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Redox-active cytotoxic diorganotin(IV) cycloalkylhydroxamate complexes with different ring sizes: Reduction behaviour and theoretical interpretation

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ABSTRACT

Two series of new diorganotin(IV) cycloalkylhydroxamate complexes with different ring sizes (cyclopropyl, cyclobutyl, cyclopentyl and cyclohexyl), formulated as the mononuclear $[R_2Sn(HL)_2]$ (1:2) (**a**, R = ^{n}Bu and Ph) and the polymeric $[R_2SnL]_n$ (1:1) (**b**, R = ^{n}Bu) compounds, were prepared and fully characterized. Single crystal X-ray diffraction for $[^nBu_2Sn\{C_5H_9C(O)NHO\}_2]$ (**3a**) discloses the *cis* geometry and strong intermolecular NH···O interactions. The *in vitro* cytotoxic activities of the complexes were evaluated against HL-60, Bel-7402, BGC-823 and KB human tumour cell lines, the greater activity concerning $[^nBu_2Sn(HL)_2]$ [HL = $C_3H_5C(O)NHO$ (**1a**), $C_6H_{11}C(O)NHO$ (**4a**)] towards BGC-823. The complexes undergo, by cyclic voltammetry and controlled-potential electrolysis, one irreversible overall two-electron cathodic process at a reduction potential that does not appear to correlate with the antitumour activity. The electrochemical behaviour of $[R_2Sn\{C_5H_9C(O)NHO\}_2]$ [R = ^{n}Bu (**3a**), Ph (**7a**)] was also investigated using density functional theory (DFT) methods, showing that the ultimate complex structure and the mechanism of its formation are R dependent: for the aromatic (R = Ph) complex, the initial reduction step is centred on the phenyl ligands and at the metal, being followed by a second reduction with Sn – O and Sn – C ruptures, whereas for the alkyl (R = ^{n}Bu) complex the first reduction step is centred on one of the hydroxamate ligands and is followed by a second reduction with Sn – O bond cleavages and preservation of the alkyl ligands. In both cases, the final complexes are highly coordinative unsaturated Sn^{II} species with the *cis* geometry, features that can be of biological significance.

1. Introduction

The anticancer activity of organotin(IV) compounds has been widely investigated [1–23]. Those with biologically active ligands have attracted a particular attention towards the design of potential antitumour agents. Hydroxamic acids, as inhibitors of 5-lipoxygenase, can behave as strong bidentate O-donors with bioactivity. Many organotin(IV) hydroxamates have been prepared [17–27], and some of them possess strong antitumour activities against several tumour cell lines. Within our contribution to this field [16–23], we synthesized a series of diorganotin(IV)/arylhydroxamate complexes with a variety of substituents at the benzene ring (OH, NH_2, OCH_3, NO_2, Cl, F) with the aim of a structural optimization of the ligand and correlation with bioactivity. Such structure–activity relationships indicated that: (i) polymeric diorganotin/arylhydroxamate $[R_2SnL]_n$ complexes with R = ^{n}Bu are more active than related mononuclear $[R_2Sn(HL)_2]$ complexes; and (ii) the inhibitory potencies of the diorganotin(IV) arylhydroxamates are related not only to their lipophilic properties but also to the electron-withdrawing ability of the aryl ring (in L).

Encouraged by those results and taking into account that cycloalkyl groups can display better hydrophobicity than aryl groups and different electronic properties, we investigated the effect of a cycloalkyl moiety in the arylhydroxamate ligand. The selected cycloalkylhydroxamic molecules and their obtained organotin(IV) derivatives are summarized in Fig. 1. The choice of the *n*-dibutyltin(IV) and diphenyltin(IV) assemblies is based upon a previously established optimal balance between cytotoxicity, water solubility and lipophilicity. The *in vitro* cytotoxic activities of the novel compounds were essayed against four different human cell lines [promyelocyticfina leukemic (HL-60), hepatocellular carcinoma (Bel-7402), nasopharyngeal carcinoma (KB) and gastric carcinoma (BGC-823)].

