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POLYESTERS FROM REACTION OF 3,5-PYRIDINEDICARBOXYLIC ACID AND GROUP V-CONTAINING DIHALIDES AND THEIR PRELIMINARY AND COMPARATIVE ABILITY TO INHIBIT CANCER CELL GROWTH

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ABSTRACT

Group VA-containing polyesters are formed from the interfacial polymerization of the Group VA triphenylmetal dihalides with the salt of 3,5-pyridenedicarboxylic acid. Yield and molecular weight decrease as the size of the metal atom increases. Infrared spectroscopy, IR, shows formation of the M-O linkage with the geometry about the metal atom being a combination bridged and non-bridged. MALDI MS shows the presence of metal-containing ion fragment clusters of 5 to 7 repeat polymer units. Isotopic abundance for the antimony products is consistent with the presence of one, two, and three metal atoms in the particular ion fragment cluster. The polymers exhibit good inhibition of all of the tested cancer cell lines including two pancreatic cancer cell lines that represent about 90% of human pancreatic cancers. In comparison to other metal-containing polymers derived from 3,5-pyridenedicarboxylic acid the Group VA polymers have EC_{50} values similar to organotin polymers and lower than for the Group IVB metallocene polymers. Conversely, the metallocene polymers exhibit higher CI_{50} values.

Keywords: *Group VA polymers, 3,5-pyridendicarboxylic acid, metal-containing polymers, interfacial polycondensation, pancreatic cancer, breast cancer*

INTRODUCTION

Our group has focused on the synthesis of a variety of metal-containing agents for different reasons including most recently combating unwanted microbes. This effort has been reviewed for tin [1,2], platinum [3], Group IVB metallocenes [4] and Group VA metals [5]. Recently we began synthesis of Group VA-containing polymers because some of these showed good inhibition of pancreatic cancer cell lines [6].The biological activity of organoarsenic, organoantimony and organobismuth compounds is well established [6-10]. The topic of Group VA polymers has been reviewed [4,8,9]. A number of different condensation polymers have been synthesized from the reaction of simple organometallic dihalides or dinitrates with typical Lewis bases as diamines, salts of dicarboxylic acids, and diols [10-16].

One driving force for our specific syntheses is to couple Lewis acids, generally the metal-containing moiety, that shows biological activity with Lewis bases, that also exhibit biological activity, hoping that the combination gives polymers with enhanced ability to inhibit unwanted microbes. 3,5-Pyridinedicarboxylic acid, PDA, also known as 5-carboxynicotinic acid, dinicotinic acid, and 3,5-pyridinedicarboxate (CAS 499-81-0) is a competitive inhibitor of bovine liver glutamate dehydrogenase [17,18]. Thus, it fits the approach of employing biologically active Lewis bases coupled with biologically active metal-containing Lewis acids. There are a number of reports describing the synthesis of polymers from 3,5-pyridinedicarboxylic acid, PDA, often employing the diester of PDA rather than PDA itself [19-24]. For example, Ogata described the synthesis of various polyamides and polyesters from the reaction of the diesters with various diamines and diacid chlorides [19]. Marvel and Vogel reported the formation of polybenzimidazoles through reaction of the phenyl ester [20].

Similarly, a number of metal-containing condensation products have been synthesized including organotin products [25-27]. Coordination polymers have also been formed from PDA with terbium salts [28,29], organotin chlorides and oxides [30] and other metal ions [31-39].

We recently reported the synthesis of organotin and metallocene polymers derived from the reaction of organotin dihalides (Figure 1, left) [40] and metallocene dihalides (Figure 1, right) with 3,5-pyridinedicarboxylic acid (Figure 1, left) [41]. Here we report the synthesis of the analogous Group VA polyesters (Figure 2).

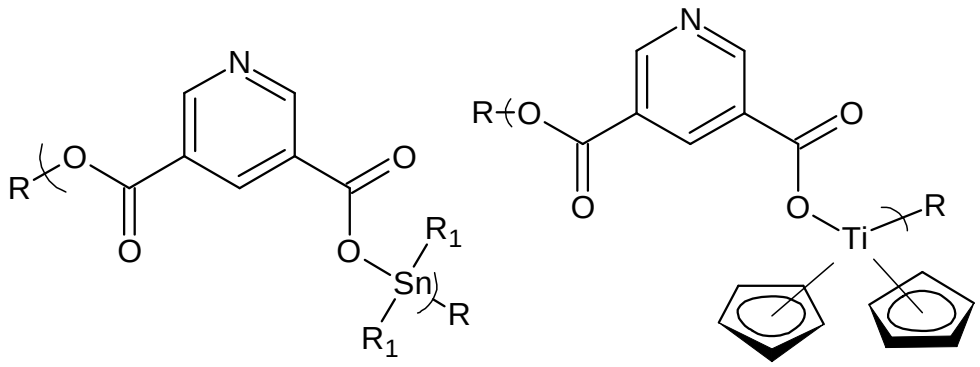


Figure 1: Repeat unit for the products of 3,5-pyridinedicarboxylic acid and organotin dihalides (left) and titanocene dichloride (right) where R represents simple chain extension

