ISSN: 0128-7680
Pertanika J. Sci. & Technol. 6(2): 131-139 (1998)

Synthesis and Characterization of Dibutyltin(IV) Complexes of Substituted Catechol

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Received 15 December 1997

ABSTRAK

Kompleks dibutilstanum(IV) dengan anion terbitan ligan 4-*tert*-butilkatekol, 4-klorokatekol, 4-nitrokatekol, 3,4-dihidroksibenzaldehid dan asid 3,4-dihidroksibenzoik disintesiskan secara menindakbalaskan dibutilstanum(IV) oksida dengan ligan bebas. Kompleks yang diasingkan dicirikan secara analisis unsur dan kaedah spektroskopi seperti inframerah, resonans magnet nukleus ^{1}H dan ^{13}C. Pembentukan kompleks di antara moieti dibutilstanum(IV) dan anion terbitan 4-tert-butilkatekol, 4-klorokatekol, 4-nitrokatekol, dan 3,4-dihidroksibenzaldehid terjadi pada kedudukan o-dihidroksi. Analisis kompleks dengan asid 3,4-dihidroksibenzoik menunjukkan bahawa kumpulan karboksilik turut terlibat dalam pembentukan kelat. Keputusan ujian biocerakinan kemautan anak udang *(Artemia salina)* menunjukkan semua kompleks menunjukkan aktiviti biologi tetapi hanya kompleks dibutilstanum(IV) dengan 4-*tert*-butilkatekol berupaya membelah DNA (plasmid pBR 322).

ABSTRACT

The complexes of dibutyltin(IV) with anions of 4-*tert*-butylcatechol, 4-chlorocatechol, 4-nitrocatechol, 3,4-dihydroxybenzaldehyde, and 3,4-dihydroxybenzoic acid were synthesized by reacting dibutyltin(IV) oxide with the corresponding free ligands. The isolated complexes were characterized by elemental analysis and spectroscopic methods such as infrared, ^{1}H and ^{13}C NMR. Complex formation between the dibutyltin(IV) moiety and the anions of 4-tert-butylcatechol, 4-chlorocatechol, 4-nitrocatechol and 3,4-dihydroxybenzaldehyde takes place with chelation at the o-hydroxy positions. However, results of analysis carried out on the dibutyltin(IV) complex of 3,4-dihydroxybenzoic acid showed that the carboxylic group is also involved in chelate formation. Results of the lethality bioassay on the brine shrimp (*Artemia salina*) indicated that all the complexes have biological activity but only the 4-tert-butylcatechol complex was able to cleave DNA (plasmid pBR 322).

INTRODUCTION

Chelates play an important role in antitumour studies. Some platinum complexes are active towards certain tumours. The complex *cis*-diamminedichloroplatinum

(II), better known as cisplatin (*Fig. 1*), is used till today for the treatment of ovarian carcinomas and testicular tumours (Crowe 1989).

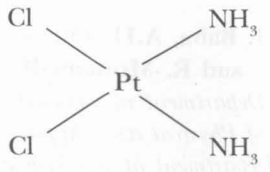

Fig. 1. Structure of cisplatin

Research on the antitumour activity of organotin compounds started as early as 1929. The potential of such compounds as antitumour agents has been extensively studied by several workers (Crowe 1989; Saxena and Huber 1989; Gielen *et al.* 1989; Gielen *et al.* 1992). Since 1980, United States National Cancer Institute has tested over 1000 tin compounds, and 170 of these were found to be active. An extensive list of organotin compounds which were tested against P388 lymphocyte leukaemia showed great promise as possible antitumour agents (Saxena and Huber 1989). The platinum complexes of catechol and substituted catechol were reported to show biological activity against leukaemia (Apfelbaum *et al.* 1991) and breast cancer (Gandolfi and Blum 1983).

The preparation and characterization of a number of tin(II) and tin(IV) catechol complexes have been reported (Mabrouk and Tuck 1988; Machell *et al.* 1989; Yang Farina 1989; Denekamp *et al.* 1993). The dibutyltin(IV) complex of catechol was first synthesized, though with very low yield, by Emeléus and Zuckermann (1964). The synthesis of triethylammonium triphenyltin(IV) catecholate and dibutyltin(IV) catecholate with increased yield was also carried out (Abdul Aziz *et al.* 1995).

Because of the importance of tin and catechol complexes as antitumour agents we here report the synthesis and characterization of dibutyltin(IV) complexes of substituted catechol. Results of biological tests such as brine shrimp (*Artemia salina*) lethality bioassay and DNA cleavage of these complexes are also reported.

