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Tin(IV) Cyanoximates: Synthesis, Characterization, and Cytotoxicity†

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In recent years, numerous organotin(IV) derivatives have exhibited remarkable cytotoxicity against several types of cancer. However, the properties of the cyanoxime-containing organotin(IV) complexes are unknown. Previously, it has been shown that cyanoximes displayed an interesting spectrum of biological activity ranging from growth-regulation to antimicrobial and pesticide detoxification actions. The work presented here attempts to combine the useful properties of both groups of compounds and investigate the likely antiproliferating activity of the new substances. A series of 19 organotin(IV) complexes, with nine different cyanoxime ligands, were anaerobically prepared by means of the heterogeneous metathesis reaction between the respective organotin(IV) halides (Cl, Br) and ML (M = Ag, Tl; L = cyanoximate anion), using an ultrasound in the CH_3CN at room temperature. The compounds were characterized using spectroscopic methods (UV–visible, IR, ^{1}H,^{13}C NMR, ^{119}Sn Mössbauer) and X-ray analysis. The crystal structures of the complexes revealed the formation of two types of tin(IV) cyanoximates: mononuclear five-coordinated compounds of $R_{4-x}SnL_x$ composition (R = Me, Et, *n*-Bu, Ph; $x = 1, 2$; L = cyanoximate anion), and the tetranuclear $R_8Sn_4(OH)_2O_2L_2$ species (R = *n*-Bu, Ph). The latter complex contains a planar $[Sn_4(OH)_2O_2]^{2-}$ core, consisting of three adjacent rhombs with bridging oxo and hydroxo groups. The tin(IV) atoms are five-coordinated and have distorted trigonal-pyramidal surrounding. This is the first instance when the organic anions were found to act as monodentate O-bound planar oxime ligands. All of the compounds were studied in vitro for antiproliferating activity, using human cervical cancer HeLa and WiDR colon cancer cell lines; cisplatin was used as a positive control substance. The two dibutyltin(IV) cyanoximates showed cytotoxicity similar and greater to that of cisplatin.

Introduction

The successful application of metal complexes in the treatment of numerous human diseases is a vigorously expanding area in biomedical and inorganic chemistry research.[1,2] Cancer is the primary target in the proposed research because it is the leading cause of premature deaths in the world. There are several ways to induce irreparable DNA damage, which may cause the arrest of its replication and create conditions for apoptosis (Scheme 1). Ionizing radiation causes indirect damage to the DNA via reactive

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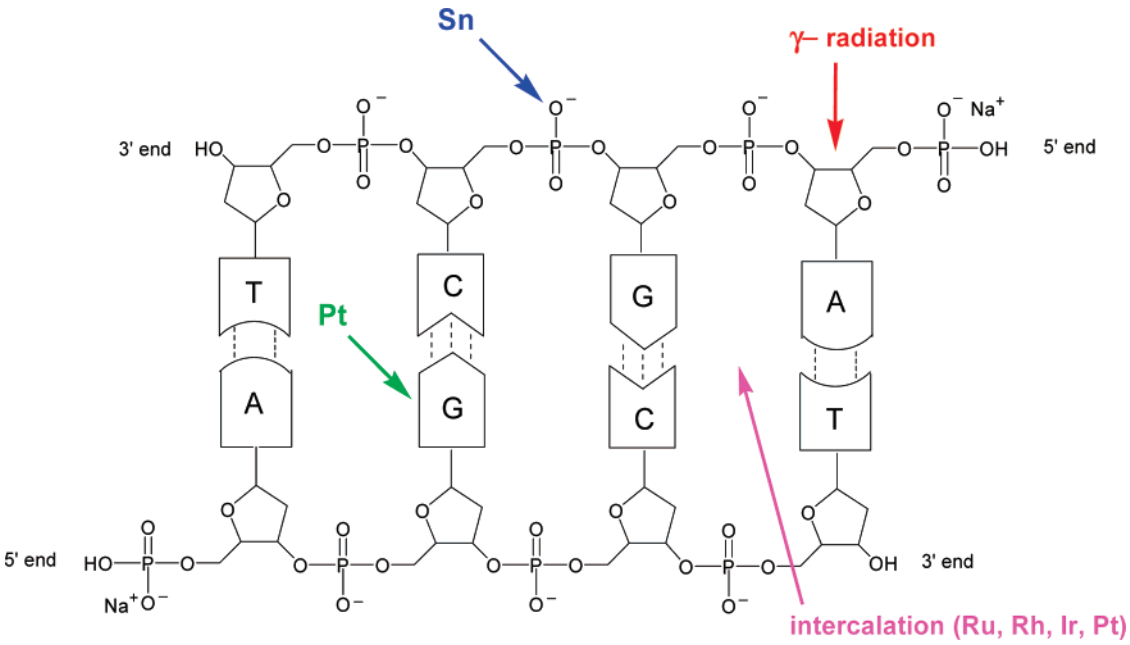
Scheme 1



oxygen species, whereas chemotherapy uses chemical substances that directly interact with DNA. Research has proven that the most effective and widely used coordination compounds as anticancer drugs are the DNA nitrogen base binding cisplatin, oxalylplatin, nedaplatin and carboplatin, all of which are metallocomplexes of platinum(II).[2,3] In spite of its high activity, the application of cisplatin and similar compounds has significant disadvantages that include: (1) poor water solubility, (2) severe side effects that are typical of heavy metals toxicity, and (3) the development of drug tolerance by the tumor. The last two are the major driving force behind current research in the field of novel anticancer agent development.

A substantial investigation of other metals (Ti, Ga, Ge, Pd, Au, Co, and Sn) is underway that may help to avoid, or improve, the problems associated with the use of platinum compounds as therapeutic agents.[4] In vitro screening of new coordination compounds, followed by selecting the best performing anticancer active compounds, is still the best way of identifying potential drug candidates. The QSAR principles,[5] successfully developed for numerous organic and identified natural compounds, are not fully applicable for metal complexes because of their unpredictable stability and kinetics toward ligand substitution reactions. There is, however, promising and recent success in using different organotin(IV) derivatives, which have shown acceptable in vitro cytoxicity and antiproliferative in vivo[6] activity as new chemotherapy agents. Tin biodistribution and the history of its medical applications, including anticancer activity, is summarized in S1 of Supporting Information. In studied cytotoxic compounds, the organotin(IV) moiety is bound to a phosphate group of the DNA backbone,[7] contrary to the platinum family of drugs (Scheme 1), and alters the intracellular phospholipid metabolism of the Golgi apparatus and the endoplasmic reticulum.[8] Organotin(IV) complexes also exhibit other attractive properties such as increased water solubility, lower general toxicity than platinum drugs,[11] better body clearance, fewer side effects, and no emetogenesis. Most importantly, organotin complexes do not develop the tumor drug tolerance that is well established for cisplatin and its analogs. Recent first attempts in developing the quantitative structure/activity and the structure/property relationships for organotin compounds have been reviewed.[9] Some emerging patterns in the area of predicting anticancer

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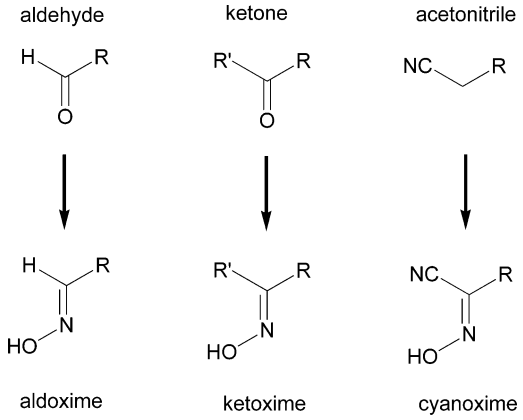
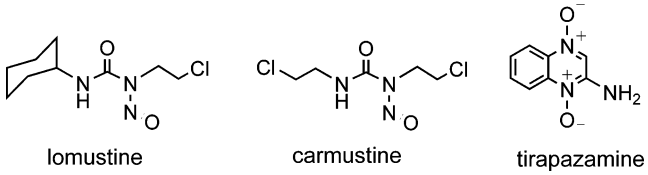
activity based on the R and L groups in the R_2SnL_2 moiety of the diorganotin carboxylates and $R_2SnX_2L_2$ (L = bidentate ligand with O and/or N donor atoms) were recently described in considerable detail.[10,12] Di(*n*-butyl) compounds were found to be the most active.[10a] Therefore, as one searches for the best performing compound, the selection of other ligands attached to the dibutyltin(IV) moiety is of great importance. Some of the organotin(IV) complexes were found to be even more active in vitro than the conventional cisplatin.[13]

Oximes[14] and cyanoximes[15] (Scheme 2), compounds having the general formula NC−C(=N−OH)−R, where R is an electron-withdrawing group, are known as biologically active compounds. They have shown pronounced cytotoxicity, anticancer[16] and antimicrobial[17] activity, to regulate growth in plants,[18] to exhibit molluscocide and insecticide[19] activity, and demonstrated detoxifying properties of agricultural pesticides[20] (Scheme 3). In addition, oximes resemble

Scheme 2



adopted anticancer NO-containing drugs[21,22] Lomustine, Carmustine, and Tirapazamine.



It was interesting to combine the anticancer properties exhibited by the organotin(IV) compounds with the established biological effects of oximes and cyanoximes.

With the exception of one publication,[23] there are, to date, no systematic studies of organotin cyanoximates. The primary objective of this work was the synthesis and characterization of a large group of new tin(IV) cyanoxime derivatives where only the dibutyltin(IV) complexes are the focus of the cytotoxicity studies. The choice for the *n*-butyltin(IV) derivatives was based upon previously estab-

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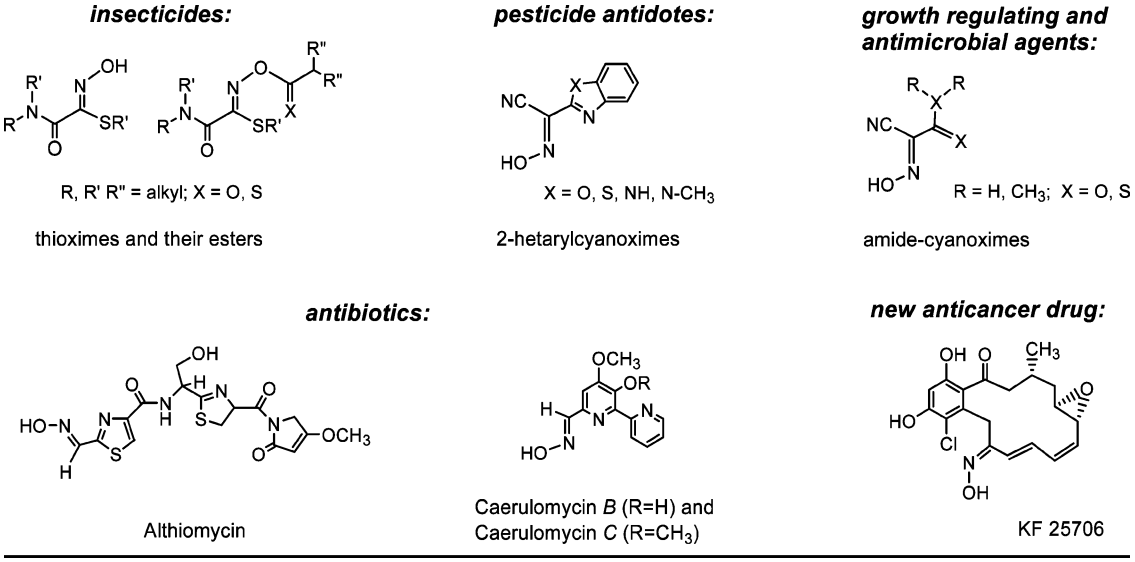
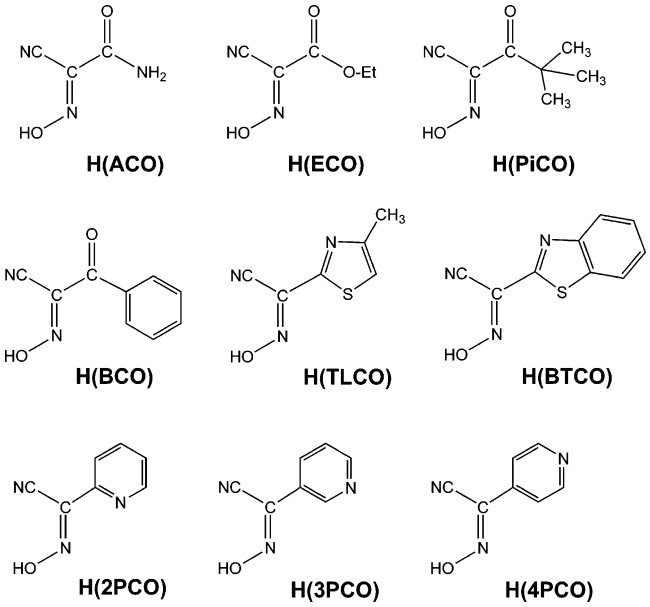
Scheme 3