Moreover, the 'activation by reduction' mechanism of metal-based drugs has become popular with platinum(IV) and ruthenium(III) compounds which, as with other metals, can exist in rather inert high oxidation states in aqueous solution but are more labile and active in lower

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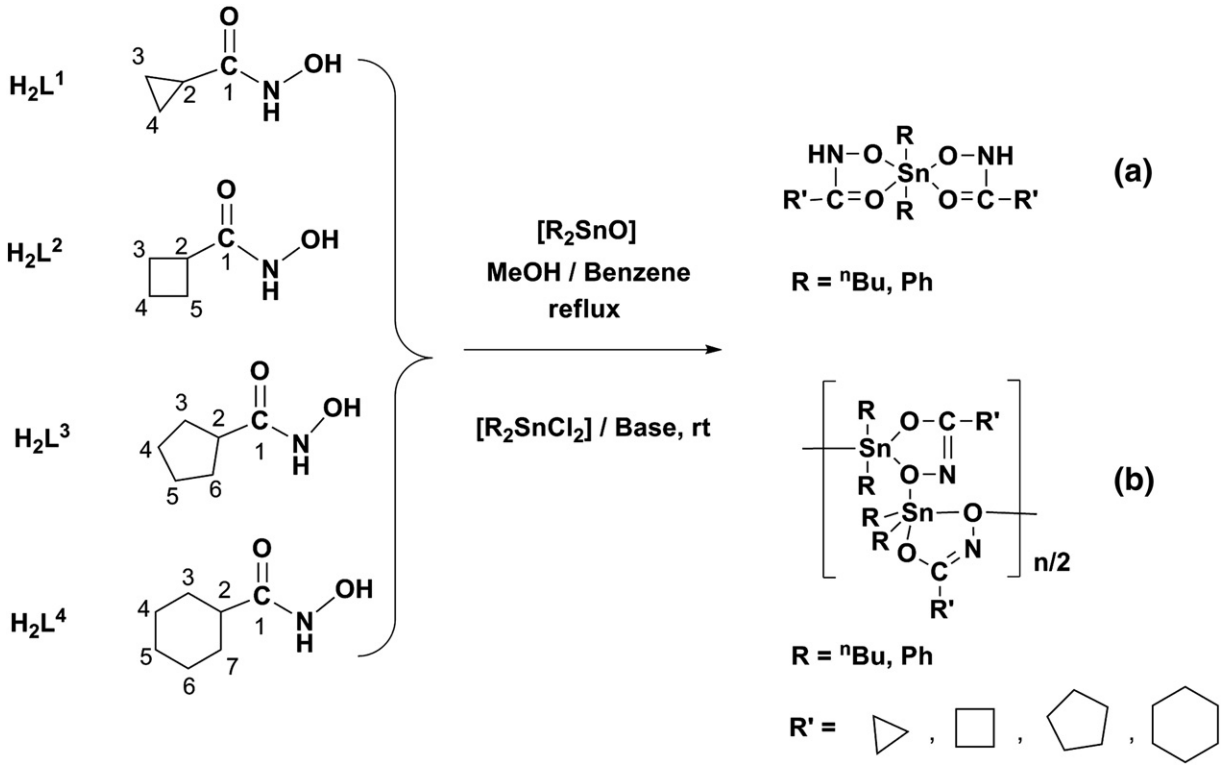

Fig. 1. Two classes of diorganotin(IV) cycloalkylhydroxamates: (a) $[R_2Sn(HL)_2]$ [R = ^{n}Bu; R′ = cyclopropyl (**1a**), cyclobutyl (**2a**), cyclopentyl (**3a**), and cyclohexyl (**4a**). R = Ph; R′ = cyclopropyl (**5a**), cyclobutyl (**6a**), cyclopentyl (**7a**), and cyclohexyl (**8a**)]; (b) $[R_2SnL]_n$ [R = ^{n}Bu; R′ = cyclopropyl (**1b**), cyclobutyl (**2b**), cyclopentyl (**3b**), and cyclohexyl (**4b**)].

oxidation states. The reduction to Pt^{II} and Ru^{II} is believed to be essential for the anticancer activity of many Pt^{IV} and Ru^{III} complexes [28–33]. However, the mechanism of action of tin(IV)-based drugs is usually still unknown, but insights are expected to be provided by electrochemical and theoretical studies.