MATERIALS AND METHODS

Materials

The ligands 4-*tert*-butylcatechol ($tbcH_2$), 3,4-dihydroxybenzoic acid ($catCOOHH_2$) and 4-nitrocatechol ($catNO_2H_2$) were supplied by Fluka Chemica while 3,4-dihydroxybenzaldehyde ($catCHOH_2$) was obtained from E. Merck. Reagent grade 4-chlorocatechol ($catClH_2$) was purchased from TCI. Commercial grade dibutyltin(IV) oxide was purchased from Fluka Chemica and used without further purification. All the preparations were carried out with nitrogen using thoroughly de-aerated solutions.

Synthetic Methods

A warm methanolic solution of dibutyltin(IV) oxide was added to a warm methanolic solution of the ligand. A few pellets of molecular sieve were added and the reactants were heated under reflux for 2 hours. The solid product which separated upon cooling was filtered and washed with cold methanol (3 x 10 ml) and then dried over silica gel under vacuum. An outline of the reaction scheme is given in *Fig. 2.*

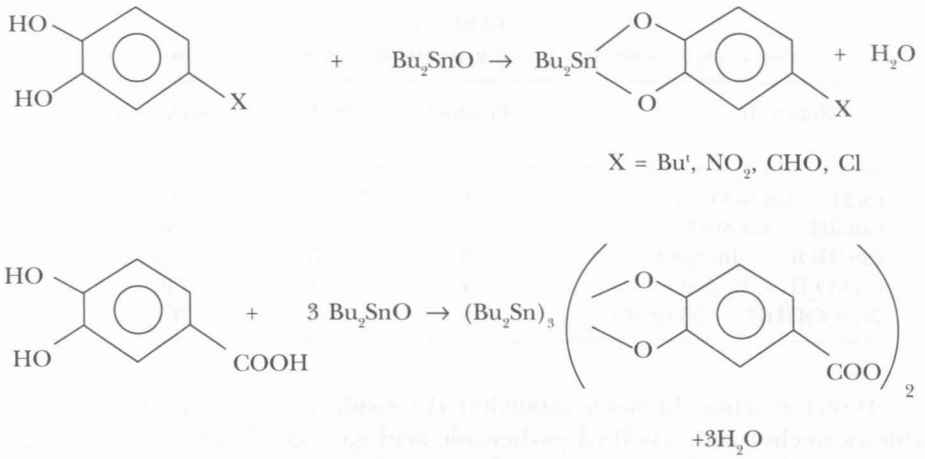

Fig. 2. Reaction scheme

Analyses and Instrumentation

Elemental C, H and O analyses were carried out on a Fison EA 1108 CHNS-O analyser. Tin was determined gravimetrically, by igniting a known quantity of each complex to SnO_2. The infrared spectra were recorded using potassium bromide discs on a Perkin-Elmer 1310 spectrophotometer. The ^1H and ^{13}C nuclear magnetic resonance spectra were recorded on a Bruker AC-P 300 FT-NMR instrument at the School of Chemical Sciences, Universiti Sains Malaysia, Penang.

Brine Shrimp Bioassay

Brine shrimp (*Artemia salina*) (Leach) eggs were obtained from a local pet shop. The eggs were placed in natural sea water (31°C) and hatched after 48 h to produce large numbers of larvae (nauplii). Each complex was tested at initial concentrations of 10, 100 and 1000 ppm (or µg/ml) in vials containing 5 ml of brine and ten shrimps in each of three triplicates. Survivors were counted after 24 h. These data were processed with a simple program on a personal computer to estimate LC_{50} values with 95% confidence intervals for statistically significant comparisons of potencies. LC_{50} values greater than 200 ppm are considered inactive biologically (Anderson *et al.* 1991).

DNA Cleavage Bioassay

DNA (plasmid pBR 322) cleavage tests were carried out by Assoc. Prof. Dr. Rahmah Mohamed at the Department of Biochemistry, Universiti Kebangsaan Malaysia using electrophoresis methods.

RESULTS AND DISCUSSION

The percentage yields and melting points of the products isolated from each reaction are presented in Table 1.

TABLE 1
Percentage yields and melting points of the obtained products

Reaction	Product	Yield (%)	Melting Point (°C)
$tbcH_2 + Bu_2SnO$	1	60	265 - 267
$catClH_2 + Bu_2SnO$	2	65	238 - 239
$catCHOH_2 + Bu_2SnO$	3	35	245 - 246
$catNO_2H_2 + Bu_2SnO$	4	44	246 - 247
$2catCOOHH_2 + 3Bu_2SnO$	5	83	367 - 369

Direct reaction between dibutyltin(IV) oxide and 4-*tert*-butylcatechol, 4-chlorocatechol and 3,4-dihydroxybenzoic acid gave good yields of 1, 2 and 5 respectively. The yields of products 3 and 4 were low. An attempt was made to improve yields of 3 and 4 by reacting the ligands in the anionic form with dibutyltin(IV) chloride, but no solid product could be isolated. The condensation reaction between the free ligand and dibutyltin(IV) oxide afforded the complex and water. A few pellets of molecular sieve were added to the reaction to adsorb all the water produced. The melting points of all the complexes indicate that they are fairly pure. All the complexes are only soluble in dimethyl sulphoxide, thus making further purification by recrystallization difficult.