Scheme 4



lished[24] optimal balance between the cytotoxicity, solubility, and lypophilicity. We selected nine cyanoxime-bearing molecules (Scheme 4), which possessed different degrees of hydrophobicity, and a variety of structural and electronic properties, and synthesized a large group of their organotin(IV) derivatives. In this article, we report the first results of a spectroscopic and structural investigation of the obtained metal complexes and the data from in vitro studies of their anticancer activity against the HeLa (cervical cancer) and WiDR (colon carcinoma) cell lines. These represent cells of a different morphology and were used in the initial cyto-

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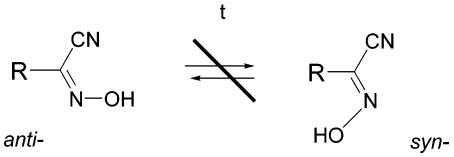
toxicity screening, with the intention of selecting the best performing compounds for subsequent studies involving a much larger pool of human cancers and the following in vivo experiments using small animals.

Results and Discussion

All nine cyanoxime ligands were obtained in high yield using a modified nitrosation Meyer[25,26] reaction of substituted acetonitriles with varying reaction conditions depending upon the activity of the substrates.[30,70] Nineteen new organotin(IV) cyanoximates were synthesized using a high-yield and fast metathesis reaction in acetonitrile at ambient conditions between the respective organotin halides and monovalent silver and thallium (for one complex) salts of the cyanoximes.

Organic Ligands. Four of the nine obtained cyanoximes existed as a mixture of syn and anti geometrical isomers in solutions, according to the data of ^{1}H and ^{13}C NMR spectroscopy (S4−S6, Supporting Information). Thus, the ^{13}C{^{1}H} NMR spectra of H(3PCO), H(4PCO), HTLCO, and HBTCO demonstrated a double set of signals, indicating the presence of the two isomers. There was no interconversion of the isomers observed upon heating dmso-d_6 solutions of these compounds up to 100 °C. This is contrary to previously found thermally induced conversion of the isomers for cyanoximes containing amides as an R group.[16a]



With the exception of the pale-yellow H(BTCO), all of the synthesized cyanoximes are colorless crystalline compounds. These compounds are soluble in light alcohols, acetone, ether, acetonitrile, THF, DMF, DMSO, and ethylacetate, but slightly soluble in toluene and chloroform, and insoluble in water, benzene, and carbon tetrachloride. The anionic cyanoximates in their tetrabutylammonium or alkali metal salts have a yellow/orange color. The UV-spectra of all of the studied cyanoxime anions contained characteristic transitions of the CN-chromophore at ∼220 nm, and a strong $\pi \rightarrow \pi^*$ transition of the aromatic region at ∼280−300 nm (Figure 1). The visible region contained n $\rightarrow \pi^*$ transitions in the NO-chromophore ($\epsilon = 40-200$), and very weak n* $\rightarrow \pi^*$ transitions[27] ($\epsilon = 1-5$) at ∼700 nm (Table 1). All of the obtained and studied cyanoxime anions exhibited a strong negative solvatochromism.[28] A detailed description of this interesting phenomenon is beyond the scope of this article and will be published separately.

Anionic Cyanoximates as Alkali Metal Salts, Silver(I), Thallium(I), and Organotin(IV) Derivatives. Numerous organotin(IV) derivatives were previously prepared using organotin(IV) halogenides and either protonated organic

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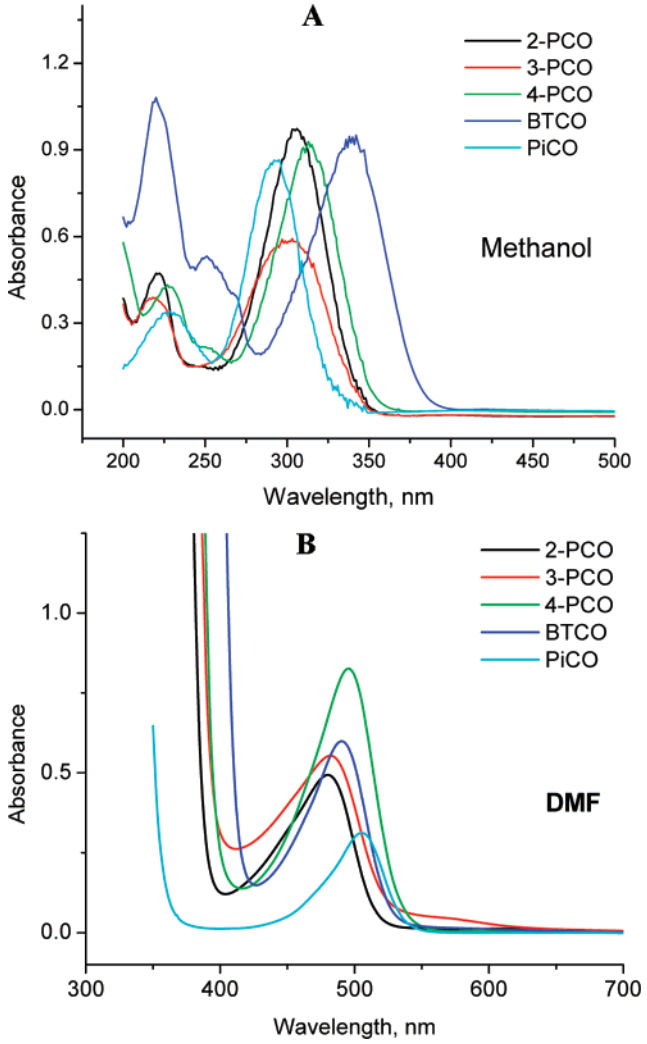

Figure 1. UV−visible spectra of anionic cyanoximes.

ligands or their Na-salts.[7a−c,29] These conventional procedures required a prolonged anaerobic reflux, which often provokes thermal decomposition of the product or makes the hydrolysis of the tin(IV) species possible. The procedures also are inconvenient, relatively low in yield, and are time-consuming preparations. Furthermore, complexes obtained in such a way require purification (recrystallization). In this article, we introduce a suitable and *fast* room-temperature synthesis of the organotin(IV) cyanoximates, based on the heterogeneous metathesis reaction between silver(I) or thallium(I) cyanoximates and organotin(IV) halides (bromides or chlorides), as shown in Scheme 6. The reaction is driven toward the formation of silver halides, because they are less soluble in organic solvent compounds than the initial silver(I) cyanoximates. Use of the ultrasound bath (Branson, 1510) significantly improved the most important element for a heterogeneous reaction condition—thorough mixing—and in many cases lead to a quantitative preparation of the organotin(IV) cyanoximates. Therefore, silver(I) cyanoximates were used as key precursors for the latter compounds. AgL are easily accessible complexes that can be prepared at room temperature in aqueous solutions from NaL according to the reactions shown below.

$$HL + MOH \rightarrow ML(s) + H_2O\ (M = Na^+, K^+, Cs^+, NMe_4^+) \quad (1)$$

$$AgNO_3(aq) + NaL(aq) \rightarrow AgL(s) + NaNO_3(aq) \quad (2)$$

(where L = cyanoxime ligands from Scheme 4).

The vast majority of silver(I) cyanoximates are insoluble in water and *light-insensitive* yellow/orange[30] substances. Details of the preparation of the Na^+, Cs^+, and Ag^+ salts with a variety of other cyanoxime ligands are available.[31] Ionic sodium, cesium, or tetramethylammonium salts are

Table 1. Results of UV−visible[a] Spectroscopic Studies of the Cyanoxime Anions (as Alkali Metal or Tetrabutylaamonium Salts) in *n*-Propanol Solutions

	bands wavelength, nm (ϵ, $M^{-1}cm^{-1}$)		
cyanoxime anion	$\pi \rightarrow \pi^*$ CN group	$\pi \rightarrow \pi^*$	n $\rightarrow \pi^*$ NO-chromophore
$2PCO^-$	223(9140)	311(19 700)	407(130)
$3PCO^-$	sh[b]	306(11 100)	403(80)
$4PCO^-$	231(7000)	320(15 700)	423(90)
$BTCO^-$	219(19 900)	339(17 400)	427(130)
$PiCO^-$	224(4390)	296(15 400)	445(60)
BCO^-	251(8900)	309(14 200)	457(85)
ECO^-	sh	292(12 700)	430(70)
ACO^-	227(12 000)	290(20 300)	405(25)

[a] UV-spectra (190−350 nm range) were recorded in 1 mm cuvettes at 0.5 mM compound concentration; visible spectra (350−1000 nm range) were obtained from 5 mM solutions using a 1 cm cell with all of the measurements at 298 K. [b] Shoulders around 210 nm on an intense band of $\sigma \rightarrow \sigma^*$ transitions in far UV region (<190 nm).

