APPLIED ORGANOMETALLIC CHEMISTRY
Appl. Organometal. Chem. 2007; **21**: 203–208
Published online in Wiley InterScience
(www.interscience.wiley.com) DOI:10.1002/aoc.1192

Semiempirical studies on the interactions of dialkyldi(aquo)tin cations, $[R_2Sn(H_2O)_2]^{2+}$, with selected nucleotides

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Received 28 April 2006; Revised 16 May 2006; Accepted 20 November 2006

Semiempirical calculations have been carried out on the interactions of $[R_2Sn(H_2O)_2]^{2+}$, [R = $H(CH_2)_n$: $n = 1–8$], mainly with five nucleotides, 5′-adenosine monophosphate (5′-AMP), but also with guanosine 5′-monophosphate (5′-GMP), cytidine 5′-monophosphate (5′-CMP), uridine-5′-monophosphate (5′-UMP) and inosine 5′-monophosphate (5′-IMP). The preferred sites of interaction were calculated to be the ribose O2 and O3 hydroxyl oxygens and/or the phosphate oxygens, with the nitrogen sites in the bases the least attractive to the tin compounds. This is in general agreement with experimental findings. Structures of the 1 : 1 coordination complexes vary from distorted tetrahedral, to distorted trigonal pyramidal to distorted octahedral geometries. Copyright © 2007 John Wiley & Sons, Ltd.

KEYWORDS: diorganotin; nucleotides; AMI calculations

INTRODUCTION

Various organometallic species exhibit significant anti-tumour activities.[1] Arguably the best known of these compounds is *cis*-platin, *cis*-$[Pt(NH_3)_2Cl_2]$, which interacts mainly with the N7 atoms of two guanine moieties in the same DNA strand.[2] A number of organotin compounds, mainly diorganotin species, R_2SnX_2, but also triorganotins, R_3SnX, have been found to have excellent *in vitro* anti-tumour activites,[3,4] in some cases even higher than *cis*-platin.[3] However so far results from *in vivo* studies are less encouraging.

Initially it was considered that the mode of interaction of the organotin compounds would parallel that of *cis*-platin and related Pt drugs[5] in binding to the nitrogen centres in the heterocyclic bases of nucleic acids, but subsequent study of interactions of model nucleotides, such as those shown in Fig. 1, with organotin halides in aqueous media using vibrational and NMR (^1H, ^{13}C, ^{15}N, ^{31}P and $^{117,119}Sn$ NMR, using, where appropriate, one- and two-dimensional techniques) spectroscopies (see, for example Ghys *et al*.,[6] Jancso *et al*.,[7] Yang *et al*.[8] and Nafisi *et al*.[9]), as well as stability constant studies,[10,11] has revealed that this is not the case. Solid-state studies of isolated complexes, using NMR,[6] Mössbauer,[8–16] and IR spectroscopies, and frozen solutions, using Mössbauer spectroscopy, similarly confirm this.

While organotin halides could be the added reagents in these studies, hydration and hydrolysis to hydroxyl- and oxy-diorganotin compounds can occur to varying extent depending on the pH, and this must be taken into consideration in analysing the species present.[6,10,17–19]

There are several potential binding sites in nucleotides: the phosphate oxygens, the ribose oxygens and nitrogens in the bases. All these types of donor centres have been shown, in non-nucleotide compounds, to be able to bind to a tin centre.[20] It has been generally found that the binding of the diorganotin species to model nucleotides in aqueous media varies with pH: at low pH values, the diorganotin moiety binds to phosphate oxygens, at high pH to the deprotonated ribose hydroxyls at C2′ and C3′ atoms and in the intermediate pH range no binding can be detected. Significantly at no pH

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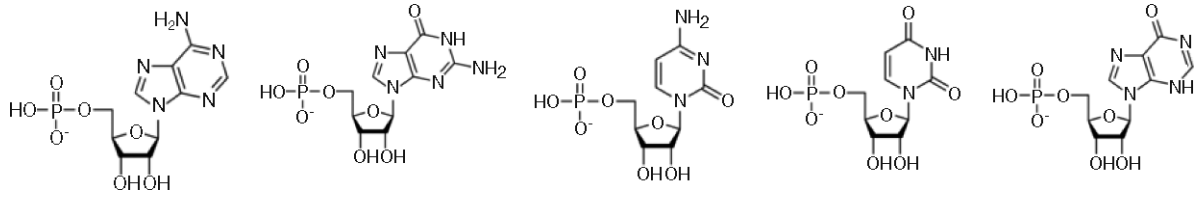
Contract/grant sponsor: CNPq-Brazil.