The results of elemental analysis are given in Table 2 and are in fairly good agreement with the values calculated for the suggested formulae. This data also show that monochelates of catechol are produced in each reaction, except for 5. The presence of the chelated catecholate anion is substantiated by means of spectroscopic data.

The assignments of the important infrared bands are presented in Table 3. A survey of the infrared spectra of 1, 2, 3, 4 and 5 showed two prominent peaks at 1450 and 1250 cm^{-1}. The presence of these two peaks gave strong indication that the catecholate anion is chelated, in accordance with the observations of other authors (Wicklund and Brown 1976; Griffith *et al.* 1986). The absence of strong peaks at 1660, ν(C=O) and 1440 cm^{-1}, ν(C—O) indicate the absence of o-quinone and o-semiquinone species respectively (Brown and Hemphill 1979). The absence of ν(O-H) in all the infrared spectra indicate

TABLE 2
Quantitave data for 1, 2, 3, 4 and 5

Product	Suggested formula	%C	%H	%O	%Sn
1	$Bu_2Sn(tbc)$	55.27 (54.47)	7.69 (7.56)	7.75 (8.07)	29.04 (29.88)
2	$Bu_2Sn(catCl)$	44.68 (44.80)	5.70 (5.60)	8.50 (8.50)	30.68 (31.60)
3	$Bu_2Sn(catCHO)$	48.25 (48.84)	6.10 (5.97)	12.09 (13.02)	33.18 (32.16)
4	$Bu_2Sn(catNO_2)$	44.09 (43.58)	5.58 (5.44)	14.82 (16.60)	29.82 (30.74)
5	$(Bu_2Sn)_3(catCOO)_2$	44.86 (45.59)	5.96 (5.99)	14.50 12.79)	34.83 (35.60)

Calculated values are given in parentheses

TABLE 3
Infrared data for complexes 1, 2, 3, 4 and 5

Compound	ν(C—C)	ν(C-O) (cm^{-1})	δ(O-Sn-O)
1	1462	1282	686
2	1480	1246	676
3	1488	1266	682
4	1488	1270	670
5	1435	1268	676

that the oxygen atoms are now coordinated to the dibutyltin(IV) moiety. Gielen *et al.* (1989) observed a strong sharp peak centred at 670 cm^{-1} in the infrared spectra of organotin derivatives of malonic acids and assigned this peak to O-Sn-O bending. A similar band was observed at around 640 cm^{-1} in the infrared spectra of 1, 2, 3, 4 and 5, and thus tentatively assigned to O-Sn-O bending. The infrared spectrum of 5 showed a medium peak at 1590 cm^{-1} assigned to ν(C=O) of the carbonyl group. The shift to low frequency of ν(C=O) relative to the free ligand (1650 cm^{-1}) indicates that the carboxyllic group is also involved in complex formation.

The ^1H NMR spectra for all the free ligands and complexes were recorded in [$^2H_6$]dimethylsulphoxide solutions. The relevant data are presented in Table 4. Chemical shift values are relative to an internal TMS reference. There is a

TABLE 4
^{1}H NMR data for complexes 1, 2, 3, 4 and 5 and the related free ligands

Compound	δH(arom)	δH(aliph)	δH(OH)
$tbcH_2$	6.9(m), 6.7(m)	Bu^t: 1.3(s)	8.7(s)
1	6.6(m), 6.3(m)	Bu^t: 1.2(s) Bu: 1.5-0.8(m)	-
$catClH_2$	6.8(m)	-	9.2(s), 9.1 (s)
2	6.5(m), 6.3(m)	1.5-0.8(m)	-
$catCHOH_2$	7.4(m), 7.0(m)	-	9.8(s), 9.6(s)
3	7.0(m), 6.6(m)	1.5-0.8(m)	-
$catNO_2H_2$	7.7(m), 6.9(m)	-	10.3(b)
4	7.5(m), 6.6(m)	1.5-0.8(m)	-
$catCOOHH_2$	7.4(m), 6.8(m)	-	9.8(b)
5	7.2(m), 6.5(m)	1.5-0.8(m)	-

m = multiplet; s = singlet; b = broad

small upfield shift of the aromatic protons resonances of the ligands upon chelation with the dibutyltin(IV) moiety. The same effect has been reported (Wicklund and Brown 1976; McArdle *et al.* 1978; Nielson and Griffith 1978; Mabrouk and Tuck 1988; Yang Farina 1989). These shifts may be attributed to decreased electron density in the catechol ring due to electron withdrawing ability of the organotin(IV), which in turn decreases the ring current and deshielding of the ring protons. Hence a stronger field is required to bring the aromatic protons to resonance. The disappearance of resonances due to hydroxy protons was strong evidence of the involvement of the phenolate oxygens in the bonding. The resonances of the butyl groups in the complexes appeared as a series of peaks in the range 1.54-0.8 ppm.