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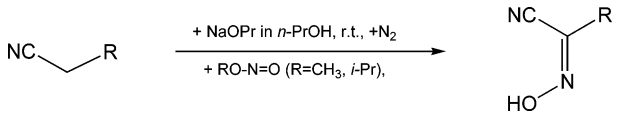
Table 2. Some Properties of the Alkali Metal Salts, Silver(I), and Thallium(I) Cyanoximate Precursors for the Organotin(IV) Complexes

compound	yield (%)	color	elemental content % calcd, (% found)			
			C	H	N	S
K(PiCO)	75	pale-yellow	43.73	4.72	14.57	
			(43.89)	(4.92)	(14.62)	
NMe_4(BCO)	65	pink	63.14	6.93	16.98	
			(63.60)	(7.16)	(16.64)	
Na(4PCO)	90	pale-yellow	49.71	2.38	24.85	
			(49.80)	(2.49)	(24.67)	
Na(TLCO)	85	bright-yellow	38.09	2.13	22.91	16.95
			(38.18)	(2.24)	(22.07)	(16.64)
Ag(2PCO)	80	lemon-yellow	33.10	1.59	16.54	
			(33.81)	(1.58)	(16.85)	
Ag(4PCO)	85	pale-yellow	33.10	1.59	16.54	
			(32.35)	(1.57)	(16.19)	
Tl(3PCO)·H_2O	65	straw-yellow	22.81	1.64	11.40	
			(22.82)	(1.17)	(10.88)	
Ag(TLCO)	90	yellow	26.30	1.47	15.33	11.70
			(26.11)	(1.60)	(15.24)	(11.53)
Ag(BTCO)	95	orange-brown	34.86	1.30	13.55	10.34
			(34.88)	(1.22)	(13.50)	(10.03)

Scheme 5



intermediates in the preparation of silver(I) cyanoximates and were not isolated in bulk quantities during this research phase. However, small samples of alkali metal and NMe_4^+ salts were obtained for spectroscopic studies (primarily IR, UV−visible, and ^{13}C NMR) and analytical characterization (Table 2). As mentioned, the metathesis reaction between the respective organotin(IV) derivatives and the silver cyanoximates represents a clean, one-step, high-yield process that is depicted in Scheme 6. The anhydrous Tl(3PCO) complex was used for the metathesis reaction instead of the silver salt because the silver(I) complex of this ligand turned out to be inconveniently light-sensitive. The former compound was obtained by reaction **3** previously used for the synthesis of other thallium(I) salts:[32]

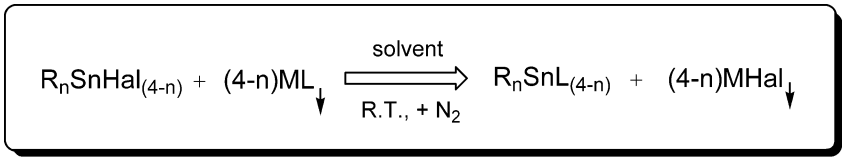
$$2H(3PCO)(s) + Tl_2CO_3(aq) \xrightarrow{+95\ °C,\ water} 2Tl(3PCO)(s) + H_2O + CO_2(g) \quad (3)$$

Concentration of the organotin(IV) cyanoximate acetonitrile solutions under a vacuum affords microcrystalline or waxy solids (Scheme 6). Highly concentrated solutions (∼10 mL) of the complexes were used for growing crystals for X-ray analysis; two different techniques were applied for the same purpose (S7).

Spectroscopic Studies. Vibrational frequencies with the participation of the oxime fragment in the IR spectra of HL, ML (M = K, Rb, Cs; L = cyanoxime residue) and several organotin compounds were assigned, using the bands' comparison, in the spectra of the ^{14}N- and ^{15}N-labeled (50%) compounds (Table 4). The data indicated a monodentate coordination of the oxime ligands to the metal center in organotin(IV) complexes via the oxygen atom of the >C═N−O fragment. This is evident from a significantly low-frequency shift of the ν(N−O) vibration in the IR spectra of the tin(IV) complexes, as compared to the band position in the spectra of ionic ML where the oxime ligand is noncoordinated.[32b,33,34] The cyano group participated in additional coordination to the central atom in monomeric R_2SnL_2 (R = Me, *n*-Bu, Ph; L = ACO^-, ECO^-, $2PCO^-$, $3PCO^-$, $4PCO^-$, BCO^-, $PiCO^-$) complexes. This is reflected in the typically high frequency shift of the ν(C≡N) vibration upon coordination, compared to that in the IR spectra of alkali metal cyanoximates. Therefore, cyanoximes often act as anionic bridging groups in these complexes. However, there is no indication that the CN group participates in the coordination to the neighboring metal centers in the tetranuclear complexes. The IR spectroscopy data evidenced only monodentate coordination of the anions to the tin(IV) atoms via oxygen atoms of the oxime group (Table 4).

The Mössbauer spectra of the selected mononuclear alkyltin(IV) cyanoximates suggest five-coordinated surrounding of the central atom in studied complexes, instead of the suspected tetrahedral structures (Table 5). In these com-

Scheme 6



M = Ag^+, Tl^+ L = cyanoxime anion R= *n*-C_4H_9, C_6H_5, CH_3
Hal = Cl^-, Br^- Solvent: THF, CH_3CN

n = 1 (for $TLCO^-$, R = CH_3); n = 2; n = 3 (for ACO^-, R = C_2H_5)

Table 3. Composition and Some Properties of the Obtained Organotin(IV) Cyanoximates

complex	yield (%)	color	mp °C	elemental content % calc, (% found) C	H	N	Sn[a] or S[b]
$Me_3Sn(TLCO)$	88	colorless	119	32.76 (33.26)	3.97 (4.12)	12.73 (12.51)	9.72 (9.45)[b]
$Et_3Sn(ACO)$	90	colorless	89	34.02 (34.59)	5.39 (5.62)	13.22 (13.17)	37.33 (37.08)[a]
$Me_2Sn(ACO)_2$	95	colorless	150[c]			22.15 (22.48)	31.85 (31.45)[a]
$Me_2Sn(ECO)_2$	80	pale-yellow	165[c]			14.04 (14.21)	27.56 (27.67)[a]
$Me_2Sn(PiCO)_2$	75	colorless	170[c]			12.31 (12.12)	26.11 (26.57)[a]
$Bu_8Sn_4(OH)_2O_2(ACO)_2$	90	colorless	96	37.35 (38.03)	6.43 (6.54)	6.88 (6.91)	
$Bu_2Sn(ACO)_2$	85	pale-yellow	114	36.79 (35.62)	4.86 (4.98)	18.39 (18.56)	25.97 (25.31)[a]
$Bu_2Sn(BCO)_2$	95	pale-yellow	82−86	53.91 (54.14)	4.87 (5.02)	9.67 (9.43)	20.49 (20.05)[a]
$Bu_2Sn(BTCO)_2$	82	yellow	110	49.01 (49.93)	4.11 (4.85)	13.19 (12.88)	10.06 (9.89)[b]
$Bu_2Sn(ECO)_2$	95	pale-yellow	90[c]	5.48 (42.39)	41.97 (5.87)	10.88 (10.41)	23.04 (22.62)[a]
$Bu_2Sn(PiCO)_2$	90	pale-yellow	83[c]	49.03 (50.20)	6.73 (6.92)	10.38 (10.17)	
$Bu_2Sn(2PCO)_2$	86	colorless	78−85	50.31 (50.63)	4.99 (5.14)	16.01 (15.78)	
$Bu_2Sn(3PCO)_2$	60	colorless	120	50.31 (50.47)	4.99 (5.25)	16.01 (15.62)	
$Bu_2Sn(4PCO)_2$	72	yellow	110[c]	50.31 (50.78)	4.99 (5.21)	16.04 (16.15)	
$Ph_2Sn(ACO)_2$	86	colorless	200[c]			16.91 (16.71)	23.89 (23.56)[a]
$Ph_2Sn(PiCO)_2$	80	pale-yellow	158			9.67 (9.71)	20.48 (20.36)[a]
$Ph_2Sn(ECO)_2$	78	pale-yellow	132			10.71 (10.53)	22.75 (22.82)[a]
$Ph_8Sn_4(OH)_2O_2(ACO)_2$	90	colorless	99−106	49.94 (48.99)	3.36 (3.41)	6.08 (6.17)	
$Ph_8Sn_4(OH)_2O_2(PiCO)_2$	86	pale-yellow	82[c]	50.86 (51.17)	4.13 (4.38)	3.83 (3.96)	

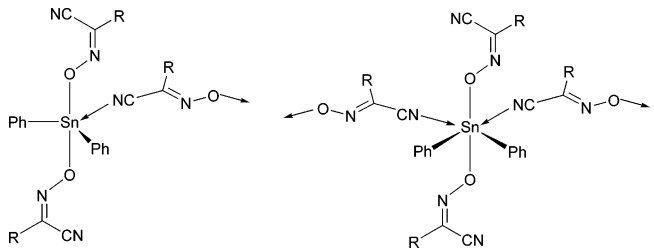
[a] Tin content was determined using gravimetric analysis with SnO_2 as the weigh form. [b] Sulfur content was measured using the combustion method. [c] Beginning of changing color (darkening) and decomposition occurred in a closed capillary tube.

Table 4. Results of IR Spectroscopic Studies of Synthesized Compounds: Selected Listing for Ionic Alkali Metal Salts and Covalent Organotin(IV) Derivatives

compound	assigned bands (cm^{-1}) ν(C≡N)	ν(C=O)	ν(C=N)[a]	ν(N−O)[a]	ν(Sn−C)
Cs(ACO)	2223	1685	1380[b]	1290[b]	
$Et_3Sn\{ACO\}$	2220	1640	1510	1065	555
$Ph_2Sn\{ACO\}_2$	2237	1680	1528	1062	[d]
$Bu_8Sn_4(OH)_2O_2\{ACO\}_2$	2220	1682	1525	1065	560
$Ph_8Sn_4(OH)_2O_2\{ACO\}_2$	2222	1688	1523	1062	[d]
Na(PiCO)	2205	1635	1390[b]	1250[b]	
$Me_2Sn\{PiCO\}_2$	2230	1632	1533	1058	560
$Ph_2Sn\{PiCO\}_2$	2232	1630	1530	1055	[d]
$Ph_8Sn_4(OH)_2O_2\{PiCO\}_2$	2209	1640	1534	1052	
Na(TLCO)	2220		1530[c]	1210[b]	
$Me_3Sn\{TLCO\}$	2230		1535[c]	1040	545
Cs(ECO)	2200	1710	1382	1280[b]	
$Me_2Sn\{ECO\}_2$	2236	1720	1490	1070	560
$Bu_2Sn\{ECO\}_2$	2238	1714	1496	1072	563
$Ph_2Sn\{ECO\}_2$	2235	1712	1500	1071	[d]

[a] Vibrations in the oxime fragment assigned using ^{15}N as a label. [b] In ionic alkali metal salts assigned[34] as ν(CNO) and ν(NO). [c] ν(C=N) vibrations in the thiazoline ring. [d] Obscured for observation by other bands.

pounds, the values of both QS and IS are in agreement with the distorted trigonal-bipyramidal structures of coordination polyhedrons.[35] It is interesting to note that the five-coordinated structures of these complexes were first suggested after an analysis of their IR spectra. Thus, the 12−35 cm^{-1} increase in the ν(C≡N) vibrational frequencies of the organotin(IV) derivatives as compared to those of ionic alkali metal cyanoximate salts indicated the participation of the cyano group of the neighboring molecule in coordination (Table 4). The Mössbauer spectra of the two studied diphenyltin(IV) cyanoximates contained two doublets that corresponded to the mixture of the five-coordinated and six-coordinated species at approximately equal amounts (Table 5). The ACO^- and $PiCO^-$ anions in these complexes acted as a monodentate (via the oxygen atom of the oximegroup) and bridging (via the nitrogen atom of the cyano group) ligands.



The cis position of phenyl groups in the six-coordinated $Ph_2Sn(ACO)_2$ and $Ph_2Sn(PiCO)_2$ complexes is consistent with the literature values reported for this type of geometry (Table 5).