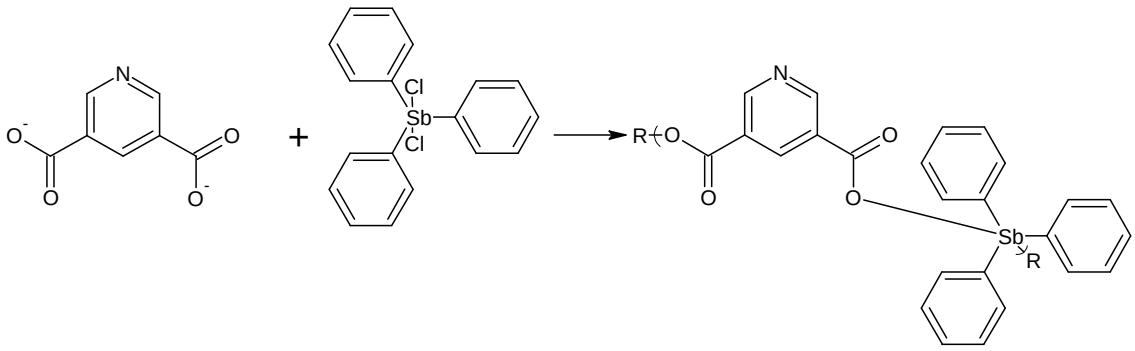


Figure 2: Reaction between the salt of 3,5-pyridinedicarboxylic acid and triphenylantimony dichloride were R represents simple chain extension

EXPERIMENTAL

Synthesis

Reactions were carried out using the interfacial polycondensation technique. An aqueous solution (10.0 ml) containing PDA, (0.00200 mol) and sodium hydroxide (0.0040 mol) was transferred to a one quart Kimax emulsifying jar fitted on top of a Waring Blender (model 1120; no load speed of about 18,000 rpm; reactions were carried out at about 25 ^{o}C). Stirring was begun and a chloroform (for the triphenylantimony and arsenic solutions and carbon tetrachloride for the triphenylbismuth solution) solution (10.0 ml) containing the Lewis acid dihalide (0.00200 mol) was rapidly added through a hole in the jar lid using a powder funnel. The resulting solution was blended for 5 seconds. The precipitate was recovered using vacuum filtration and washed several times with deionized water and chloroform (or carbon tetrachloride) removing unreacted materials and unwanted by-products. The solid was washed onto a glass Petri dish and allowed to dry at room temperature.

Triphenylarsenic dibromide (3313-89-1) was synthesized as described by Brickleband and co-workers [42]. Triphenylbismuch dichloride (594-30-9) and 3,5-pyridinedicarboxylic acid (499-81-0) were purchased from Aldrich Chemical Co., Milwaukee, WS; triphenylantimony dichloride (594-31-0) dichloride was purchased from Strem Chemical Co., Newburyport, MA.

Physical Characterization

Light scattering photometry, employing a Brice-Phoenix Universal Light Scattering Photometer Model 4000, was used to obtain polymer molecular weight from DMSO solutions. Infrared spectra were obtained employing attenuated total reflectance infrared spectroscopy utilizing a Thermo Scientific Nicolet iS5 FTIR equipped with an id5 ATR attachment. ^{1}H NMR spectra were obtained in d-6 DMSO employing Varian Inova 400 MHz amd Varian 500 MHz spectrometers.

High resolution electron impact positive ion matrix assisted laser desorption ionization time of flight, HR MALDI-TOF, mass spectrometry was carried out employing a Voyager-DE STR BioSpectrometer, Applied Biosystems, Foster City, CA. The standard settings were used with a linear mode of operation and an accelerating voltage of 25,000 volts; grid voltage 90% and an acquisition mass range of 500 to 2,500 Da. A graphite matrix was employed. Graphite from a number 2 pencil was marked on the sample holder and sample placed onto the graphite mark.

Cell Testing

The toxicity of each test compound was evaluated for a group of cell lines. Cells were seeded into a 96-well culture plate at a density of 20,000 cells per well in 100 µL of culture medium. Following a 24 h incubation period, the test compounds were added at concentrations ranging from 0.0032 to 32,000 ng/ml and allowed to incubate at 37°C with 5% CO_2 for 72 h. Following incubation, Cell Titer-Blue reagent (Promega Corporation) was added (20ul/well) and incubated for 2 h. Fluorescence was determined at 530/590 nm and converted to % cell viability versus control cells.

All cytotoxicity values are calculated against a base-line value for each line that was generated from "mock-treatment" of the normal and tumor cell lines with media supplemented with all diluents used to prepare the chemotherapeutic compounds. For example, if the compounds were dissolved in DMSO and serial dilutions prepared in MEM to treat the cells, then the mock-treated cells were "treated" with the same serial dilutions of DMSO without added chemotherapeutic compound. This was done to ensure that any cytotoxicity observed was due to the activity of the compound and not the diluents. For the studies reported here, the mock-treatment never resulted in a loss of cell viability of more than one percent, demonstrating that the activity observed was not due to cytotoxicity of any of the diluents used, but was due to activity of the tested compounds. The inhibition curve is sigmoid and the EC_{50} determined at the midpoint of the curve. Once

inhibition begins the concentration difference between the initial inhibition and final total inhibition is small with the region between initial inhibitions to final total inhibition essentially linear.

RESULTS AND DISCUSSION

Yield and Chain Length

Table 1 presents the yield and average chain length (degree of polymerization, DP-simply number of repeat units) for products formed from reaction of the salts of PDA and Group VA triphenylmetal dihalides.

Table 1: Product yield, molecular weight and chain length as a function of Lewis Base

Lewis Base	% Initial Yield	Total Yield	Mol. Wt.	DP
Ph_3AsBr_2	13	21	9.0×10^5	1900
Ph_3SbCl_2	6	20	2.2×10^4	43
Ph_3BiCl_2	4	16	1.5×10^4	25

Reaction is rapid giving product within five seconds stirring. The rapidity of the polymerization is a consequence of the low activation energy associated with the reaction of the metal-containing halide and Lewis base [1,2,4]. Yield is decent ranging from 16-21%. As in other polymerizations employing Group VA triphenylmetal halides, additional product precipitates from the reaction system after the initial product is formed [5,6,12-16]. Column 3, Table 1, contains the total yield, including that initially precipitated, column 2. The arsenic products are a high polymer, but the other two, while polymers, are moderate chain length. There is a slight trend with respect to yield, chain length and the metal atom such that both yield and chain length decrease as the size increases and electronegative decreases. The arsenic product is a brown color because of the presence of the As-Ph brown color site. The bismuth and antimony products are white because of the absence of a color site in the camphoric acid and triphenylantimony and triphenylbismuth moieties.