5′-Adenosine monophosphate 5′-AMP | 5′-Guanosine monophosphate 5′-GMP | 5′-Cytidine monophosphate 5′-CMP | 5′-Uridine monophosphate 5′-UMP | 5′-Inosine monophosphate 5′-IMP

Figure 1. Nucleotides investigated in this study.

was there interaction involving the heterocyclic bases, hence the organotins make a great contrast with *cis*-platin. Neither does the organotin species bind to the ribosyl ring oxygen.

The pH values for specific interactions vary with the nucleotide and diorganotin species. Some examples are: (i) binding of Et_2Sn^{2+} to 5′-IMP and 5′-GMP in aqueous media occurs to phosphate oxygens at pH < 4.0, to O2′ and O3′ at pH >9.5, with no interaction occurring between 4.0 and 9.5;[8,9] (ii) interactions of Et_2Sn^{2+} with the pyrimidine nucleotides, 5′-CMP and 5′-UMP occur to phosphate oxygens between pH = 0.5–3.5 and to ribose oxygens for pH > 9.0;[6] (iii) in the Me_2Sn^{2+} – 5′-GMP system binding to phosphate oxygens occurs at pH <8, and coordination to ribose oxygens at pH >9.0; there is no interaction between 8 and 9.[7] The conclusions from solution studies, particularly that of Ghys *et al*.,[6] was that the coordination of tin, at low pH values, was 6. From frozen solutions of Me_2Sn^{2+} and 5′-AMP, Mössbauer spectra indicated bidentate phosphate coordination, as well as the presence of tin-hydroxyl bonds.[9,10]

Solid R_2Sn^{2+}—nucleotide complexes have also been isolated from low pH media. While suitable crystals of complexes have yet to be obtained for X-ray crystallography, spectroscopy (Mössbauer, NMR etc.) invariably supports Sn–phosphate bonds, e.g., as in $Bu_2Sn(5'\text{-GMP})^{\bullet}H_2O$,[21,22] $Bu_2Sn(5'\text{-AMP})^{\bullet}H_2O$,[21,22] $(Et_2Sn)_2(5'\text{-IMP})_2{}^{\bullet}2(H_2O)$,[8,9] $(Et_2Sn)_3(5'\text{-CMP})_2(OH)_2{}^{\bullet}H_2O$,[8,9] $[Et_2Sn(5'\text{-CMP})(OH)Cl]_2$,[6] $\{[Et_2Sn(5'\text{-UMP})_2\}_2O]_2$,[6] and $Me_2Sn(5'\text{-AMP})^{\bullet}2(H_2O)$.[7] Solid complexes, formed from Et_2Sn^{2+} with 5′-AMP, 5′CMP or 5′GMP, have also been examined by ^1H NMR after dissolution in DMSO.[23] Ghys *et al*. indicated that the solid isolated at high pH from the Et_2Sn^{2+} and 5′-CMP interaction was [Et_2Sn(O,O,-ribosyl-5′-CMP].[6] The formulae of these solid complexes were generally, but individually, derived from combinations of spectral techniques and other data, including elemental analyses. While definite structures remain unconfirmed, some highly probable and inspired assumptions, based on structures for known compounds, have been made. Generally the tin environments for the diorganotin–nucleotide complexes are considered to be similar in both solution and solid-state phases.[6]

We now report the results of a semi-empirical theoretical study, AMI, of the interactions of dialkyldiaquotin cations, $[R_2Sn(H_2O)_2]^{2+}$ [R = $H(CH_2)_n$: $n = 1-8$)], mainly with the nucleotide, 5′- AMP, but also to a lesser extent with 5′- CMP, 5′-GMP 5′-UMP and 5′-IMP.