The ^1H and $^{13}C\{^1H\}$ NMR spectra of synthesized organotin(IV) cyanoximates did not show significant changes in signal positions of the methyl, *n*-butyl, or phenyl groups as

Table 5. Data of ^{119}Sn Mössbauer Spectra for Several Synthesized Organotin(IV) Cyanoximates and Related Compounds

compound	IS	QS[a]	Γ1	Γ2	coordination number, central atom geometry	ref
		(all parameters in mm/s)				
Me_4Sn	1.20	0			4, tetrahedral	35, 36, 37
Ph_4Sn	1.15	0			4, tetrahedral	35, 36, 37
Me_3SnL^1	1.30	3.68			5, normal trig. bipyramid	38
Ph_3SnL^2	1.10	1.94			5, distorted trig. bipyramid	39
Me_3Sn(TLCO)	1.28	2.86			5, distorted trig. bipyramid	this work
Et_3Sn(ACO)	1.32	3.70	1.10	1.23[b]	5, distorted trig. bipyramid	this work
$Me_2Sn(ACO)_2$	1.34	3.43	1.11	1.22[b]	5, distorted trig. bipyramid	this work
$Me_2Sn(ECO)_2$	1.53	3.32	1.14	1.29[b]	5, distorted trig. bipyramid	this work
$Me_2Sn(PiCO)_2$	1.33	3.55	1.13	1.22[b]	5, distorted trig. bipyramid	this work
$Ph_2Sn(ACO)_2$	1.29	3.31[c]	1.12	1.12	5, distorted trig. bipyramid	this work
	0.70	1.97[d]	1.55	1.56	6, distorted octahedral	
$Ph_2Sn(PiCO)_2$	1.28	3.03[e]	1.11	1.11	5, distorted trig. bipyramid	this work
	0.68	1.85[f]	1.60	1.60	6, distorted octahedral	
$Me_2Sn(L^3)_2$	0.77	2.02			6, cis-octahedral	36
$BuSnCl(L^3)_2$	0.85	1.67			6, cis-octahedral	38
$BuSn(L^3)_3$	0.70	1.82			7, caped octahedral	38

[a] Modular values; L^1, acetate anion; L^2, anion of N-benzoyl-N-phenylhydroxamate: N,O-chelating ligand; L^3, anion of 8-hydroxyquinoline: N,O-chelating ligand. [b] Asymmetric doublet due to the Goldanskii−Karyagin effect.[40] [c] The relative doublet intensity of the five-coordinate complex is 32%. [d] The relative doublet intensity for the six-coordinate complex is 68%. [e] The relative doublet intensity for the five-coordinate complex is 56%. [f] The relative doublet intensity of the six-coordinate complex is 44%.

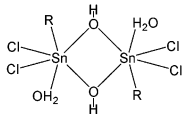
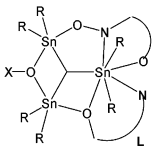
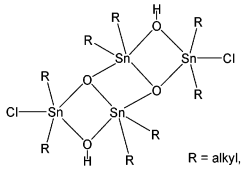
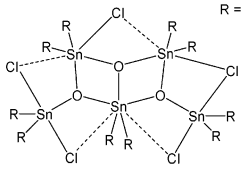
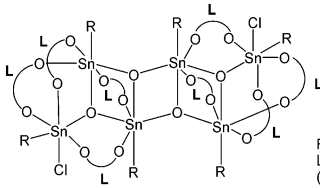
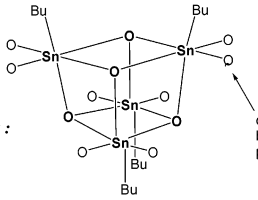
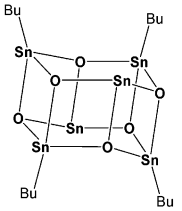
compared to those for the initial organotins. This is consistent with the retention of the monodentate O-binding mode of anions to the metal center in solutions. It should be noted that at room temperature the $^{13}C\{^1H\}$ NMR spectra of many of the dibutyltin(IV) cyanoximates in $CDCl_3$ exhibited significant line broadening of signals in both aliphatic and oxime carbon atoms (S8). We associated this phenomenon with the large thermal motion of the *n*-butyl chains and the formation of at least two species (even in $CDCl_3$ solutions, S8) that might be engaged in a dynamic complex equilibrium with solvent participation.[41,42] Also, in the $^{13}C\{^1H\}$ NMR spectra of the synthesized organotin(IV) cyanoximates we were unable to detect a $^{119/117}Sn-^{13}C$ coupling becuase of an overall relatively low signal-to-noise ratio (S/N < 10) and insufficient spectra quality. This is because of the poor solubility of the complexes in $CDCl_3$ and acetone-d_6; even saturated solutions of many of the obtained compounds required prolonged acquisitions with the number of repetitions routinely exceeding 30,000, which made further detailed studies of these compounds rather difficult. Therefore, the use of the Lockhart[43] empirical correlations between the $^1J(^{119}Sn-^{13}C)$ coupling constants and the C−Sn−C angles for elucidation of the structure of compounds in solutions was not possible. However, the $^{119/117}Sn-^{13}C$ coupling constants were measured for the starting organotin(IV) halides because their solubility was significantly higher in these solvents (S9). The values of the C−Sn−C angles θ for those compounds were calculated[43] according to the equation $\theta = [^1J(^{119}Sn-^{13}C) + 875]/11.4$ (S9). It is important to mention that the obtained θ values are consistent with the angle change due to the solvent coordination in the CD_3CN solutions. Thus, the C−Sn−C angle determined for the alkyltin(IV) halides in presumably noncoordinating $CDCl_3$ is smaller and close to the expected ∼110° value in tetrahedral complexes (S9). The same C−Sn−C angle is greater in acetonitrile-d_3 solutions, which indicates participation of the solvent in coordination to the metal center (S9). Deuterated DMSO, DMF, and pyridine were not used as a solvent in the NMR spectroscopic measurements of the organotin(IV) cyanoximates because of their strong tendency to coordinate to the metal center, changing its geometry or even substituting coordinated organic molecules in the complex.

$^{119}Sn\{^1H\}$ NMR spectra were recorded for all of the initial organotin(IV) halides and several cyanoximates, where their solubilities were sufficient for obtaining spectra in a reasonable time frame (S9−S11). The values of ^{119}Sn chemical shifts for the organotin(IV) cyanoximates in $CDCl_3$ were typical for the diorganotin and triorganotin(IV) compounds range. Solutions in acetone and acetonitrile showed multiple ^{119}Sn resonances (S9, S10), which were attributed to different species due to solvent coordination[44] and possible dynamic equilibrium between several complexes.[41,42] Detailed NMR studies of the synthesized organotin(IV) cyanoximates in solutions were not in the scope of the current investigation but are planned for a future comprehensive characterization of most of the cytotoxic compounds identified in this work.

Conclusions regarding the monodentate coordination of anions drawn from spectroscopic methods were confirmed during structural investigation of some of the organotin(IV) cyanoximates and are presented below.

Structures of the Organotin(IV) Complexes. Formation of the rhombic stannoxane units Sn_2O_2, $Sn_2(OH)_2$—as products of a partial or complete hydrolysis[45] of different complexes—was proposed and later confirmed by ^{119}Sn NMR,[36] Mössbauer, and potentiometric studies.[46] A variety of structural motifs, which include these building blocks, are summarized in Table 6. Some structures represent complex coordination polymers, although the vast majority of the hydrolysis products are molecular compounds. The established binding modes of the oxime-bearing ligands in several organotin(IV) compounds are presented in Table 6. Aldoximes form a variety of interesting polynuclear organotin(IV) complexes.[41] However, no structural information about the ketoxime or cyanoxime complexes of tin(IV) existed prior

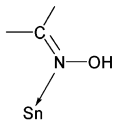
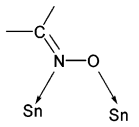
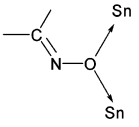
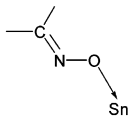
Table 6. Structural Types of Products of Hydrolysis of Organotin(IV) Halogenides that Contain Stannoxane Sn_2O_2 Rhombs

type	complex	reference
I	***Dimers :***  R = alkyl	47
II	***Trimers :***  R = alkyl, X = OH, OMe, F L = bidentate chelate ligand	42
III	***Tetramers :***  R = alkyl, phenyl	45,48,49
IV	***Pentamers :***  R = alkyl	49
V	 ***Hexamers :*** R = *n*-Butyl, L = carboxylic acid (bidentate binding)	50
VI	***Cubanes :***  oxygen atoms of bis(cyclohexane) phosphoric acid	51
VII	 ***Double-deckers and drums:*** oxygen atoms of six bidentate cyclopentane carboxylate residues are not shown	52,53

to this study. Established coordination modes of oximes in organotin(IV) complexes are summarized in Table 7. The first known examples of monodentate O-coordination of the oxime group to the tin(IV) centers are presented and discussed in this article.

Molecular structure of $(CH_3)_3Sn(TLCO)$. Single crystals of the trimethyltin(IV) 2-(4-methylthiazolyl) cyanoximate, suitable for X-ray analysis, were grown in an argon-filled, closed system in a refrigerator, using a slow ether-vapor

Table 7. Crystal Data and Structure Refinement for $(Bu)_8Sn_4(OH)_2O_2(ACO)_2$ (**I**), $(Ph)_8Sn_4(OH)_2O_2(ACO)_2\cdot(C_2H_5)O$ (**II**), and $(CH_3)Sn(TLCO)$ (**III**)

coordination type	structural features	reference
	Monodentate N-coordination, the oxime group is protonated and the ligand is nearly planar.	41b
	Bridging coordination via both atoms of the oxime fragment; the oxime group is deprotonated (anionic) and the ligand is not planar.	41a, 42
	Bridging function of the oxygen atom of the anionic oxime; the ligand is not planar.	41
	Monodentate O-coordination; the oxime group is deprotonated and anion formed is planar.	This work

diffusion into the acetonitrile solution of the complex (**1**, S7). The crystal and refinement data are shown in Table 8; selected bond distances and angles for the structure of $(CH_3)_3Sn(TLCO)$ are presented in Table 9. The molecular structure of this complex is shown in Figure 2, whereas the packing diagram for the compound is displayed in Figure 3. The metal complex has a distorted trigonal bipyramidal structure of the coordination polyhedron (S12) despite the compound's stoichiometry. The crystal structure of the complex indicates an interaction between the tin atom of one molecule and the nitrogen atom N(3) of the cyano group of a neighboring molecule below the Sn−C(8)−C(7)−C(9) plane (Figure 3). This interaction is also reflected in the IR spectrum of the complex (Table 4) as the increase in the ν(C≡N) vibration frequency of the CN group, as a result of its coordination. Therefore, the thiazolylcyanoxime anion acts as the bridge between the tin(IV) atoms in the chains of complexes in the crystal. The heterocyclic $TLCO^-$ ligand is in the *oxime* form and adopts a planar trans-anti configuration. The oxime group has geometrical parameters normal for the monodentate coordinated via the oxygen atom cyanoxime ions.[30,54,55]

Molecular Structure of $Et_3Sn(ACO)$. Single crystals of this compound were obtained when a small portion (∼0.2 g) of the white solid complex was anaerobically redissolved in 5 mL of acetonitrile, and carefully overlaid with 50 mL of anhydrous ether, using method **1** (S7). Unfortunately, the quality of the obtained crystals and the excessive thermal motion of the ethyl groups precluded an accurate solution of the structure of this complex, and we were unable to bring the R factor below 18%. Nevertheless, the polymeric structural motif of this compound was established and shown in S13.