Because the diacid form of 3,5-pyridinedicarboxylic acid is not a sufficiently strong nucleophile, base is added converting 3,5-pyridinedicarboxylic acid to its salt which is a reasonably strong nucleophile allowing formation of the desired ester linkage.

Infrared Vibration Spectroscopy

Infrared spectral analysis was conducted on the products and reactants and assignments are based on prior work by us and others [5,6,12-16,40,41,43-46]. Results for the products appear in Tables 2 and 3. The presence of C-H stretching bands appearing in the aromatic region about 3000 cm^{-1} (all vibration bands are given in wave numbers, cm^{-1}) characteristic of both camphoric acid and the triphenylmetal moieties (above 3000) are present consistent with the product containing moieties from both reactants. New bands appear about 1260 (symmetrical stretch) and 740 (asymmetrical stretch) assigned to the formation of the M-O linkage. Other important bands and assignments appear in Tables 2 and 3.

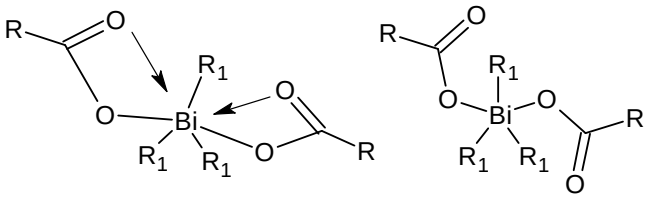
The esters can exist as bridging or distorted seven-bonded bridged structures (Figure 3, left) and non-bridging or triangular bipyramidal structures (Figure 3, right) with respect to the geometry about the metal atom. Infrared spectroscopy is the easiest way to determine the structure about the metal. Bridging asymmetric carbonyl absorptions are found around 1550-1600 (all infrared bands are given in cm^{-1}). The bridging symmetric carbonyl band is found around 1410-1440. Non-bridging asymmetric carbonyl bands are found about 1600-1700; and the corresponding symmetric carbonyl band found about 1330-1345.

Table 3 contains bands associated with bridging and non-bridging for the polymers. Bands associated with both bridging and non-bridging are found so the product contains a mixture of bonding about the metal atom. Bands associated with non-bridging increase as the metal atom increases in size while those associated with bridging increase as the metal atom size decreases. The larger atom size requires that bridging occur over an energetically less favorable longer distance.

Table 2: Selected infrared spectral band assignments for titanocene dichloride, PDA and the polymers derived from reaction of various metallocene dichlorides with PDA.

Assignment	Ph_3AsBr_2	PDA	Ph_3As/PDA	Ph_3SbCl_2	Ph_3Sb/PDA	Ph_3Bi/PDA
C-H st (Ar)	3103	3090	3090,3052	3060	3092,3067	3091,3054
C=O St, non-bridg		1640	1638		1638	1635
Ring st		1565	1578		1575	1575
C=O St, bridging			1588		1597	1556
C=C st	1465		1465	1460	1460	1469
M-Ph	1438		1437	1440	1437	1437
C=C ip	1362		1366		1368	1368
OH ip wag		1337,1330				
M-O asy st			1265		1263	1274
C-C	1152		1157	1152	1160	1160
M-Ph sym st	1050		1083	1048	1050	1050
CH ip wag		1015	1015		1021	1027
Ring Breathing	997	996	996	995	997	984
CH op wag		889	900	890	890	899
Skelatal-C Inversion		854	848	840	850	850
CH op bending	820		828		818	825
M-O sym st			737		732	735
Aryl op	690		682	690	687	694

Where op = out of plane; ip= in plane; sys=symmetrical; st=stretching; asy=asymmetric



Seven Bonded-Bridge-Like Linkage

Symmetrical Non-Bridged Linkage

Figure 3: Geometrical arrangements about the metal atom, here the bismuth metal atom

Table 3: Presence of bridging and non-bridging associated bands and location

Organometal Moiety	Asym bridging	Sym bridging	Asym Non- Bridging	Sym Non- Bridging
Ph_3As	1588(m)	1437 (l)	1638(m)	1335(s)
Ph_3Sb	1597(s)	1436(s)	1647(m)	1333(l)
Ph_3Bi	1556(s)	1436(s)	1633(l)	1334(l)

Where l = large, m= moderate, s= small;

Matrix-Assisted Laser Desorption/Ionization Mass spectrometry

While Matrix-assisted laser desorption/ionization mass spectrometry, MALDI MS was developed for the analysis of non-volatile samples with special use in the identification of polymers its potential for the analysis of a wide range of materials has not been fulfilled. This is largely due to the inability of many materials to be soluble in somewhat volatile liquids to a decent extent allowing good mixing of the polymer with matrix material. This has largely eliminated most synthetic high-polymers from being suitably analyzed employing MALDI MS.

For about a dozen years we and others have been employing MALDI MS for the identification of a number of non-volatile metal and non-metal containing polymers. This has been recently reviewed [47-50]. The technique employed by us is not straight forward MALDI MS but it is applicable to soluble and insoluble products so has wide potential for application. The technique focuses on the fragments that are created in the MALDI MS process.

Recently graphite has been employed by us as the matrix material because it gives good results with few interfering ion fragments produced above 500 mass which is the typical lower mass range employed in our studies [51, 52]. Two general MALDI MS modes were employed. These are the reflective and linear mode. The reflective mode has a longer focal length than the linear mode. Results for the reflective mode allow finer features, such as isotopic abundances, to be more accurately determined but generally results in the detection of lower masses. By comparison, the linear mode has a shorter flight distance and results in the detection of higher masses. Following are results for the polymers.

