higher than that of the β-forms, respectively, and the inhibitory effect of β–($C_4H_7O_2Sn$)$_3$ GeW_9 is higher than that of α-form. It is of interest to note that the order of the antitumor activity of the complexes is increasing with the oxidation ability of the polyanions either in the series of monosubstituted complexes or trisubstituted complexes.

In order to compare the antitumor activity of the isomers, the effective cell 50% lethal concentration (IC_{50}) against SSMC-7721 and Hela cancer cells and the $E_{1/2}$ values for the reported previously isomers are given in Table 4.

The sequence of antitumor activities of the complexes is consistent with the order of oxidation ability of polyanions among a couple of isomers possessing the same polyanion and organometallic group whether in the series of monosubstituted complexes or trisubstituted complexes as well in the sandwich compounds, as indicated in Table 4. An electrophoresis experiment indicated that α-SiW_9($CpTi$)$_3$ complex exhibits a strong interaction with DNA. This result implies that the antitumor mechanism of polyoxometalates based on the cleavage of DNA may be related to its redox property. This work is in progress.

Table 4. IC_{50} of isomers and their polarographic half-wave potentials

Compound	IC_{50} / $\mu g \cdot mL^{-1}$		$E_{1/2}$ / V		
	SSMC-7721	Hela	E_I	E_{II}	E_{III}
α-$(C_4H_7O_2Sn)_3SiW_9$	90.9	93.2	-0.774	-0.994	
β-$(C_4H_7O_2Sn)_3SiW_9$	61.7	80.6	-0.676	-0.916	
α-$(C_5H_9O_2Sn)_3SiW_9$	90.9	93.0	-0.736	-0.921	
β-$(C_5H_9O_2Sn)_3SiW_9$	61.1	79.3	-0.667	-0.911	
α-$(NC_3H_4Sn)_3SiW_9$	43.2	76.2	-0.804	-1.016	
β-$(NC_3H_4Sn)_3SiW_9$	29.9	68.3	-0.768	-0.952	
α-$(C_4H_7O_2Sn)_3(SiW_9)_2$	60.7	87.6	-0.608	-0.776	
β-$(C_4H_7O_2Sn)_3(SiW_9)_2$	53.1	77.5	-0.600	-0.824	
α-$(NC_3H_4Sn)_3(SiW_9)_2$	28.7	61.1	-0.763	-0.952	
β-$(NC_3H_4Sn)_3(SiW_9)_2$	19.8	54.9	-0.703	-0.887	
α-$(CpTi)_3SiW_9$	21.6	38.7	-0.526	-0.808	
β-$(CpTi)_3SiW_9$	18.6	33.6	-0.524	-0.732	-0.912
α-$(CpTi)_3GeW_9$	11.2	21.3	-0.460	-0.646	-0.816
β-$(CpTi)_3GeW_9$	23.7	25.6	-0.463	-0.668	-0.847

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