Table 8. Crystal Data and Structure Refinement for $(Bu)_8Sn_4(OH)_2O_2(ACO)_2$ (**I**), $(Ph)_8Sn_4(OH)_2O_2(ACO)_2 \cdot 2(C_2H_5)_2O$ (**II**), and $(CH_3)_3Sn(TLCO)$ (**III**)

	I	II	III
formula	$C_{38}H_{78}N_6O_8Sn_4$	$C_{62}H_{66}N_6O_{10}Sn_4$	$C_9H_{13}N_3OSSn$
M	1221.82	1529.97	329.97
T (K)	220	220	220
Cryst syst	monoclinic	triclinic	monoclinic
space group	$C2/c$	$P1$	$P2_1$
Z	4	1	2
a (Å)	24.7571(15)	10.0983(4)	8.295(2)
b (Å)	22.4751(14)	12.3380(5)	7.3320(10)
c (Å)	9.7846(6)	13.4727(6)	11.095(2)
β (deg)	100.22(1)	$\alpha = 91.15(1)$, $\beta = 103.77(1)$, $\gamma = 100.70(1)$	100.12(3)
V (Å^3)	5358.0(6)	1598.31(12)	664.3(2)
μ(Mo Kα) (cm^{-1})	1.889	1.604	2.061
D_{calcd} (g cm^{-3})	1.515	1.590	1.650
θ_{max} (deg)	25.93	27.48	30.02
reflns	14 117	10 137	3260
indep. reflns	5183	6995	3103
indep. reflns > 2$\sigma(I)$	3508	5895	2852
R_{int}	0.042	0.0134	0.010
params refined	126	370	137
R1, wR2 [$I > 2\sigma(I)$]	0.053, 0.161	0.032, 0.078	0.0263, 0.0724
R1, wR2 (all data)	0.071, 0.173	0.040, 0.082	0.0302, 0.0745
max, min peak (eÅ^{-3})	1.22, −0.96	1.27, −1.06	1.04, −0.61

Table 9. Selected Bond Lengths and Valence Angles in Structures of Synthesized Tin(IV) Cyanoximates

$Me_3Sn(TLCO)$		$Bu_8Sn4(OH)_2O_2(ACO)_2$		$Ph_8Sn_4(OH)_2O_2(ACO)_2$	
bonds (Å)	angles (deg)	bonds (Å)	angles (deg)	bonds (Å)	angles (deg)
cyanoxime[a]		*cyanoxime*[b]		*cyanoxime*[c]	
C1−N1 = 1.294(4)	N1−C1−C3 = 121.9(3)	C1−N1 = 1.2285(7)	N1−C1−C3 = 122.1(5)	C1−N1 = 1.298(4)	N1−C1−C3 = 122.9(3)
C1−C3 = 1.446(5)	N1−C1−*C2* = 120.6(3)	C1−C3 = 1.433(8)	N1−C1−*C2* = 119.8(5)	C1−C3 = 1.445(4)	N1−C1−*C2* = 120.9(3)
C1−C2 = 1.454(4)	C3−C1−*C2* = 117.5(3)	C1−C2 = 1.469(8)	C3−C1−*C2* = 118.1(5)	C1−C2 = 1.489(5)	C3−C1−*C2* = 116.0(3)
C3−N3 = 1.130(6)	N3−C3−C1 = 175(2)	C2−O2 = 1.255(6)	O2−C2−C1 = 119.8(5)	C2−O2 = 1.229(4)	O2−C2−C1 = 118.8(3)
N1−O1 = 1.368(5)	C1−N1−O1 = 113.0(3)	C2−N2 = 1.323(7)	O2−C2−N2 = 123.3(5)	C2−N2 = 1.320(5)	O2−C2−N2 = 124.1(3)
	N1−O1−Sn = 107.8(2)	C3−N3 = 1.127(8)	N2−C2−C1 = 116.8(5)	C3−N3 = 1.143(5)	N2−C2−C1 = 117.0(3)
		N1−O1 = 1.301(5)	N3−C3−C1 = 178.2(7)	N1−O1 = 1.334(3)	N3−C3−C1 = 176.1(4)
			C1−N1−O1 = 115.6(4)		C1−N1−O1 = 114.2(3)
			N1−O1−Sn1 = 111.0(3)		N1−O1−Sn1 = 113.36
metal center:		*metal centers, Sn1:*		*metal center, Sn1:*	
Sn−O1 = 2.115(3)	C9−Sn−C7 = 118.1(7)	Sn1−C10 = 1.75(2)	O4−Sn1−C10 = 118.5(7)	Sn1−O4 = 2.006(2)	O4−Sn1−C10 = 117.29(11)
Sn−C7 = 2.115(11)	C9−Sn−O1 = 94.07(14)	Sn1−C20 = 1.83(2)	O4−Sn1−C20 = 121.9(7)	Sn1−C10 = 2.126(3)	O4−Sn1−O3 = 74.15(8)
Sn−C8 = 2.129(11)	C9−Sn−C8 = 117.3(6)	Sn1−O4 = 2.013(4)	O4−Sn1−O3 = 73.5(15)	Sn1−O3 = 2.127(2)	O4−Sn1−C4 = 113.28(11)
Sn−C9 = 2.113(4)	C7−Sn−O1 = 98.5(4)	Sn1−O3 = 2.136(4)	O4−Sn1−O1 = 79.10(14)	Sn1−C4 = 2.134(3)	O4−Sn1−O1 = 81.65(8)
	C7−Sn−C8 = 119.3(3)	Sn1−O1 = 2.190(4)	C10−Sn1−C20 = 119.6(10)	Sn1−O1 = 2.168(2)	C10−Sn1−O3 = 94.45(11)
	O1−Sn−C8 = 100.5(4)	C10−Sn1−O4 = 118.5(7)			C10−Sn1−C4 = 129.25(13)
			C20−Sn1−O3 = 97.4(8)		C10−Sn1−O1 = 94.48(11)
			C10−Sn1−O1 = 96.4(8)		O3−Sn1−C4 = 95.14(11)
			C20−Sn1−O1 = 93.6(8)		O3−Sn1−O1 = 155.69(8)
			O3−Sn1−O1 = 152.27(15)	C4−Sn1−O1 = 96.59(11)	
		metal center, Sn2:		*metal center, Sn2:*	
		Sn2−C40 = 1.87(2)	O4−Sn2−C30 = 97.3(5)	Sn2−C22 = 2.116(3)	O4−Sn2−C22 = 108.34(11)
		Sn2−C30 = 1.932(18)	O4−Sn2−C30 = 119.3(6)	Sn2−O4 = 2.0641(19)	O4−Sn2−C16 = 109.48(10)
		Sn2−O4 = 2.042(4)	O4−Sn2−O40 = 105.0(6)	Sn2−C16 = 2.124(3)	O4−Sn2−O3 = 72.67(8)
		Sn2−O4 = 2.117(4)	O4−Sn2−O40 = 121.9(6)	Sn2−O3 = 2.143(2)	O4−Sn2−O4 = 72.60(9)
		Sn2−O3 = 2.165(4)	C30−Sn2−C40 = 118.5(8)	Sn2−O4 = 2.159(2)	C22−Sn2−C16 = 141.68(12)
			C40−Sn2−O3 = 93.7(6)		C22−Sn2−O3 = 100.55(11)
			C30−Sn2−O3 = 98.9(6)		C22−Sn2−O4 = 92.44(10)
			O3−Sn2−O4 = 72.28(15)		C16−Sn2−O3 = 96.27(11)
			O3−Sn2−O4 = 145.34(15)		C16−Sn2−O4 = 92.99(10)
			O4−Sn2−O4 = 73.06(16)		O3−Sn2−O4 = 145.19(8)

[a] Geometries of the thiazolyl and methyl groups are normal and are not shown. [b] *n*-Butyl groups in this complex are thermally disordered; only carbon atoms adjacent to tin(IV) atoms have acceptable parameters. [c] Geometry of the phenyl group is normal and not shown.

Molecular Structure of $Bu_8Sn_4(OH)_2O_2\{ACO\}_2$. Single crystals of octabutyl-tetra-tin(IV)-μ^2-dihydroxo-μ^2-dioxo-bis-(carbamoylcyanoxime) that were of suitable quality for X-ray analysis were grown in open system **2** (S7) in a refrigerator. Crystal and refinement data for the complex are shown in Table 8, and selected bond distances and angles are presented in Table 9. The molecular structure of the thermally ordered complex core is shown in Figure 4, and the figure for the whole molecule, including the numbering scheme, is present in S14. A significant thermal motion (disorder) of the *n*-butyl groups was observed in this structure. However, the tetranuclear metal core and cyanoxime moiety in the structure were firmly resolved. The ACO ligand is in the oxime form in the complex and adopts a planar trans-anti configuration. The four tin(IV) atoms form an essentially planar $Sn_4O_2(OH)_2$ core in the complex and have significantly distorted

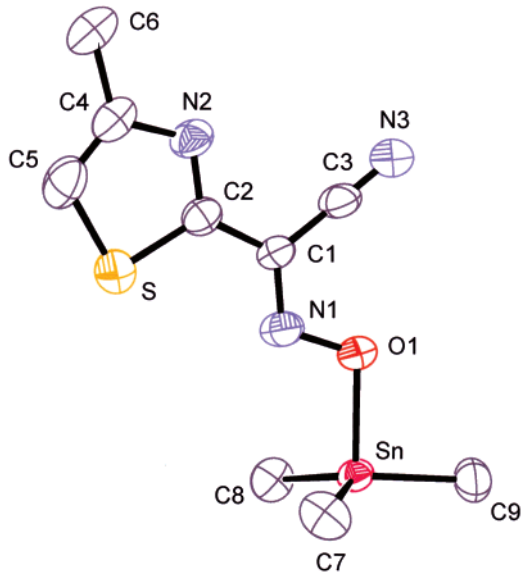


Figure 2. Molecular structure of $SnMe_3\{TLCO\}$. An ORTEP representation[67] at 50% thermal ellipsoids probability level; H-atoms are omitted for clarity.

trigonal bipyramidal geometry (Table 6, S14), similar to that observed for this type of structure.[48] The distances Sn(1)−Sn(2−7) = 3.354 Å and Sn(2)−Sn(2−7) = 3.342 Å in the three-rhombs core are longer than the Sn−Sn bond (2.81 Å).[58]

Molecular Structure of $Ph_8Sn_4(OH)_2O_2\{ACO\}_2$. Single crystals of octaphenyl-tetra-tin(IV)-μ^2-dihydroxo-μ^2-dioxo-bis(carbamoylcyanoxime) and $Ph_8Sn_4(OH)_2O_2(ACO)_2$, suitable for X-ray analysis, were grown from a CH_3CN solution in a manner similar to the above *n*-butyltin(IV) derivative. The crystal and refinement data are shown in Table 8, and selected bond distances and angles for the structure of the tetranuclear tin complex are presented in Table 9. The molecular structure of this compound is shown in Figure 5, whereas the geometry of the $C_8Sn_4(OH)_4O_2$ core, which consists of three planar adjacent Sn_2O_2 rhombs, is shown in S15. No significant thermal motion of atoms in the phenyl groups was observed in the structure of this complex. The structure of the $Ph_8Sn_4(OH)_2O_2(ACO)_2$ complex was similar to the *n*-butyl organotin(IV) derivative described above: the oxime anion adopts a planar anti-trans configuration and acts as a monodentate ligand (Figure 5). Its geometry is normal for this type of coordination.[55,56] The arrangement around the Sn(1) and Sn(2) atoms represents a distorted trigonal bipyramidal structure (Figure 5, S15). The distance between Sn(1)−Sn(2) is 3.337 Å, which is larger than the covalent Sn−Sn bond.[57a] The O-coordination of oxime anions in all of the the organotin(IV) cyanoximates reported in this article reflects the pronounced oxophylicity of the tin: the enthalpy of the Sn−O bond is 548 kJ/M and is the largest[58] among all of the chemical bonds formed by this metal (S16).