The major ion fragments for the triphenylantimony product with 3,5-pyridinedicarboxylic acid, PDA, are given in Table 4 and shown in Figures 4 and 5. Abbreviations are employed to describe tentative assignments. These are PDA for 3,5-pyridinedicarboxylic acid minus two protons; Ph is the phenyl moiety; U is one repeat unit; 2U is two repeat units. (Examples of repeat units are given in Figures 2.) Sodium is a common contaminant. All masses are given in Daltons, Da.

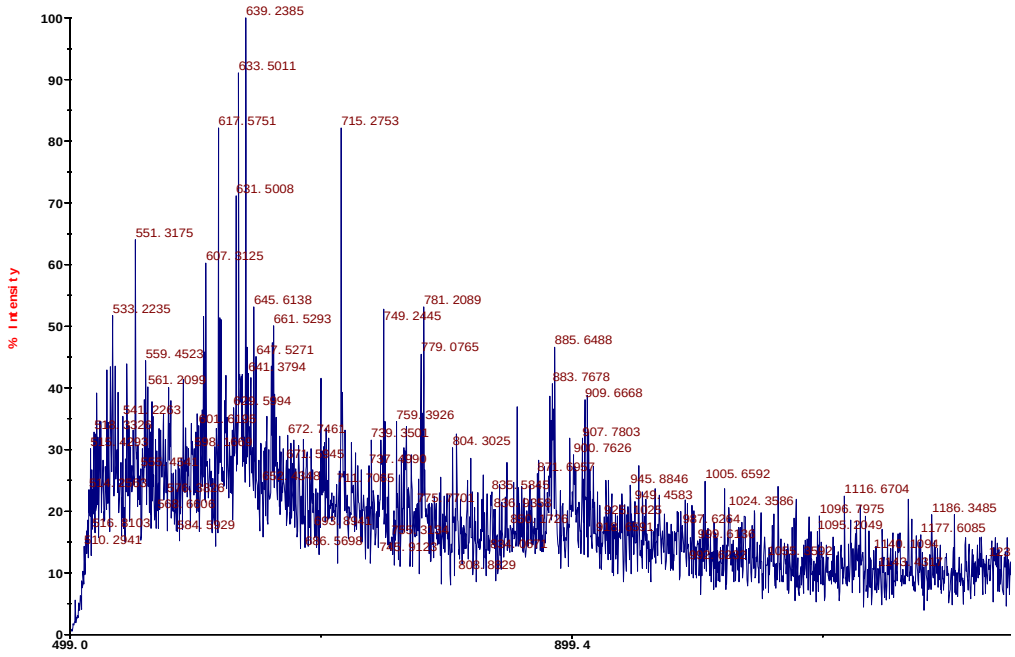


Figure 4: MALDI MS of the product of triphenylarsenic dibromide and PDA over the mass range of 500 to 1200 Da using the reflective mode

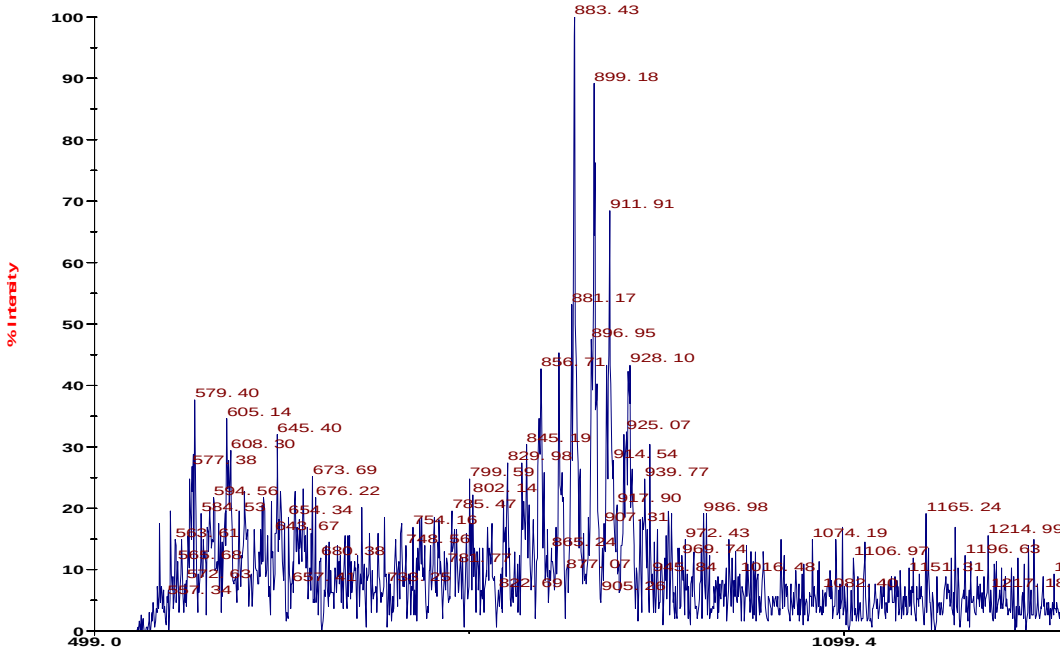


Figure 5: MALDI MS of the product of triphenylarsenic dibromide and PDA over the mass range of 500 to 1200 Da using the linear mode

Table 4: Major ion fragments for the product of triphenylarsenic dibromide and PDA