EXPERIMENTAL METHODS

The present study was carried out on a 256 MHz Intel Pentium III computer with 800 Mb of RAM memory. The molecular modeling used semiempirical AM1 calculations contained in the package of computational programs TITAN (Wavefunction Inc. and Schrödinger Inc., Irvine, CA).

RESULTS AND DISCUSSION

Nucleotides

Initially, equilibrium energies and thermodynamic properties of the nucleosides were calculated. The starting point for the calculations was supplied by *The Nucleic Acid Database* (http://ndbserver.rutgers.edu).[24] All calculations were carried out considering gaseous phase in the absence of a dielectric medium. The free standard energies of formation were calculated from the standard heats of formation and the standard entropies, using $\Delta G^{o}_{f} = \Delta H^{o}_{f} - T\Delta S^{o}_{f}$ (T = 298.15 K). Values are shown in Fig. 2.

Table 1 lists the calculated the HOMO energies for the nucleotides. For all the nucleotides, the calculated densities were found to be highest on the sugar oxygen atoms, the phosphate and the base nitrogen, i.e. on the donor sites, as expected.

Table 1. HOMO energies of the nucleotides

Nucleotide	HOMO energy (eV)
5′-AMP	−8.76010
5′-CMP	−9.60527
5′-GMP	−8.64401
5′-UMP	−10.1625
5′-IMP	−9.00185

DOI: 10.1002/aoc

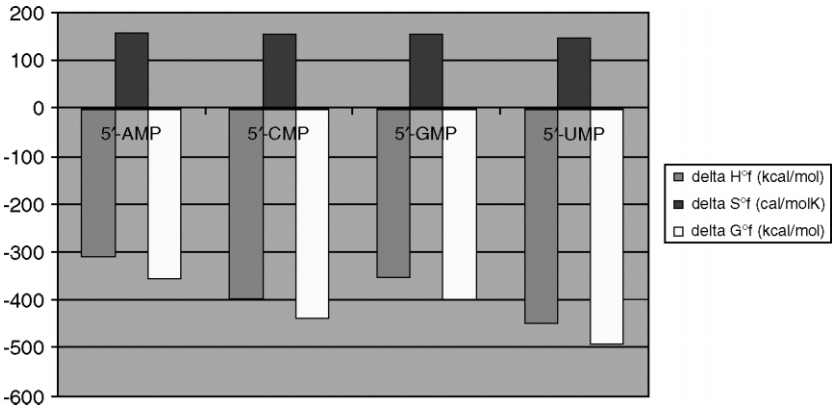


Figure 2. Standard values of entropy, heat of formation and Gibbs free energy calculated for the nucleotides.

Dialkyltin dichlorides

Heats of formation, standard entropies of formation and Gibbs free energies of formation of the diorganotin dichlorides were initially calculated. From the values calculated, linear regression analysis provided equations (1)–(3) for R_2SnCl_2 [$R = H(CH_2)_n : n = 1–8$]. The lowest unoccupied orbitals, LUMO, for R_2SnCl_2 were calculated to be all similar, with values of -1.703 ± 0.13 eV.

$$\Delta S^o_f = -0.0264n^2 + 14.278n + 84.3179 \text{ cal/mol K} \quad (1)$$

$$\Delta H^o_f = -0.1443n^2 - 12.077n - 61.24 \text{ cal/mol K} \quad (2)$$

$$\Delta G^o_f = -0.1364n^2 - 16.334n - 86.379 \text{ cal/mol K} \quad (3)$$

where n is the number of carbon atoms in $R = H(CH_2)_n$.

$[R_2Sn(H_2O)_2]^{2+}$ cations

As indicated in the Introduction, organotin halides undergo hydrolysis to hydroxyl- and oxy-diorganotin compounds or hydrated dialkyltin cations, $[R_2Sn(O_2H)_2]^{2+}$ in aqueous media to varying extent depending on the pH.[6,10,13,14] As we are concerned with interactions of diorganotin compounds with the nucleotides in aqueous media at physiological pH, it clearly is appropriate to consider some hydrolysed derivative of the dialkyltin dichloride rather than the dialkyltin dichlorides themselves. From all the possible species, we have just considered hydrated dialkyltin cations, $[R_2Sn(O_2H)_2]^{2+}$ in the calculations which follow. The LUMO and HOMO energies calculated for these species are shown diagrammatically in Fig. 3.