Complex formation is clearly evidenced by the ^{13}C NMR spectra. The ^{13}C NMR spectra data collected for 2, 3, 4 and 5 and the related free ligands which were carried out at 26°C are given in Table 5. The same solvent was employed as in the recording of the ^{1}H NMR spectra. The ^{13}C NMR spectrum of 1 could not be obtained due to its poor solubility in the deuterated solvents available. It can clearly be seen that upon complex formation with the organotin, the C-O resonances of the catecholate anion are shifted downfield compared to the free ligand. Such shift could be attributed to decreased electron density at the carbon atoms when the oxygen is bound to a metal ion (Nielson and Griffith

TABLE 5
^{13}C NMR data for complexes 2, 3, 4 and 5 and related free ligands

Compound	C-O	C-H	C-subs (ppm)	Others
CatCl	146.4 144.6	118.8, 116.6 115.5	122.2	
2	155.1 152.8	114.8, 112.9 112.2	118.6	Bu - 26.4, 26.7, 24.3, 13.4
catCHO	152.3 145.3	125.7, 116.2 115.3	130.9	CHO - 191.5
3	162.4 153.9	124.4, 112.9 110.7	126.0	CHO - 190.1 Bu : 26.4, 25.5, 25.0, 13.4
$catNO_2H_2$	152.9 145.4	118.1, 116.0 111.7	142.1	-
4	163.7 153.8	115.5, 112.1 107.1	136.6	Bu - 30.8, 26.0, 25.6, 13.6
$catCOOHH_2$	150.0 144.9	121.7, 116.6 115.2	121.9	COOH - 167.3
5	152.8 150.0	117.7, 113.9 112.5	120.3	COO - 159.6 Bu - 26.5, 25.8, 24.5, 13.5

1978; Griffith *et al.* 1986; Mabrouk and Tuck 1988; Yang Farina 1989). The resonances due to the *n*-butyl group appear as a set of four peaks in the region 30.8 -13.4 ppm which correspond to the four carbon atoms.

The results of the brine shrimp lethality and DNA cleavage bioassays are given in Table 6. In the prescreen brine shrimp lethality bioassay all the complexes were found to have LC_{50} values of less than 200 ppm and therefore

TABLE 6
Biological activity data for complexes 1, 2, 3, 4 and 5

Compound	LC_{50}/ppm	Interaction with pBR 322 plasmid
1	68.0	Yes, at 5×10^{-3} M
2	57.5	No
3	< 10.0	No
4	63.6	No
5	8.5	No

can be considered biologically active (Anderson *et al.* 1991). Results of the DNA cleavage tests, however, showed that only the 4-*tert*-butylcatechol complex is able to cleave the pBR 322 plasmids.

CONCLUSION

The reaction between molar equivalents of dibutyltin(IV) oxide and the free ligands 4-*tert*-butylcatechol, 4-chlorocatechol, 4-nitrocatechol and 3,4-dihydroxybenzaldehyde gave monochelated dibutyltin(IV) catecholates of general formula $Bu_2Sn(L)$. The reaction between dibutyltin(IV) oxide and 3,4-dihydroxybenzoic acid gave a complex of general formula $(Bu_2)_3Sn(L)2$. Spectroscopic results show that chelation occurs at the o-dihydroxy sites in complexes $Bu_2Sn(L)$ while the case of 3,4-dihydroxybenzoic acid complex also showed that the carboxylic group appeared to be involved in complex formation. All the complexes show biological activity in the brine shrimp lethality bioassay which was used as the antitumour prescreen test. However, only the complex of 4-*tert*-butylcatechol was able to cleave DNA (plasmid pBR 322). Hence, it can be concluded that the dibutyltin(IV) complexes of substituted catechol show biological activity and are therefore currently undergoing *in vitro* tests against CECM .7 (human acute lymphoblastic leukaemia).

ACKNOWLEDGEMENTS

We would like to thank the National Science Council for R & D, Malaysia for funds (IRPA 2-07-03-017) and Dr. Mas Rosemal Hakim Mas Hakim from Universiti Sains Malaysia for recording the NMR spectra. Technical assistance from members of the Department of Chemistry, Universiti Kebangsaan Malaysia is gratefully acknowledged.

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