Mass,Da/Linear	Mass,Da/Reflective	(Tentative) Assignment	Mass,Da/Linear	Mass,Da/Reflective	(Tentative) Assignment
579		U+PDA-CO_2,O	1319		3U-Ph,O
605	607	U+PDA-20	1366		3U-Ph+Na
	639	U+PDA	1401		3U-O
645	645	U+PDA,Na-O	1582		3U+PDA
	662	U+PDA,Na		1661	3U+ Ph_2As,O
	715	U+ Ph_2As,O	1711		3U+ Ph_3As
749	749	U+ Ph_2As,CO_2		1853	4U-O
	781	U+ Ph_3As		1959	4U+PDA-Ph,O
820		U+ Ph_3As,CO_2		2077	4U+PDA,Na
856		U+ Ph_3As,2CO_2		2180	4U+ Ph_3As
883	886	U+ Ph_3As,2CO_2,Na		2225	4U+ Ph_3As,2O
912	910	2U-2O	2353		5U
926		2U-O		2371	5U-O
	946	2U	2502		5U+PDA-O
987		2U+CO_2	2618		5U+ Ph_2As,2O
	1005	2U+CO_2,Na	2738		5U+ Ph_3As,CO_2,O,Na
	1117	2U+PDA	2891		6U+CO_2,Na
1165		2U+ Ph_2As	3041		6U+ Ph_2As,O
	1186	2U+ Ph_2As,O	3268		7U-O
1215		2U+ Ph_2As,CO_2	3345		7U+CO_2
1268		2U+ Ph_3As,O			

Ion fragments are found corresponding to up to seven units long.

Table 5 contains results for the product of triphenylantimony dichloride and PDA. Ion fragments to over 6 units are found.

Table 5: Major ion fragments for the product of triphenylantimony dichloride and PDA

Mass,Da/ Linear	Mass,Da/ Reflective	(Tentative) Assignment	Mass,Da/ Linear	Mass,Da/ Reflective	(Tentative) Assignment
	526	U-O		1744	3U+PDA,Na
608	609	U+PDA-CO_2,O		1894	3U+ Ph_3Sb
	635	U+PDA-CO_2		2021	4U-CO_2
791	794	U+Ph_2Sb	2071		4U
857	856	U+ Ph_3Sb		2232	4U+PDA
883	883	U+ Ph_3Sb,O	2387		4U+ Ph_2Sb,CO_2
	912	U+ Ph_3Sb,CO_2	2485		4U+ Ph_3Sb,CO_2.O
	966	U+ Ph_3Sb,2CO_2	2635		5U+CO_2
1032	1035	2U	2763		5U+PDA,Na-O
	1415	2U+ Ph_3Sb,2O	3054		6U-CO_2
1498		3U+Na-Ph	3197		6U+PDA-Ph
	1523	3U-CO	3345		6U+Sb,CO_2
	1598	3U+CO_2			

Antimony contains two isotopes allowing isotopic matches to be made. Table 6 contains such matches containing one, two, and three antimony atoms. The structures given in the top line of each table correspond to the structure of the particular ion fragment cluster. The agreement to the expected listed as "Standard", appearing in the two most left-hand columns, is reasonable consistent with the present of one, two, and three antimony atoms within these ion fragment clusters.

Table 6: Isotopic abundance matches for ion fragments derived from the product of triphenylantimony dichloride and PDA

Known for Sb		U+PDA-CO_2,O		U+PDA-CO_2	
121	100	608	100	635	100
123	75	610	74	637	76

Known for 2Sb		U+Ph_2Sb		U+Ph_3Sb,O	
242	67	792	68	881	69
244	100	794	100	883	100
246	37	796	34	885	38

Known for 3Sb		3U-CO		3U+CO_2	
363	45	1521	41	1596	46
365	100	1523	100	1598	100
367	75	1525	77	1600	74
369	19	1527	21	1602	18

Table 7 contains the major ion fragment found for the product of triphenylbismuth and PDA.

Table 7: Major ion fragment clusters for the product from triphenylbismuth dichloride and PDA

Mass,Da/ Linear	Mass,Da/ Reflective	(Tentative) Assignment	Mass,Da/ Linear	Mass,Da/ Reflective	(Tentative) Assignment
606	606	U		1574	2U+ Ph_2Bi
643	645	U+CO_2	1621	1625	2U+ Ph_2Bi+CO_2,O
	745	U+PDA-CO_2	1710		2U+ Ph_2Bi+CO_2,Na
885	881	U+Bi	1847	1850	3U+CO_2
	912	U+Bi,Na		2003	3U+PDA,Na
923	924	U+Bi,2O		2216	3U+ Ph_2Bi+CO_2
943	942	U+Bi,CO_2	2240		3U+ Ph_3Bi
1012	1010	U+Bi,2CO_2,Na		2270	3U+ Ph_3Bi,O
	1071	U+ Ph_2Bi,2CO_2,Na		2324	3U+ Ph_3Bi,CO_2
	1141	2U-Ph+O	2342	2340	3U+ Ph_3Bi,CO_2,O,Na
	1160	2U-Ph+CO_2	2619		4U+PDA,Na
1187		2U-Ph+CO_2,Na	2740		4U+Bi,Na
1266	1267	2U+CO_2	3140		5U+PDA-CO_2
	1306	2U+PDA-CO_2,O	3164		5U+PDA-2O
1326		2U+PDA-CO_2			

Ion fragments to over five repeat units are found.

There is little loss of the phenyl unit on the metal. As in other studies, this loss occurs at the site of bond scission [43-46,49]. The pyridine ring unit remains intact consistent with the mildness of MALDI MS. As in other studies, bond scission occurs at the hetero-bond sites in the polymer chain. Figure 6 shows these sites for the repeat unit from triphenylbismuth/PDA.