Sites of interaction in the nucleotides with $[R_2Sn(H_2O)_2]^{2+}$

Calculations were carried out on the interactions of $[R_2Sn(H_2O)_2]^{2+}$ at the following specific sites in the nucleotide:

1. Nitrogen in the purine bases (N7) or pyrimidine bases (N3). These are the sites of reactions with *cis*-$Pt(NH_3)_2Cl_2$. Coordination of a tin species to the nitrogen atom of a purine ring has only been detected in methanol solutions.[20]
2. Oxygen atoms, O(2) of the ribose moiety. As indicated in the Introduction, this appears to be a site of coordination by a tin species at high pH values, i.e. when the hydroxyl groups are de-protonated.[8,9,15]
3. Oxygen atoms, O(3) of the ribose moiety. Interactions are potentially similar to those mentioned for O2.

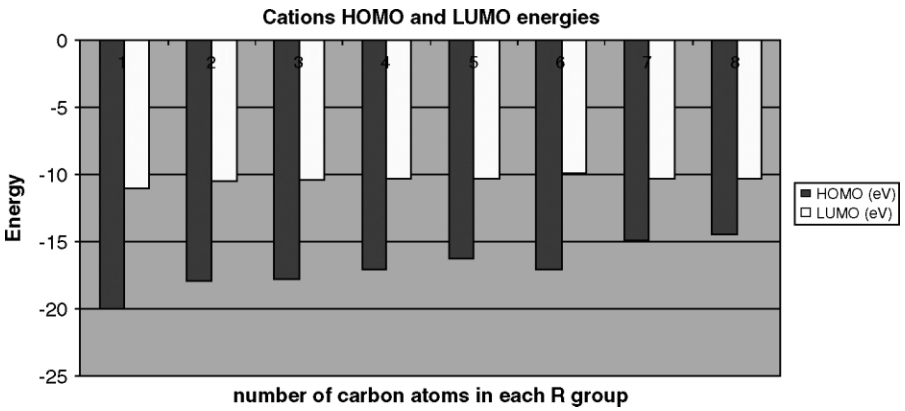


Figure 3. Frontier orbital energies of dialkyldiaquotin cations calculated using AM1.

DOI: 10.1002/aoc

4. Oxygen atoms, O(4), the ring oxygen of the ribose moiety. There are no experimental data which suggest that this site is used in coordination with a tin centre.
5. Phosphate oxygens. As pointed out in the Introduction, these can be the target sites in the nucleotide at higher pH values.[21–23]

Calculations were carried out with the nucleotides in the dianionic form, i.e. $ROP(O)(O^-)_2$ form, as present at physiological pH. The charge of each coordination complex, obtained from interaction at a specific site in the dianionic form of the nucleotide with $[R_2Sn(H_2O)_2]^{2+}$, was adjusted to zero, if necessary, by the addition or subtraction of hydrogen atoms to the nucleotide phosphate oxygen atoms. For each interaction, the equilibrium geometry, standard heat of formation, standard entropy of formation, free Gibbs energy of formation, HOMO energy, LUMO energy and potential density graphs were calculated.

Interactions between $[R_2Sn(H_2O)_2]^{2+}$ and dianionic 5′-AMP

The standard free energies of formation of the complexes formed from interaction of $[R_2Sn(H_2O)_2]^{2+}$ at different sites in 5′-AMP were determined. Four distinct types of complex were calculated; see Fig. 4. It must be pointed out that the calculated structures are far from ideal polyhedra, and must be considered as being highly distorted. In many calculations, the optimized geometry obtained after the various cycles of calculations differed greatly from the initial proposed structure. The heat of formation was used as the parameter to determine the most stable compound formed from all the possible interaction sites with $[R_2Sn(H_2O)_2]^{2+}$. In no case was the heterocyclic nitrogen atoms or the ribose ring oxygen found to be the preferred reaction sites. This is in agreement with experimental results. In most cases, little energy differences were found between different $\{[R_2Sn(H_2O)_2]^{2+} - 5'\text{-AMP}\}$ complexes, suggesting that solvation effects and solubilities in solution will have profound influences on what is actually obtained in solution and in the solid state, respectively.

