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Theoretical investigation of organotin(IV) complexes of substituted benzohydroxamic acids

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ABSTRACT

The complexing abilities of *para*-substituted benzohydroxamates to the tin metal center of organotin(IV) ions have been investigated using DFT, since organotin(IV) compounds have been touted as promising anti-cancer agents. We have studied the coordination structures of Sn(IV) complexes (R_2SnL_2) with organoligands (R = Me, Et, *n*-Bu) and *para*-substituted benzohydroxamate ligands (L) so as to study the effect of electron withdrawing (Cl, F, NO_2) and electron donating substituents (OCH_3, NH_2) in the ligand as well as in the alkyl group of the organotin compound. The structures of all the complexes are found to be intermediate between distorted octahedron and bicapped tetrahedron, in agreement with experiment. We have analyzed all the complexes in detail, using their Mayer bond orders, ESP charges, HOMO-LUMO plots and Fukui indices. Of all the complexes, the one having methyl as the alkyl group and the *para*-amino benzohydroxamate ligand is found to be the most stable. This is owing to the stronger ionic and covalent interaction of Sn(IV) with the *para*-amino benzohydroxamate ligand and methyl group, respectively.

1. Introduction

Metal-based drugs are known for their potency and have been in use as therapeutic agents. They are used for the treatment of a variety of diseases, ranging from cancer, rheumatoid arthritis to inflammatory and cardiovascular diseases [1,2]. This therapeutic property of metal-based drugs prompted researchers all over the world to look for new metal-based compounds with superior activities, especially against tumors [3].

Among the metal-based compounds, organotin(IV) compounds form a widely studied class because of their apoptotic inducing character [4,5]. Organotin(IV) compounds exhibit remarkable anti-tumor, anti-bacterial, anti-viral, anti-inflammatory and anti-tuberculosis activities [6–14]. Recently, many researchers have reported the cytotoxic effects of organotin(IV) compounds against various cancer cell lines, including human tumor cell lines [15–21]. One more advantage of these compounds is that they are useful in overcoming the multidrug resistance generally associated with chemotherapeutic treatment by other metal-based drugs [6]. Despite their promising activity against a wide range of tumors, organotin(IV) compounds-related studies have failed to reach the clinical trials due to their severe neurotoxicity [22], the mechanism of which is still a mystery [23]. However, their extra-ordinary anti-cancer activity surmounts their negative effects [24]. The aim has now shifted to developing more specific organotin(IV)-based anti-tumor agents, keeping these disadvantages in mind.

In the search for more effective carriers for organotin(IV), interactions of organotin(IV) acceptors with the structurally and biologically relevant class of hydroxamic acids have been extensively studied [25–27]. Most of the bioactivities of hydroxamic acids are due to their chelating behavior [28–33]. Among the hydroxamic acids, complexes of benzohydroxamic acid (BHA) and its derivatives with diorganotin (IV) acceptors were found to be effective against a series of human tumor cell lines *in vitro* [34–37]. The interaction of BHA with organotin (IV) has been studied extensively because BHA itself is a nucleoside reductase inhibitor, due to which it has anti-cancer activity [38]. Sn(IV) complexes (R_2SnL_2) have been studied with organoligands (R = Me, Et, *n*-Bu) and *para*-substituted BHA ligands (L). These complexes were characterized by FT-IR, ^1H, ^{13}C, ^{119}Sn NMR spectroscopies, elemental analysis, melting point measurements and X-ray diffraction analysis [30,31]. Their anti-tumor activity *in vitro* was tested on various human tumor cell lines (immature granulocyte leukemia (HL-60), nasopharyngeal (KB), hepatocellular (Bel-7402) and ovarian (Hela) carcinomas) and mouse tumor cell lines (lymphocyte carcinomas B & T). X-ray studies showed that BHA forms complexes with diorganotin(IV) having structures intermediate between distorted octahedron and bicapped tetrahedron, as shown in Scheme 1 [30,31].

Since the biological activity of organotin(IV) compounds is greatly influenced by their molecular and electronic structure, we have studied

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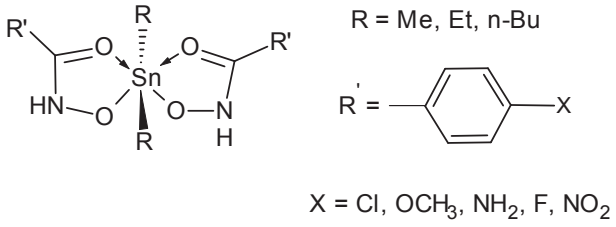


Scheme 1. The mode of binding of complexes of diorganotin(IV) with BHA and its derivatives.

the coordination structures of the Sn(IV) complexes (R_2SnL_2) with organoligands (R = Me, Et, *n*-Bu) and *para*-substituted benzohydroxamate ligands (L), which have so far not been investigated theoretically, though extensive experimental data are available [30,31]. The effect of the R and L groups on the stability of the resulting complex is also analyzed in this work. The structural properties of the complexes are also studied in detail.

2. Computational details

The GGA-PBE functional [39] was used for our calculations using the DMol^3 code [40–44] in the Materials Studio 5.5 package. The numerical basis sets used were of double-ζ quality plus polarization functions (DNP), the numerical equivalent of the Gaussian 6-31G** basis set. The integration grid was set to Fine. The core was modeled using DFT semi-core pseudopotentials (DSPP) [44]. The complexes were geometry optimized and their Gibbs energies calculated using standard thermochemical equations. The bond orders were calculated using Mayer's procedure [45]. The charges reported here are the electrostatic potential fitted (ESP) charges [46]. For aqueous phase calculations, we took the optimized geometries of all molecules in the gas phase as our initial geometries, and employed the conductor like screening model (COSMO) [47] for computing the solvation energies.