Because the crystals of both described tetranuclear compounds, formed in solutions, were exposed to traces of moisture, we believe that complexes $R_8Sn_4(OH)_2O_2(ACO)_2$ represent thermodynamically stable final products of the hydrolysis of the originally obtained $R_2Sn(ACO)_2$ species (R = Bu, Ph).

In Vitro Cell Culture Experiments.

General Considerations. One of the problems in the studies of different organotin(IV) complexes with respect to biomedical applications is the speciation of compounds in solution. Thus, organometallic complexes hydrolyze to form several species in a solution, depending on its pH.[46] Products of this process at physiological pH ~7.4 were found to be $R_2Sn(OH)_2$, $R_3Sn(OH)$, and $RSn(OH)_2(H_2O)_n$ complexes. However, a pronounced and well-established difference in the biological activity between the studied complexes was attributed, undoubtedly, to the presence of the organic ligand bonded to the tin(IV) in the active compound. This observation implied a significant difference in stability and the rate of hydrolysis for a variety of the obtained and studied organotin(IV) compounds. Despite the cited difficulties in the isolation and assignment of cytotoxicity to a particular organotin(IV) species, they remain an attractive class of compounds as potential anticancer agents. It should be noted that a similar example arose when Paul Erchlich's arsenic-containing antisyphilitic medicine, salvarsan, turned out to be the mixture of two cyclic As_3 and As_5 compounds, instead of the long-believed noncyclic structure.[59] Despite a discrepancy between the actual and erroneously assigned structures, salvarsan in the pre-penicillin era saved hundreds of thousands of lives. Some of the organotin(IV) compounds are patented[60,61] as drug substances and are currently involved in various phases of clinical trials.[10a,62] Therefore, we believe that further research for anticancer active dibutyltin(IV) compounds is warranted.

Cytotoxicity Results. The cells were counted by tallying the total number of attached cells in each photograph of the wells and then tallying the total number of blue stained nonviable cells in each photograph. Averages of these values were calculated, for comparison purposes, and used in all further calculations. The percentage of relative cell loss (% RCL) was calculated by subtracting the average of the total attached cells for each treatment from the average number of control cells and then dividing by the average number of control cells. The percentage of nonviable cells (% NVC) was determined by dividing the average number of nonviable cells for each compound by the average of the total number of cells for each tested compound. Activity levels were established to compare the results of the cell viability analysis. The % RCL and % NVC were added together to get an overall value of total cell loss (TCL). If the TCL was less than 10%, an activity assignment of (−) was assigned. If the TCL was between 10 and 25%, a (+) activity assignment was made. If the TCL was between 25 and 50%, then an activity of (++) was assigned. If the TCL was between 50 and 75% a (+++) activity assignment was made. If the TCL was between 75 and 90%, the score (++++) was given. If the TCL was greater than 90%, the score of (+++++) was assigned. Results of the cell culture experiments are presented in Table 10 and Table 11. Representative images of the photographs used in determining these results are presented in Figures 6 and 7.

On the basis of the preliminary screening results, presented in this article, it is evident that the dibutyltin(IV) carbamoyl

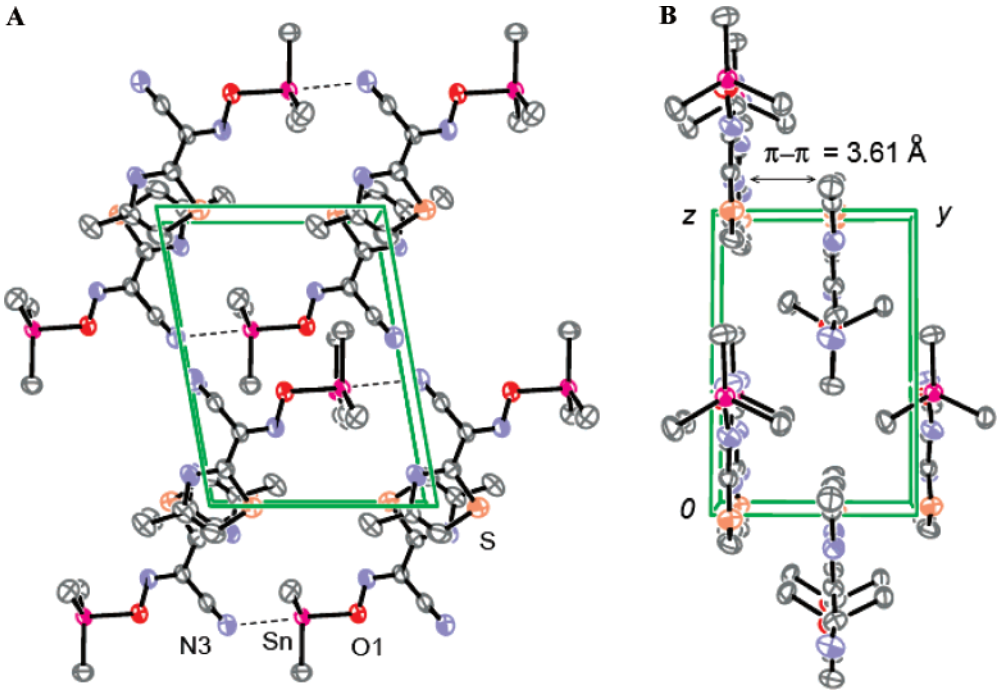


Figure 3. Packing of $Me_3Sn\{TLCO\}$ into crystal. **A**, view of the unit cell along the *y* direction showing additional coordination of neighboring molecules to tin(IV) centers and **B**, perpendicular view that displays the planarity of the cyanoxime ligand and the $\pi-\pi$ stacking interactions between molecules.

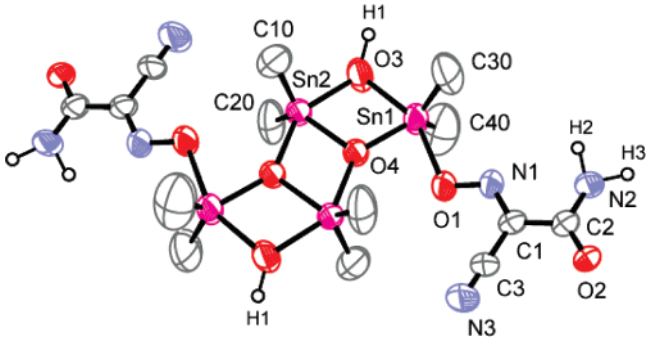


Figure 4. Thermally ordered part of the structure of $Bu_8Sn_4(OH)_2O_2(ACO)_2$, shown geometry of the planar tetranuclear core comprised of three adjacent rhombs and the inversion center of the molecule.

cyanoximate is active against both the HeLa cervical cancer epithelial cells and the WiDr colon carcinoma cells, receiving the highest (+++++) activity rating against both cell lines. For the HeLa cell line, the activity of the $Bu_2Sn(ACO)_2$ complex was actually greater than that for cisplatin, which only received a (++++) score under the studied conditions. All of the other complexes are relatively inactive against the HeLa cell line in these studies. Against the WiDr cell line, the $Bu_2Sn(4PCO)_2$ compound demonstrated significant activity in these tests, receiving a (++++) score. Because of the absence of direct structural information, we speculate that the latter complex also has a monodentate O-coordinated 4-pyridylcyanoxime ligand. The cytotoxicity of $Bu_2Sn(4PCO)_2$ was slightly lower than that exhibited by cisplatin and $Bu_2Sn(ACO)_2$, both of which had activity levels in the (+++++) category. No other obtained and studied compound demonstrated comparable activity against the WiDr cell line. The activity of the two most cytotoxic complexes—$Bu_2Sn(4PCO)_2$ and $Bu_2Sn(ACO)_2$—can be attributed to the ability of the ACO^- and $4PCO^-$ ligands to form unobstructed H-bonds that may facilitate an intracellular uptake of complexes.

Future Plans. Further testing of the most active compounds will be conducted using a larger number of different human cancer cell lines, including the cisplatin resistant cell line. IC_{50} values for $Bu_2Sn(4PCO)_2$ and $Bu_2Sn(ACO)_2$ will be determined in a statistical series of experiments and reported in a separate publication. The ES mass spectrometric investigations of solutions of compounds in cell culture media will reveal their speciation and, possibly, speed of hydrolysis at physiological pH. Detailed ^{13}C, ^{119}Sn NMR spectroscopic studies of $Bu_2Sn(4PCO)_2$ and $Bu_2Sn(ACO)_2$ will be conducted to understand the compounds' structure in solutions, and the results of such investigations will be published in the near future.

Experimental Section

Reagents and Solvents. The inorganic chemicals and organotin(IV) starting materials—Me_3SnCl, Et_3SnCl (Strem), Me_2SnBr_2, *n*-Bu_2SnCl_2, and Ph_2SnBr_2 (Aldrich)—were of good quality according to their ^1H and ^{13}C NMR signatures, and were used without additional purification. *cis*-diamminedichloroplatinum(II) for cytotoxicity studies was obtained from Sigma. All, but one acetonitrile (precursor for HTLCO[26]), were purchased from Aldrich and used as received because they were of acceptable purity. Organic solvents employed in the reactions *with* organotins (ether and CH_3CN) were thoroughly purified and dehydrated according to standard procedures.[57b] All of the operations with organotin(IV) compounds were carried out anaerobically using the appropriate Schlenkware. Other organic solvents were of HPLC grade (Fisher) and were used without further purification. TLC on silica gel (with 260 nm indicator) glass plates was employed to identify the obtained cyanoximes.

Instrumentation and Physical Methods. Melting points and decomposition temperatures were determined using closed (under

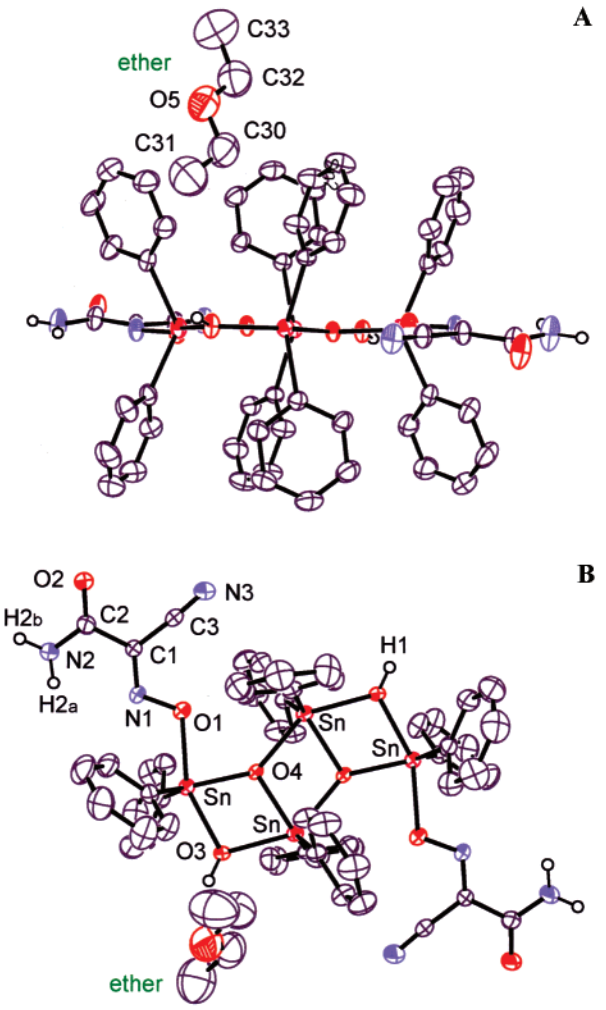


Figure 5. Molecular structure of $Ph_8Sn_4(OH)_2O_2(ACO)_2$, ether solvate. **A**, side view and **B**, top view. Hydrogen atoms at the phenyl groups are omitted for clarity.