The van der Waals radii of Sn and O are 2.17 and 1.52 Å, respectively, while a covalent single Sn–O bond is about 2.0 Å. Table 2 lists all the calculated Sn–O lengths for each complex, including those involving the aquo ligands, which fall well below the sum of the van der Waals radii sum for Sn and O. All the listed Sn–O bonds and the two Sn–C bonds have been taken into account, when deciding the distorted geometries about tin. As shown in Table 2, the 5′-AMP can act as a monodentate or chelating ligand. Monodente nucleotides (in type III and IV complexes; see Fig. 4) were calculated for $[R_2Sn(H_2O)_2]^{2+}$ [$R = H(CH_2)_n$; $n = 4–6$]. Especially noteworthy were the distorted tetrahedral, four coordinated complexes with $[R_2Sn(H_2O)_2]^{2+}$ [$R = H(CH_2)_n$; $n = 4$ and 5].

Two forms of chelate can be designated, one involving a phosphate and a ribose oxygen atoms [providing an eight-membered chelate, utilizing O(3)] or involving two ribose oxygens [providing a five-membered chelate, involving O(2) and O(3)]; see Fig. 4. No other chelate was calculated to be a possibility. Of the two types of calculated chelated structures, the five-membered chelate is very commonly found in organotin chemistry, while the eight-membered chelate is extremely rare. Especially for the complexes calculated to have eight-membered chelated structures as the most stable gas phase structures, it is considered highly probable that solvation effects and entropy effects in solution could result in different species being the more stable in solution.

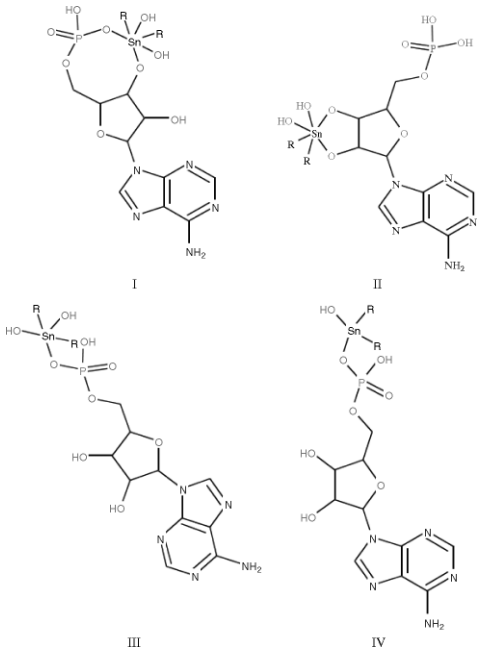


Figure 4. The four types of complexes calculated for the $[R_2Sn(OH_2)_2]^{2+}$ interactions with the nucleotides. The complexes are drawn to indicate overall zero charge; only the number of protons is important not their positioning.

Sites of interaction of $[R_2Sn(H_2O)_2]^{2+}$ with 5′-GMP, 5′-UMP, 5′-UMP and 5′-IMP

Similar and complete calculations were carried out for 5′-GMP, 5′-UMP, 5′-UMP and 5′-IMP but are not reported here. The 5′-GMP interactions followed the 5′-AMP interactions with regard to the phosphate and ribose hydroxyl oxygens, O(2) and O(3) being the most important donor sites. Calculations of the interactions between $[R_2Sn(H_2O)_2]^{2+}$ and the pyrimidine-containing 5′-UMP also indicated similar trends; however, for interactions with 5′-CMP, by far the major tendency was interactions with the ribose oxygen atoms, giving rise to five-membered chelate rings, with the phosphate oxygens much less important. 5′-IMP interactions showed a preference for phosphate as the best attack site, but in two cases (R = ethyl, propyl), eight-membered chelate rings were observed as the most stable strucutre. It was also noticed that for R = heptyl, the best site of attack was the ribose nitrogen.