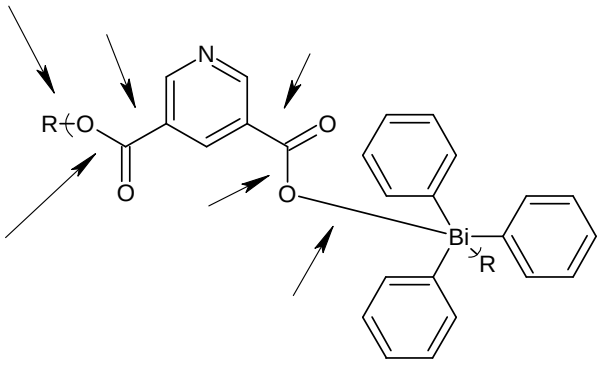


Figure 6: Locations of preferred chain bond scission

In summary, MALDI MS shows the presence of ion fragment clusters to 7 units of the arsenic product, 6 units for the antimony product, and 5 units for the bismuth. This trend occurs because it represents the upper mass limit used for each product and not for some other reason.

Proton NMR spectroscopy

Proton NMR was carried out on the products and monomers. PDA shows two proton environments associated with the pyridine ring (Figure 7). For PDA these bands appear for environment "a" at 7.4 and for "b" at 6.8 (all band locations are given in ppm). For the polymers these bands appear between 7.4-7.5 and 6.8 consistent with the presence of the PDA moiety. Because the protons in the 3,5-pyridinecarboxylic ring are isolated from the organometallic moiety, these bands appear little changed between the monomer and the various polymers. Triphenylarsenic dibromide shows three bands all derived from the phenyl group (ortho-, meta-, para- hydrogen atoms) at 8.20, 7.70, and 7.60. The triphenylarsenic/PDA polymer shows bands from the triphenylarsenic moiety at 8.5, 7.7 and 7.6 and from the PA moiety at 7.4 and 6.7. Triphenylantimony dichloride shows three bands at 8.20, 7.70, and 7.60. The corresponding polymer shows bands at 8.2, 7.7 and 7.6 from the triphenylantimony moiety and from the PDA ring protons at 7.4 and 6.8. Thus, proton NMR spectroscopy is consistent with the presence of units derived from both reactants. Because of the poor solubility of the polymers, additional implications from the data are not confidently derived.

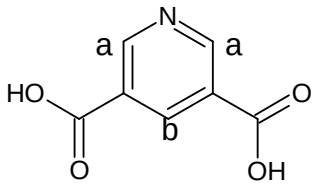


Figure 7: 3,5-Pyridinedicarboxylic acid with assigned protons locations

Tumor Analysis

The battery of test cancer cell lines used in this study is given in Table 8.

Table 8: Cell lines employed in the current study

Strain #	NCI Desig.	Species	Tumor Origin	Histological Type
3465	PC-3	Human	Prostate	Carcinoma
7233	MDA MB-231	Human	Pleural effusion breast	Adenocarcinoma
1507	HT-29	Human	Recto-sigmoid colon	Adenocarcinoma
7259	MCF-7	Human	Pleural effusion-breast	Adenocarcinoma
ATCC CCL-75	WI-38	Human	Normal embryonic lung	Fibroblast
CRL-1658	NIH/3T3	Mouse	Embyro-continuous cell line of highly contact-inhibited cells	Fibroblast
	AsPC-1	Human	Pancreatic cells	Adenocarcinoma
	PANC-1	Human	Epithelioid pancreatic cells	Carcinoma

In other studies we found that the polymer drugs are cytotoxic and cell death is by necrosis [1.2.53]. We have recently found that the anticancer activity is brought about by the intact polymer and not through polymer degradation [1-3]. This is consistent with studies that show the polymers are stable in DMSO with half-chain lives, the time for the polymer chain length to halve, generally in excess of 30 weeks [1-3,53]. Further, since the products are formed using the condensation process and are collected as a precipitate, the molecular weight distribution is believed to be relatively narrow [54-58]. Also, it is well known that most organometallic compounds associate with polar solvents such as DMSO and that the biological results are somewhat influenced by the presence of the DMSO [1,3,53,59-61]. For polymers similar to those described in the present study, this influence is found to be small, generally less than 20% [1-3].

While different measures are employed in the evaluation of a materials ability to inhibit cell growth, the two most widely used are employed in the present study. The first is the concentration dose needed to reduce growth of a particular cell line. Several names are associated with this concentration. The term effective concentration, EC, will be employed here. The concentration of a drug, antibody, or toxicant that induces a response halfway between the baseline and maximum after a specified exposure time is referred to as the 50% response concentration and is given the symbol EC_{50}.

Table 9 contains the EC_{50} values for the monomers and polymers. The cells represent a broad range of cancers. For comparison, values for cisplatin are also given. Cisplatin is among the most widely employed anticancer drugs. It is considered highly toxic and this is shown by the low EC_{50} values found towards the standard cell lines, WI-38 and NIH 3T3 cells. PDA shows no inhibition to the limits tested for most of the cancer cell lines and in the single case where it does, inhibition is only mild compared to the polymers. Further, the metal-containing monomers also exhibit mild inhibition of the cancer cell lines but again much less than the metal-containing polymers. Thus, neither monomer exhibits high inhibition of any of the cancer cell lines and it is the polymeric combination of the two reactants that is responsible for the observed ability to inhibit cancer cell line growth.

Much of our recent effort has been on discovering compounds that inhibit pancreatic cancer because pancreatic cancer does not have a generally accepted "cure" [1,2,62-65]. Thus, the set includes two widely employed pancreatic cell lines. These are the AsPC-1 cell line which is an adenocarcinoma pancreatic cell line representing the most often observed pancreatic cancer cell line found in humans (about 80%) and the PANC-1 cancer cell line which is an epithelioid carcinoma pancreatic cell line representing the second most frequently observed pancreatic cancer cell line found in humans (about 10%). All three of the polymers show good inhibition of both pancreatic cancer cell lines. The inhibition of the pancreatic cancer cell lines is similar for both the ASPC-1 and PANC-1 cells indicating that inhibition by the polymers may be general for the other pancreatic cancers.