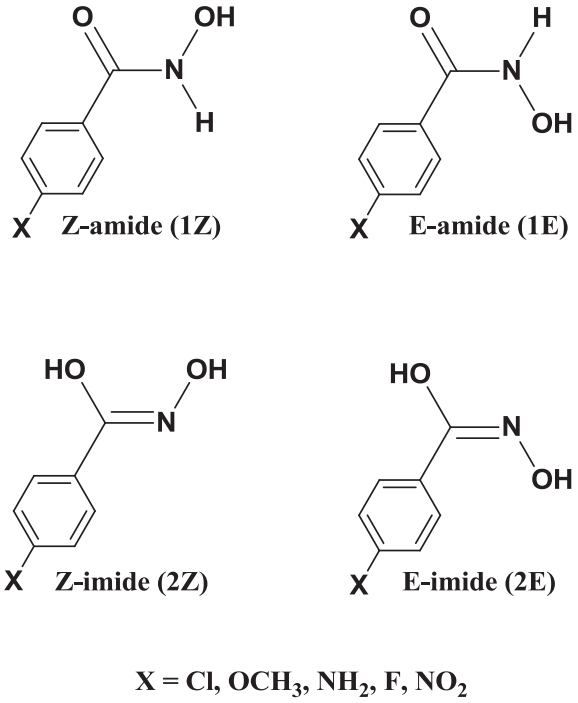
Dispersion corrections were applied using DEFT-SEDC, DFT semi-empirical dispersion interaction correction using the TS scheme [48,49]. For some of the calculations, we also used the hybrid PBE0 functional [50,51] and the dispersion corrected B3LYP hybrid functional (B3LYP-D3) [52–54]. For both these calculations, the LACVP** basis set was used. This uses the LAN2DZ (Los Alamos National Laboratory 2 Double-Zeta) Effective Core Pseudopotential (ECP) for Sn (IV) and the standard basis 6-31G** for the remaining atoms [55]. These computations were performed using Jaguar, version 9.6 [56], available from Schrodinger, Inc., New York, NY, in the Schrödinger 2017 Materials Science package.

3. Results and discussion

3.1. Structures of benzohydroxamic acids and their anions

Before studying the molecular structures of the complexes, it is imperative to study the conformational behavior of the various BHAs. As has already been discussed in detail in our earlier work [57], BHA can exhibit amide/ imide tautomerism. It can also adopt either the *Z* (*cis*) or *E* (*trans*) conformation resulting from free rotation about the C–N bond (Scheme 2). The *Z*-amide (1Z) form of BHA was found to have the least energy, both in the gas phase and in aqueous solution, and the *E*-imide (2E) form the highest energy, and was predicted to be present only in trace amounts at room temperature [57]. We therefore computed the relative energies of the three forms of the substituted BHA studied in this work, and found that, here too, the Z-amide (1Z) form has the lowest energy in both phases (Table S1, Supplementary Information, SI). The optimized structures of the stable ***Z*** forms of the substituted BHAs are shown in Fig. S1 and Table S33 (SI).

For understanding the chelating properties of the BHAs, it is important to examine their acid-base properties. The BHAs can act either as N-acids or O-acids, depending upon whether the –NH or the –OH proton is deprotonated from **1*Z*** (Scheme 2). As for the parent acid [57], the N-anion is found to be lower in energy in all cases (Table S2, SI), but, since hydroxamates coordinate in the (O,O) coordination mode [29], it is the O-anion that participates in the complexation. In the gas phase, this anion is higher in Gibbs energy by 13–14 kcal mol^{-1} (Table S2, SI), but this difference reduces to half this value in aqueous solution.



Scheme 2. Tautomers and conformers of *para*-substituted BHAs.

3.2. Structures of the complexes

We then investigated the complexes of organotin(IV) with benzohydroxamates in the gas phase. The three alkyl groups (R = methyl, ethyl, and *n*-butyl) were taken as the primary ligands of Sn(IV), and the five *para*-substituted benzohydroxamates, having chloro, methoxy, amino, fluoro and nitro groups (X) at the *para* position of the phenyl ring (Scheme 2), constituted the secondary ligands in our present study. A total of 15 complexes were therefore investigated here.

Benzohydroxamates are known to form complexes with organotin (IV) of the type shown in Scheme 1, where the benzohydroxamate moieties bind the Sn(IV) center through both the oxygen centers (carbonyl and hydroxyl), such that the four oxygen atoms are at the equatorial position (being in the same plane as Sn(IV)) and the two alkyl groups (Me, Et, *n*-Bu) are at the axial positions, above and below the plane containing Sn(IV) and the oxygen centers [30,31]. The optimized structures of all the complexes with different R and X groups are depicted in Tables S3 and S35 (SI). The numbering scheme for the complexes is given in Scheme 3.

The electronic configuration of Sn(IV) is [Kr]4d^{10}. Since all the electrons are paired, it exists in the singlet ground state. Sn(IV) forms covalent bonds with the carbons of the R groups forming $[R_2Sn(IV)]^{2+}$ ions, and is further ligated to two benzohydroxamates through both the oxygen atoms. All the complexes optimized to a coordination structure intermediate between distorted octahedron and bicapped tetrahedron (Fig. 1 & Tables S3 and S35, SI), in coherence with the experimental results [30,31]. Also, the optimized molecular structures of all the complexes, the orientation of both the benzohydroxamate moieties with respect to each other, and the orientation of the alkyl groups with