DOI: 10.1002/aoc

Table 2. Complexes formed between $[R_2Sn(H_2O)_2]^{2+}$ and $[5'\text{-AMP}]^{2-}$: selected calculated geometry parameters and heats of formation

	Selected calculated geometric parameters				
Complex type[a]	Sn–O bonds[b]	Bond length, (Å)	Other parameters (Å, deg)	Geometry at Sn: [chelate ring size][c]	Heat of formation (kcal/mol)
$[(CH_3)_2Sn(H_2O)_2(5'\text{-AMP})]$ (I)	Sn–O3	2.107	C–Sn–C = 129.43	Octahedral [8 atom]	−410.845
	Sn–OP	2.115	OP–Sn–O3 = 88.46		
	$Sn-OH_2(1)$	2.493	Sn–O2 = 4.271		
	$Sn-OH_2(2)$	2.457			
$[(C_2H_5)_2Sn(H_2O)_2(5'\text{-AMP})]$ (II)	Sn–O2	2.128	C–Sn–C = 125.02	Octahedral [5 atom]	−425.024
	Sn–O3	2.130	O2–Sn–O3 = 77.50		
	$Sn-OH_2(1)$	2.487	Sn–OP = 4.533		
	$Sn-OH_2(2)$	2.484			
$[(n\text{-}C_3H_7)_2Sn(H_2O)_2(5'\text{-AMP})]$ (II)	Sn–O2	2.127	C–Sn–C = 122.56	Octahedral [5 atom]	−436.343
	Sn–O3	2.123	O2–Sn–O3 = 77.53		
	$Sn-OH_2(1)$	2.477	Sn–OP = 4.591		
	$Sn-OH_2(2)$	2.504			
$[(n\text{-}C_4H_9)_2Sn(H_2O)(5'\text{-AMP})]$ (IV)	Sn–OP	2.067	C–Sn–C = 123.09	Tetrahedral	−454.784
	$Sn-OH_2(1)$	2.052	Sn–O3 = 5.069		
			Sn–O2 = 7.439		
			$Sn-OH_2(2)$ = 7.815		
			Sn–O4 = 7.242		
$[(n\text{-}C_5H_{11})_2Sn(H_2O)(5'\text{-AMP})]$ (IV)	Sn–OP	2.074			
	$Sn-OH_2(1)$	2.052	C–Sn–C = 125.30	Tetrahedral	−466.722
			$Sn-OH_2(2)$ = 4.971		
			Sn–O4 = 6.857		
			Sn–O3 = 6.373		
$[(n\text{-}C_6H_{13})_2Sn(H_2O)_2(5'\text{-AMP})]$	Sn–OP	2.086	C–Sn–C = 124.81	Trigonal bipyramid	−479.353
	$Sn-OH_2(2)$	2.444	Sn–O3 = 6.402		
(III)	$Sn-OH_2(1)$	2.059	Sn–O2 = 8.051		
			Sn–O4 = 5.506		
$[(n\text{-}C_7H_{15})_2Sn(H_2O)_2(5'\text{-AMP})]$ (I)	Sn–OP	2.111	C–Sn–C = 134.02	Octahedral [8 atom]	−491.459
	Sn–O3	2.106	O3–Sn–OP = 87.35		
	$Sn-OH_2(1)$	2.517	Sn–O2 = 4.281		
	$Sn-OH_2(2)$	2.463			
$[(n\text{-}C_8H_{17})_2Sn(H_2O)_2(5'\text{-AMP})]$ (II)	Sn–O2	2.127	C–Sn–C = 125.09	Octahedral [5 atom]	−505.487
	Sn–O3	2.123	O2–Sn–O3 = 77.34		
	$Sn-OH_2(1)$	2.486	OP–Sn–O4 = 53.01		
	$Sn-OH_2(2)$	2.505	Sn–O4 = 6.135		

[a] Type of complex as shown in Table 2;
[b] all Sn–O distances less than 3 Å are considered as bonds:
[c] chelated nucleotide ligand.