The two breast cancer cell lines represent a matched pair. The MDA-MB-231 (strain number 7233) cells are estrogen-independent, estrogen receptor negative while the MCF-7 (strain line 7259) cells are estrogen receptor (ER) positive. In some studies involving organotin polymers there was a marked difference between the ability to inhibit the two cell lines dependent on polymer structure [2.3.66-68]. In the current study there is little difference in the ability to inhibit the two cell lines by the polymers with the polymers inhibiting both breast cancer cell lines with about the same EC_{50}. The polymers also exhibit good inhibition of the prostrate (PC-3) and colon (HT-29) cancer cell lines.

All three polymers show good ability to inhibit all of the tested cell lines, cancer and standard. Further, inhibition is similar regardless of the nature of the metal. It is the combination of the PDA with the metal-containing moiety that allows the polymer to effectively inhibit cell growth rather than the particular metal-containing moiety. In summary, based on EC_{50} values, the polymers show good ability to inhibit a variety of cancer cell lines.

Table 9: EC_{50} Concentrations (micrograms/mL) for the tested compounds. Values given in ( ) are Standard Deviations for each set of measurements

Sample	*3465/PC-3*	*7233/MDA*	*1507/HT-29*	*7259/MCF-7*
Ph_3AsBr_2	20.0(1.7)	21.4(1.0)	16.5(1.2)	24.6(2.1)
Ph_3As/PDA	0.55(.6)	0.58(.7)	0.59(.7)	0.55(.7)
Ph_3SbCl_2	38(4)	12.4(1.1)	33.(3.1)	135(11)
Ph_3Sb/PDA	0.53(.6)	0.56(.7)	0.55(.7)	0.58(.7)
Ph_3BiCl_2	2.4(.16)	1.4(.2)	2.2(.16)	1.6(.21)
Ph_3Bi/PDA	0.55(.6)	0.59(0.7)	0.58(.7)	0.60(.5)
PDA	>32000	>32000	>32000	>32000
Cisplatin	0.0044(.004)	0.0029(.002)	0.0041(.003)	0.0057(.003)

The second widely used measure of cancer inhibition ability involves comparing the amount of drug needed to inhibit the cell growth of a standard cell line compared to the amount to inhibit the cell growth of a particular cancer cell line. Again, a variety of symbols are employed to describe similar calculations. Here, the term chemotherapeutic index, CI, will be used so that the CI_{50} is then the ratio of the EC_{50} for the standard cell lines NIH 3T3 or WI-38 cells divided by the EC_{50} for the particular test cell. Results are given in Table 10.

Two cell lines are typically employed as standards in the evaluation of the effectiveness of compounds to arrest the growth of tumor cell lines. These two cell lines are the NIH 3T3 and WI-38 cell lines. The current

study has two parts. The first is evaluation of the CI_{50} values determined using the two different standard cells. NIH 3T3 cells are mouse embryo fibroblast cells. They are part of a group of cell lines are referred to as partially transformed cells in that they are immortal unlike normal cells. They retain other characteristics of normal cells such as being contact-inhibited. Relative to most normal cells they are robust and easily maintained. WI-38 cells are normal embryonic human lung fibroblast cells. They have a finite life time of about 50 replications. Compared to NIH 3T3 cells, they are more fragile and difficult to maintain for long periods of time. Thus, NIH 3T3 cells are often favored because of ease of handling aided by an infinite life span. But, when there is a difference, CI_{50} values determined using the WI-38 cell are favored [1-3]. For the current study, the CI_{50} values using either standard cell line are similar so that either could be used in this evaluation.

The second part of the study is to use the CI_{50} values to ascertain if preferential inhibition by the test compounds is present. The CI_{50} values derived from values given in Table 10 are derived from values given in Table 9. It is preferential to find large values meaning that the tendency to inhibit the cancer cells is preferential compared to the standard cell lines. In general, CI_{50} values of two and greater are considered significant. Focusing on the three polymer samples, there are no values greater than two so that there is not a major preferential for the test compounds to inhibit cancer cell growth.

Table 10: CI_{50} results for values calculated from data given in Table 9

Sample	EC_{50} *WI-38*/ EC_{50}*AsPC*-1	EC_{50} *3T3*/ EC_{50}*AsPC*-1	EC_{50} *WI-38*/ EC_{50}*PANC*-1	EC_{50} *3T3*/ EC_{50}*PANC*-1
Ph_3As/ PDA	1.1	1.0	1.1	1.1
Ph_3Sb/ PDA	1.2	1.1	1.1	1.0
Ph_3Bi/ PDA	1.2	1.1	1.0	0.97

Sample	EC_{50} *WI-38*/ EC_{50}*7233*	EC_{50} *3T3*/ EC_{50}*7233*	EC_{50} *WI-38*/ EC_{50}*7259*	EC_{50} *3T3*/ EC_{50}*7259*
Ph_3As/PDA	1.1	1.0	1.1	1.1
Ph_3Sb/ PDA	1.1	1.1	1.1	1.0
Ph_3Bi/ PDA	1.0	0.95	1.0	0.93

Sample	EC_{50} *WI-38*/ EC_{50}*1507*	EC_{50} *3T3*/ EC_{50}*1507*	EC_{50} *WI-38*/ EC_{50}*3465*	EC_{50} *3T3*/ EC_{50}*3465*
Ph_3As/ PDA	1.1	1.0	1.1	1.1
Ph_3Sb/ PDA	1.1	1.1	1.2	1.1
Ph_3Bi/ PDA	1.0	0.97	1.1	1.0

Low EC_{50} values show that the polymer inhibits cancer growth at low concentrations. By comparison, high CI_{50} values are consistent with the polymer preferentially inhibiting cancer cell growth. Researchers disagree as to which values is most important in indicating the drug effect in animals, the EC_{50} or CI_{50} [2,40,41,65-67]. Here, the EC_{50} values for the Group VA polymers show good inhibition of the cancer cell lines but the low CI_{50} values are consistent with little preferential inhibition of the cancer cell lines by the polymers.