Table 10. Results of In Vitro Cell Studies of Synthesized Monomeric Dibutyltin(IV) Cyanoximates on WiDr Colon Carcinoma Cell Line

compound	% RCL[a]	% NVC[b]	activity
control	0	0.98	--
cisplatin	92.2	94.8	+++++
$Bu_2Sn(ACO)_2$	92.1	95.6	+++++
$Bu_2Sn(BCO)_2$	−62.6	18.2	--
$Bu_2Sn(BTCO)_2$	27.4	34.0	+++
$Bu_2Sn(ECO)_2$	−52.1	30.6	--
$Bu_2Sn(PiCO)_2$	−7.89	6.63	--
$Bu_2Sn(2PCO)_2$	−1.14	34.5	++
$Bu_2Sn(3PCO)_2$	5.17	39.7	++
$Bu_2Sn(4PCO)_2$	20.9	73.2	++++

[a] Relative cell loss. [b] Nonviable cells.

a vacuum) capillary tubes in a Thomas Hoover Uni-Melt apparatus, without correction (Tables 2 and 3). Elemental analyses on the C, H, N, and S contents were performed at Atlantic Microlab (Tables 2 and 3). Several of the organotin cyanoximates were analyzed for metal content using gravimetric analysis with SnO_2 as the weighing form[63] (Table 3). UV−visible spectra for the anionic cyanoximes (as NBu_4^+salt) were recorded in solutions on a Varian Bio-100 spectrophotometer, using 1 and 10 mm quartz cuvettes in the range of 200−800 nm (Table 1). A Nicolet Magna 550 IR spectrometer was used for recording IR spectra in the range of 600−4000 cm^{-1} (Table 4). A 400 MHz Varian Inova NMR spectrometer was used to record the ^1H and $^{13}C\{^1H\}$ spectra in

Table 11. Results of In Vitro Testing of the Obtained Monomeric Butyltin(IV) Cyanoximates on Cervical Cancer HeLa Cell Line

compound	% RCL[a]	% NVC[b]	activity
control	0	4.18	--
cisplatin	70.9	15.3	++++
$Bu_2Sn(ACO)_2$	95.4	100	+++++
$Bu_2Sn(BCO)_2$	20.9	3.52	+
$Bu_2Sn(BTCO)_2$	23.5	5.69	++
$Bu_2Sn(ECO)_2$	18.2	5.40	+
$Bu_2Sn(PiCO)_2$	−0.86	3.87	--
$Bu_2Sn(2PCO)_2$	15.7	4.30	+
$Bu_2Sn(3PCO)_2$	28.5	3.84	++
$Bu_2Sn(4PCO)_2$	21.7	3.81	++

[a] Relative cell loss. [b] Nonviable cells.

acetone-d_6, DMSO-d_6, and $CDCl_3$ (the TMS as internal reference, 0 ppm) at ambient temperature (S1−S3). The $^{119}Sn\{^1H\}$ NMR spectra were recorded using Varian Unity Plus-300 (at 111.85 MHz) and Bruker ARX-500 (at 186.50 MHz) spectrometers. $Sn(CH_3)_4$ in acetone-d_6 was an external standard (S6). Mass spectra of the organic ligands were obtained using Autospec Q and ZAB spectrometers (positive FAB, argon) and *m*-nitrobenzylic alcohol (NBA) as the matrix. The ^{119}Sn Mössbauer spectra were recorded at 80 K using a spectrometer, equipped with laser interferometers and multichannel analyzers, that operated in a constant acceleration mode. The radioactive source was $Ca^{119m}SnO_3$, and the isomer shifts were measured relative to SnO_2 (Table 8).

X-ray Analysis. Crystallographic measurements for $(Bu)_8Sn_4(OH)_2O_2(ACO)_2$ and $(Ph)_8Sn_4(OH)_2O_2(ACO)_2\cdot(C_2H_5)_2O$ (**I** and **II**, Table 8) were made at 220 K using a Siemens SMART area-detector diffractometer (Mo Kα radiation, $\lambda = 0.71073$ Å; empirical absorption corrections using SADABS).[64] The intensity data for $(CH_3)_3Sn(TLCO)$ (**III**, Table 8) were collected using a four-circle Stoe STADI4 diffractometer (absorption correction was based on psi-scans). The structures were solved by direct methods using the program SHELXS-97.[65] The refinement and all further calculations were carried out using SHELXL-97.[65] The non-H atoms were refined anisotropically, using a weighted full-matrix least-squares of F^2 (Table 8). The hydrogen atoms were included at idealized geometries (CH 0.96 Å) and then refined as riding, with $U_{iso}(H) = 1.2U_{eq}(C)$ or $1.5U_{eq}$(parent atom) for the methyl, OH, and NH_2 groups. The absolute structure of **III** was not determined, and the racemic twin refinement led to the Flack parameter $x = 0.50(7)$. All of the four unique butyl groups in the structure of **I** were badly disordered, and it was not possible to resolve the disordering scheme. Therefore, the remaining electron density was modeled using Squeeze,[66] whereas only the carbon atoms attached to the metal centers were retained and left isotropic. Further details of the X-ray experiment can be found in respective *.cif files (Supporting Information). Figures for all of the discussed structures were drawn using the ORTEP-3 software.[67]

Synthesis of the Cyanoxime Ligands. The cyanoximes, HACO,[68] HBCO,[54] HECO,[33] and HTLCO,[26] were obtained according to previously published procedures. The preparation of HBTCO,[69] H(2PCO),[26] and H(4PCO)[69] was achieved in accordance with literature procedures. The syntheses of HPiCO and H(3PCO) were performed by a different route from that previously used for the synthesis of the above ligands as a result of the low reactivity of the respective acetonitriles[70] (Scheme 5).

The procedure utilized for the preparation of H(3PCO) using freshly obtained neat isopropylnitrite[71] prior to the reaction is described below. A similar procedure was applied for the synthesis of HPiCO.

2-(Oximido)-3-pyridylacetonitrile, H(3PCO). Thinly sliced metallic sodium (0.64 g, 0.028 mol) was dissolved under a flow of

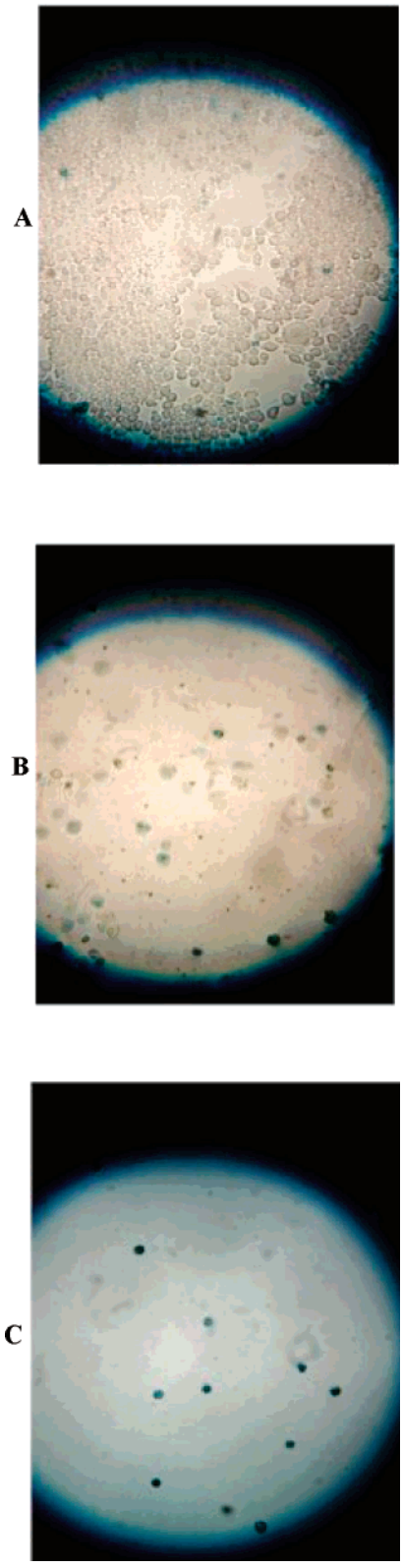


Figure 6. Pictures of HeLa cells. **A**, control, with no compounds added; **B**, with cisplatin added; and **C**, with $Bu_2Sn(ACO)_2$ added.

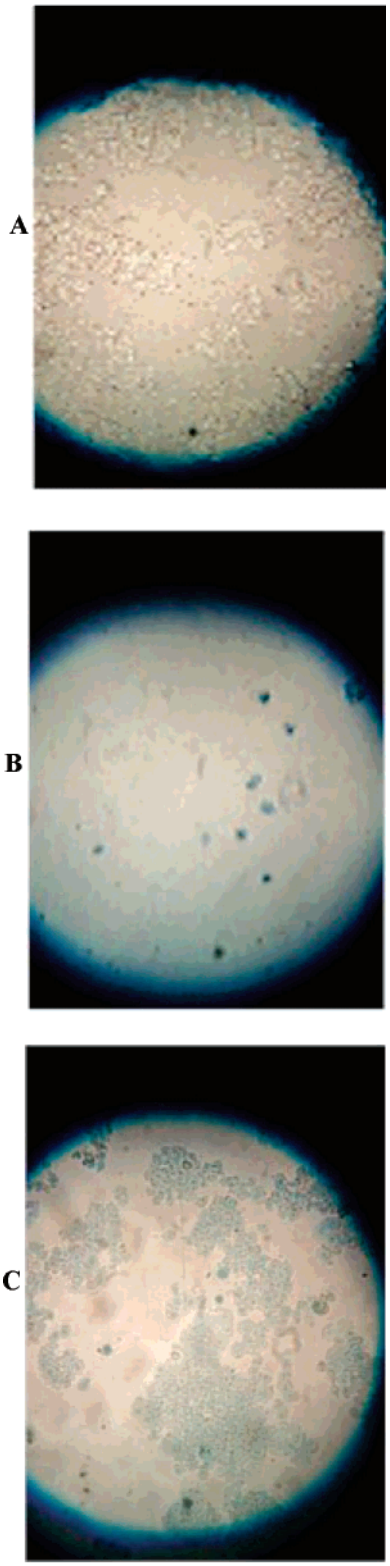


Figure 7. Photographs of WiDR cells. **A**, control; **B**, with cisplatin added; and **C**, with $Bu_2Sn(4PCO)_2$ added.

nitrogen in 50 mL of 2-propanol at 30 °C in a 200 mL Erlenmeyer flask. A solution of 3-pyridyl-acetonitrile (3.31 g, 0.028 mol) in 20 mL of 2-propanol was added dropwise to the above sodium propoxide solution under nitrogen. Neat isopropylnitrite (8.87 g; 0.084 mol) was dissolved in 20 mL of 2-propanol and added dropwise at room temperature to the sodium propoxide/3-pyridylacetonitrile solution within 1 h. The color of the reaction mixture turned yellow, and the resulting solution was kept overnight at 4 °C. The solvent was removed under a vacuum, leading to a thick yellow residue that was dissolved in 50 mL water, and the resulting

(71) Noyes, W. A. *Organic Syntheses*; Wiley & Sons: New York, 1943; Vol. 2, p 108.

solution was acidified to pH ~5 with 1 M HCl and saturated with NaCl. The cyanoxime product was extracted using three portions (30, 50, and 75 mL) of diethyl ether, and combined extracts were dried overnight over Na_2SO_4. The solvent was removed, leaving the H(3PCO) as a white solid that gives one TLC spot. Yield: 2.64 g (64%); $R_f = 0.75$ in EtOAc/hexane = 2:1 mixture; mp 135 °C (dec). ^1H and ^{13}C NMR spectra indicate the mixture of syn (47%) and anti (53%) isomers (S6). NMR data for dominant anti isomer only (dmso-d_6) ^1H: δ ~13.3 (s, 1H), 8.97 (m, 1H), 8.72 (m, 1H), 8.14 (m, 1H), 7.55 (m, 1H); $^{13}C\{^1H\}$: δ 151.8, 146.9, 133.2 and 124.2 - CH carbon atoms, 130.0 (ipso C), 126.4 (oxime), and 109.3 (CN). Mass spectrometry, FAB^+: for $C_7H_5N_3O$, calcd 147.0434; found 148.0511 (M + 1). UV−vis (*n*-C_3H_7OH; λ_{max}): 254 nm (ϵ = 11 300).