CONCLUSIONS

The results obtained are in general agreement with the reported experimental solution and solid-state findings in terms of the preferred sites of the interactions of organotin species with the nucleotide molecules, being the ribosyl hydroxyl oxygen atoms and the phosphate oxygen atoms. The semi-empirical gas phase calculations allowed the most stable structures to be evaluated. For most $[R_2Sn(H_2O)_2]^{2+}$—nucleotide pairings, energy differences were relatively small for primary attack at the ribosyl hydroxyl oxygens or the phosphate oxygen atoms. Solvation and solubility effects can readily result in different structures being isolated in solution and the solid state.

Acknowledgements

J.L.W. thanks CNPq for financial support.

REFERENCES

1. Keppler BK. *Metal Complexes in Cancer Chemotherapy*. VCH: Weinheim, 1993.

2. Bloemink M, Reedijk J. In *Metal Ions in Biology*, Siegel A, Siegel H (eds). Marcel Dekker: New York, 1996; 641.
3. Gielen M. *Co-ord. Chem. Rev.* 1996; **151**: 41.
4. Kovala-Demetertzi D, Dokorou VN, Jasinski JP, Opolski A, Wiecek J, Zervou M, Demertzis MA. *J. Organomet. Chem.* 2005; **689**: 1800.
5. Crowe AJ. *Drugs Future* 1987; **12**: 255.
6. Ghys L, Biesemans M, Gielen M, Garoufis A, Hadjiliadis N, Willem R, Martins JC. *Eur. J. Inorg. Chem.* 2000; 513.
7. Jancso A, Nagy L, Moldrheim E, Sletten E. *J. Chem. Soc., Dalton Trans.* 1999; 1587.
8. Yang Z, Bakas T, Sanchez-Diaz A, Charalampopoulos C, Tsangaris J, Hadjiliadis N. *J. Inorg. Biochem.* 1998; **72**: 133.
9. Nafisi S, Sobhanmanesh A, Esm-Hosseini M, Alimoghaddam K, Tajmir-Riahi HA. *J. Mol. Struct*. 2005; **750**: 22.
10. Jankovics H, Nagy L, Buzas N, Pellerito L, Barbieri R. *J. Inorg. Biochem.* 2002; **92**: 55.
11. De Stefano D, Gianguzza A, Giuffre O, Piazzese D, Orecchio S, Sammartano S. *Appl. Organomet. Chem.* 2004; **18**: 653.
12. Barbieri R, Silvestri A, Piro V. *J. Chem Soc., Dalton Trans.* 1990; 3605.
13. Barbieri R, Silvestri A. *J. Inorg. Biochem.* 1991; **41**: 31.
14. Piro V, di Simone F, Madonia G, Silvestri A, Guiliani AM, Ruisi G, Barbieri R. *Appl. Organomet. Chem.* 1992; **6**: 537.
15. Barbirei R, Silvestri A, Guiliani AM, Piro V, Di Simone F, Madona G. *J. Chem. Soc., Dalton Trans.* 1992; 585.
16. Barbieri R, Alonzo G, Herber RH. *J. Chem. Soc., Dalton Trans.* 1987; 789.
17. Natsume T, Aizawa SI, Hatano K, Funahash1 S *J. Chem. Soc., Dalton Trans.* 1994; 2749.
18. Arena G, Purrello R, Rizzarelli E, Gianguzza E, Pellerito L. *J. Chem. Soc., Dalton Trans.* 1989; 773.
19. Molloy KC. *Chemistry of Tin*, 2nd edn, Smith PJ (ed.). Blackie: Oxford, 1998; 138.
20. Pellerito L, Nagy L. *Coord. Chem.Rev.* 2002; 111.
21. Atkinson A, Rodriquez MD, Shewmaker TE, Walmsley JA. *Inorg. Chim. Acta* 1999; **285**: 60.
22. Barone G, Ramusino MC, Barbieri R, La. Manna G. *J. Mol. Struct. (Theochem)* 1999; **469**: 143.
23. Li Q, Yang P, Hua E, Tian C. *J.Coord. Chem.* 1991; **40**: 227.
24. Schäfer L, Ewbank JW. In *Molecular Orbital Calculations for Biological Systems*. Oxford University Press: New York, 1998.

DOI: 10.1002/aoc