In fact, we recently prepared various organotin(IV) complexes bearing the 1-(4-chlorophenyl)-1-cyclopentanecarboxylate ligand and preliminary explored, by theoretical/electrochemical studies, a possible relationship between electron-transfer induced reactions and bioactivity [16], thus disclosing the involvement, in the reduction

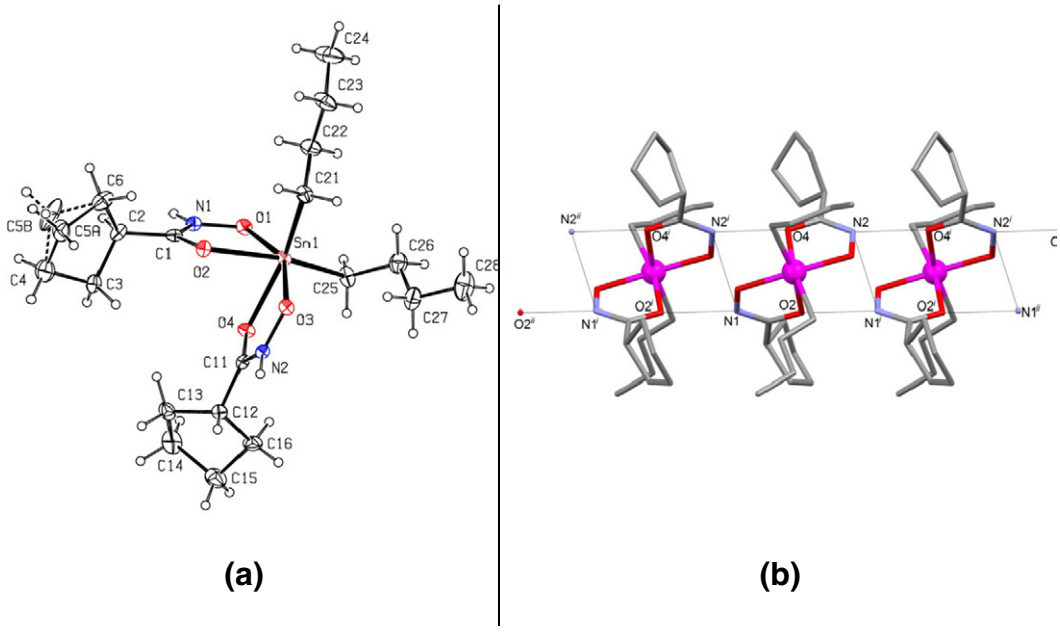

Fig. 2. (a) Molecular structure of **3a** with disorder model (shown with dashed bonds) and atomic numbering scheme. Selected bond distances (Å) and angles (°): O1 – Sn1 2.098(3), O2 – Sn1 2.278(3), O3 – Sn1 2.101(3), O4 – Sn1 2.288(3), C21 – Sn1 2.154(4), C25 – Sn1 2.159(4) , O1 – N1 1.369(5), O3 – N2 1.377(4), C1 – N1 1.300(5), C1 – O2 1.277(5), C11 – N2 1.305(5), C11 – O4 1.277(5); O1 – Sn1 – O2 73.72(11), O3 – Sn1 – O4 74.10(10), O1 – Sn1 – O3 149.29(12), C21 – Sn1 – C25 108.21(18), C21 – Sn1 – O4 162.15(15) C25 – Sn1 – O2 160.57(14). (b) Fragment of the crystal packing diagram of **3a** showing the interlinkage of the molecules through strong N – H···O contacts resulting in the formation of 1D chains. Hydrogen bond interactions [d(D···A) (Å), ∠(D – H···A) (°)]: N1 – H1···O2 2.817(5), 160; N2 – H2A···O4 2.845(5), 159. Symmetry operators for generating equivalent atoms: (*i*) x,1/2 − y,−1/2 + z; (*ii*) x,y,−1 + z.