2-(Oximido)-pivaloylacetonitrile, H(PiCO). The synthesis of H(PiCO) was analogous to the preparation of H(3PCO) as described above. The amounts of reagents used were Na (0.66 g, 0.028 mol) in 150 mL of *i*-PrOH; pivaloylacetonitrile, $NC-CH_2-C(O)C(CH_3)_3$ (3.51 g, 0.028 mol); isopropylnitrite, $ONO-C_3H_7$ (8.87 g, 0.084 mol). The HPiCO product was isolated as a white solid in 73% yield (3.15 g). Mp 174−176 °C; $R_f = 0.72$ in 2:1 ethyl acetate/hexane mobile phase; mp 174−176 °C. Anal. Calcd for $C_7H_{10}N_2O_2$: C, 54.54; H, 6.54; N, 18.17. Found: C, 54.72; H, 6.77; N, 18.20. ^1H NMR (dmso-d_6): δ 1.80 (s, 9H), 15.28 (s, 1H); $^{13}C\{1H\}$: 197.7 (C═O), 131.6 (oxime), 115.9 (CN), 28.2, 26.6 (CH_3). UV−vis (*n*-C_3H_7OH, λ_{max}): 241 (ϵ = 9880).

Metallocyanoximates.

Alkali metal salts. Ionic alkali metal salts of cyanoximes were used as precursors for the silver(I) complexes that were utilized in the synthesis of the organotin(IV) cyanoximates. Cs(ACO),[72] Cs(ECO),[33] Na(2PCO),[73] and Cs(BTCO)[74] were obtained according to published procedures using $NaOC_2H_5$, CsOH, and Cs_2CO_3. A typical synthesis of sodium salts provided for only one compound.

2-(Oximidocyanmethyl)-4-methylthiazole Sodium, Na(TLCO). Thinly sliced metallic Na (0.1 g, 4.3 mmol) was dissolved in 8 mL of dry EtOH under N_2 protection. Sodium ethoxide solution was added dropwise within 5 min, under stirring, to a solution of HTLCO (0.727 g, 4.3 mmol) in 60 mL of dry ether. The resulting bright-yellow amorphous precipitate was filtered, washed with ether, and dried under a vacuum in the desiccator over concentrated H_2SO_4 within 48 h. Na(TLCO) was obtained in 85% yield (0.722 g). Anal. Calcd for $C_6H_4N_3NaOS$: C, 38.09; H, 2.13; N, 22.21; S, 16.95%. Found: C, 38.18; H, 2.24; N, 22.07; S, 16.64.

Monovalent Silver Salts. Silver(I) cyanoximates are key intermediates in the synthesis of the organotin(IV) complexes. Compounds Ag(ACO),[15c,34b] Ag(ECO),[33] Ag(PiCO),[75] and Ag(BCO)[54] were obtained according to the published procedures using $AgNO_3$ and ML (M = Na^+, K^+ or Cs^+; *L* = cyanoxime anion). A typical synthesis of silver(I) salt was shown for only one compound.

2-(Oximido)-2-benzthiazoleacetonitrile Silver(I), Ag(BTCO). Orange Cs(BTCO) (0.250 g, 0.74 mmol) was dissolved in 15 mL of water and added dropwise, under intense stirring, to a solution of $AgNO_3$ (0.126 g, 0.074 mol) in 10 mL of water. A thick yellow precipitate was immediately formed but left stirring for another 25 min. Ag(BTCO) was filtered, washed with 10 mL of water and then with 10 mL of ethanol and 20 mL of ether, and dried over 48 h in a vacuum desiccator over concentrated H_2SO_4. The yield of tan-yellow Ag(BTCO) was 92% (0.212 g). Anal. Calcd for $C_9H_4AgN_3OS$: C, 34.86; H, 1.30; N, 13.55; S, 10.34. Found: C, 34.96; H, 1.38; N, 13.69; S, 10.11.

Some properties and analytical data for alkali metal, silver(I) and thallium(I) cyanoximates are summarized in Tables 2 and 3.

Organotin(IV) Cyanoximates. Typical preparation of the organotin(IV) cyanoximates is provided only for one complex. Some properties and analytical data for the 19 obtained cyanoxime-based tin(IV) organometallic compounds are shown in Table 3.

2-Cyano-2-isonitrosoacetamido-triethyltin(IV), Et_3Sn(ACO). Triethyltin chloride (0.360 g; 1.50 mM) was dissolved in 10 mL of degassed CH_3CN. The solution formed was slowly added using a stainless steel cannula to a suspension of 0.330 g (1.50 mM) of a solid powdery Ag(ACO) in 15 mL of acetonitrile under intensive stirring. After the addition was completed in a dim light, a Schlenk flask was placed into a Branson C40 sonicator for 2 min. The reaction mixture produced a very fine white precipitate of AgCl and pale-yellow solution. Silver(I) chloride was filtered, and the obtained clear solution was concentrated under a vacuum. Et_3Sn(ACO) resulting in a white solid in the amount of 0.450 g (~95% yield), mp = 89 °C was obtained. Anal. Calcd for $C_9H_{17}N_3O_2Sn$: C, 34.02; H, 5.39; N, 13.22; Sn, 37.33. Found: C, 34.59; H, 5.62; N, 13.17; Sn, 37.08.

Synthesized organotin(IV) complexes are soluble in dry acetonitrile, DMF, Py, HMPA, THF, and DMSO and in aqueous and alcohol solutions (with partial hydrolysis), are sparingly soluble in acetone, chlorohydrocarbons, and are insoluble in CCl_4 and hydrocarbons.

In Vitro Cytotoxicity Studies. The cyanoxime ligands and their dibutyltin(IV) derivatives were in vitro tested on WiDr colon cancer and HeLa epithelial cervical cancer cells (obtained from the ATCC) using developed technique[76] and cytotoxicity protocols.[77] The Trypan Blue exclusion method was used for assessing cell viability. *cis*-(Dichlorodiammine)platinum(II), cisplatin from Sigma, was used as a cytotoxic positive control.[12a] Images of the cell cultures were taken with a digital camera attached to an Olympus BX41 microscope, at 100× magnification, using phase contrast microscopy. Two fields of each well were photographed and analyzed for cell viability and compared to an untreated control and positive control treatments. Details of the used cytotoxicity protocol are presented in S17.

SAFETY NOTE! *Organotin(IV) halides are relatively volatile and toxic and inhalation should be avoided. Special care should be taken during procedures using thallium compounds because of their toxicity,*[57,78] *and the use of rubber gloves during handling is recommended.*

Concluding Remarks

1) A series of nine cyanoximes were synthesized using a modified high-yield Meyer reaction. The compounds obtained were characterized using ^1H, ^{13}C NMR, UV−visible, IR spectroscopy, and mass spectrometry.

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2) A group of 19 new organotin(IV) cyanoximates was obtained using fast room-temperature heterogeneous metathesis reactions between solid AgL (or TlL) and solutions of organotin(IV) halides in acetonitrile. Synthesized complexes were characterized by elemental analysis, ^{13}C and ^{119}Sn (in some cases) NMR spectroscopy in solutions, solid-state IR and ^{119}Sn Mössbauer spectroscopy, and X-ray analysis. The structures of two compounds revealed the monodentate binding of the cyanoxime anion and the formation of a tetranuclear tinoxane species. The third complex, characterized by X-ray analysis, showed the structure with the cyanoxime anion acting as a bridge using the nitrogen atom of the CN group. In all of the crystallographically characterized complexes, the tin(IV) centers adopt a distorted trigonal bipyramidal geometry.

3) A monodentate O-coordination of planar oxime ligands in synthesized organotin(IV) cyanoximates was documented for the first time.

4) Eight new dibutyltin(IV) cyanoximates were selected for testing in vitro against HeLa cervical cancer epithelial cells and WiDr colon cancer cells for antiproliferating activity, using cisplatin as a positive control. Data showed that $Bu_2Sn(ACO)_2$ exhibited pronounced in vitro cytotoxicity at the same level as, or higher than cisplatin toward both cell lines. Antiproliferative activity comparable to that for cisplatin was observed for $Bu_2Sn(4PCO)_2$ only on the WiDr cell line. Formation of unobstructed intermolecular H-bonds by the coordinated ACO^- and $4PCO^-$ ligands may facilitate enhanced intracellular uptake of these complexes, leading to higher activity. The latter two complexes will be further examined using different cell lines and then tested in vivo on animal models.

Acknowledgment. N.G. thanks Dr. Ernest Pol'shin and Prof. Laszlo Korecz (Mössbauer spectra) for their help at the beginning of this work. In addition, N.G. is grateful for the financial support received from the ACS PRF (grant 39079-B3). The kind help of Dr. Luo Rensheng with the NMR measurements and data processing is greatly appreciated. The authors are indebted to Prof. Joahim Sieler (Leipzig University) for his kind support with the X-ray diffraction studies. N.G. greatly appreciates the kind help and practical advice of Dr. Valeri Mossin regarding biological testing. T.M. expresses thanks to Mrs. Elizabeth Bowen and Mrs. Marcy Abbey for their help with the cell cultures and special thanks to Ms. Crystal Wood for all her help in the counting of cells.

Supporting Information Available: Biomedical aspects of tin (S1−S3); tabulated ^1H, $^{13}C\{^1H\}$ NMR spectra of the synthesized cyanoximes (S4−S6); experimental setup for crystal growth (S7); $^{13}C\{^1H\}$ NMR spectrum of one dibutyltin(IV) cyanoximate (S8); tabulated date of ^{13}C, ^{119}Sn chemical shifts and $^nJ(^{119/117}Sn-^{13}C)$ coupling constants for organotin(IV) compounds (S9, S10); $^{13}C\{^1H\}$ and $^{119}Sn\{^1H\}$ NMR spectrum of $Bu_2Sn(ACO)_2$ (S11); coordination polyhedron in $Me_3Sn(TLCO)$ (S12); structural motif for $Et_3Sn(ACO)$ (S13); view of the $Bu_8Sn_4(OH)_2O_2(ACO)_2$ structure (S14); views of planar $Ph_8Sn_4(OH)_2O_2$ core (S15); values of enthalpy for the Sn−X bonds (S16); cytotoxicity protocol (S17). An X-ray crystallographic file (CIF) is available for all of the reported structures. This material is available free of charge via the Internet at http:/pubs.acs.org.

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