COMPARISON OF CELL RESUTLS

We have synthesized PDA-containing polymers containing organotin [40], metallocene groups [41] and in this report Group VA units. Following is a brief study of the ability of these polymers to inhibit cancer cell lines allowing a comparison of the effect of the particular metal atom on the ability to inhibit cancer cell growth. Table 11 contains EC_{50} values for the various polymers. Values for the current new polymers are added for easy referral.

Table 11: EC_{50} values in microgram/mL as the metal-containing moiety is varied

	WI-38	PAN-1	AsPC-1	PC-3	MDA	HT-29	MCF-7
Cp_2Ti/PDA	18	2.1	4.4	5.1	5.7	2.3	4.4
Cp_2Zr/PDA	20	1.1	5.5	17	19	14	18
Cp_2Hf/PDA	20	4.6	3.7	1.1	4.1	4.7	2.7
Cp_2V/PDA	20	2.2	7.5	3.1	6.6	4.0	2.8
Me_2Sn/PDA	0.71	0.61	0.60	0.62	0.62	0.62	0.61
Et_2Sn/PDA	0.72	0.71	0.69	0.67	0.60	0.64	0.63
Bu_2Sn/PDA	0.63	0.69	0.66	0.70	0.63	0.67	0.67
Oc_2Sn/PDA	0.68	0.62	0.63	0.60	0.71	0.63	0.62
Ph_2Sn/PDA	0.62	0.64	0.67	0.67	0.63	0.68	0.66
Ph_3As/PDA	0.62	0.55	0.58	0.55	0.58	0.59	0.55
Ph_3Sb/PDA	0.61	0,57	0.53	0.53	0.56	0.55	0.58
Ph_3Bi/PDA	0.60	0.58	0.52	0.59	0.59	0.58	0.60

With respect to EC_{50} values, those polymers where the metal is organotin and Group V have the lowest values showing the greatest ability to inhibit cancer growth. The EC_{50} values are similar for all of the organotin and Group V metal derived polymers and cancer cell lines. By comparison, the results for the metallocenes are varied but in all cases the EC_{50} values are greater than for the organotin and Group V derived polymers. For the metallocenes the EC_{50} values vary with the cancer cell line and metal though the values are generally within a decade of one another. Further, the Group IVB metallocene polymers are the least toxic towards the WI-38 human non-cancer cell line.

Table 12 contains the CI_{50} values calculated from the data given in Table 11.

Table 12: CI_{50} values calculated from data given in Table 11

	EC_{50}WI-38/ EC_{50}PANC-1	EC_{50}WI-38/ EC_{50}AsPC-1	EC_{50}WI-38/ EC_{50}PC-3	EC_{50}WI-38/ EC_{50}MDA	EC_{50}WI-38/ EC_{50}HT-29	EC_{50}WI-38/ EC_{50}MCF-7
Cp_2Ti/PDA	8.6	4.1	3.5	3.2	7.8	4.1
Cp_2Zr/PDA	1.8	3.6	1.2	1.1	1.4	1.2
Cp_2Hf/PDA	4.4	5.4	18	4.9	4.3	7.4
Cp_2V/PDA	9.1	2.7	6.5	3.0	5.0	7.1
Me_2Sn/PDA	1.1	1.2	1.1	1.1	1.2	1.3
Et_2Sn/PDA	1.0	0.80	1.2	1.2	1.1	1.1
Bu_2Sn/PDA	0.91	0.95	0.90	1.0	0.94	0.94
Oc_2Sn/PDA	1.1	1.1	1.1	0.96	1.1	1.1
Ph_2Sn/PDA	0.97	0.93	0.93	0.98	0.91	0.94
Ph_3As/PDA	1.1	1.1	1.1	1.1	1.0	1.1
Ph_3Sb/PDA	1.1	1.1	1.1	1.1	1.1	1.2
Ph_3Bi/PDA	1.0	0.95	1.0	1.0	0.97	1.1

CI_{50} values of two and larger are generally considered significant [1-3]. Only the metallocene products exhibit such values with the highest values found for the titanocene, hafnocene, and vanadocene polymers showing good CI_{50} values for all of the cancer cell lines.

Thus, while the metallocene polymers are the least toxic towards the cancer cell lines as measured through EC_{50} values they show the highest CI_{50} values. Further, for these polymers, the organotin and Group V products exhibit similar good toxicity towards the cancer cell lines as measured by EC_{50} values but the CI_{50} values exhibit little differentiation with respect to toxicity between the standard WI-38 and cancer cell lines.

Additionally, all of the products described here, except for the triphenylarsenic dibromide, are commercially available. Also, the interfacial polycondensation system employed in the synthesis of the polymers is commercially employed to synthesize aramid fibers and polycarbonates. Thus, scale-up can be readily accomplished.

CONCLUSIONS

Group VA-containing polyesters have been synthesized from the interfacial polymerization of 3,5-pyridinedicarboxylic acid with Group VA triphenyl organometallic dihalides with yield and chain decreasing as the size of the metal increases. With the exception of the triphenylarsenic dibromide, all of the reactants are commercially available. Further, the interfacial polycondensation system is industrially employed in the synthesis of aramides and polycarbonates so that the polymers can be readily synthesized in milligram to ton quantities. IR shows new bands assigned to the formation of the M-O linkage and is consistent with the geometry about the metal atom being of a combination of bridging and non-bridging. MALDI MS shows the formation of ion fragment clusters of 5 to 7 repeat units with breakage occurring at the heteroatom sites. The polymers show good inhibition of all of the tested cancer cell lines including two pancreatic cancer cell lines. A comparison of polymers derived from various metal-containing reactants and 3,5-pyridinedicarboxylic acid show similar EC_{50} values when the metal is Group VA and tin, but the CI_{50} values are more favorable for the metallocene polymers.

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