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ORIGINAL ARTICLE

2nd Cancer Update

Theoretical investigation of inclusion complex formation of Gold (III) – Dimethyldithiocarbamate anticancer agents with cucurbit[*n* = 5,6]urils

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DFT calculation

Abstract Gold (III)-N,N-dimethyldithiocarbamate [DMDT(Au)X_2] complexes have recently gained increasing attention as potential anticancer agents because of their strong tumor cell growth–inhibitory effects, generally achieved by exploiting non-cisplatin-like mechanisms of action. The goal of our research work is to encapsulate the gold(III) dimethyldithiocarbamate complexes as anticancer with cucurbit[*n*]urils (CB[*n* = 5, 6]) by accurate calculations, to predict the inclusion complex formation of gold(III) species with cucurbiturils (CB[*n* = 5, 6]). The calculations were carried out just for the 1:1 stoichiometric complexes. Upon encapsulation, binding energy, thermodynamic parameters, structural parameters and electronic structures of complexes are investigated. The results of the thermodynamic calculations and the binding energy show that the inclusion process is exothermic and the CB[6]/[DMDT(Au)Br_2] complex is more stable than other complexes. The final geometry of CB[*n*]/drugs indicates that the drugs were expelled from the cavity of CB[*n*]. NBO calculations reveal that the hydrogen bonding between CB[*n*] and drugs and electrostatic interactions are the major factors contributing to the overall stabilities of the complexes.

1. Introduction

Since the introduction of Pt(II)-based first anticancer agents, metal complexes and organometallic compounds have been gaining growing importance in cancer therapy. The impressive clinical effectiveness of cisplatin is limited by significant side effects and by acquired or intrinsic resistance to the treatment (Kelland, 2007). Thus, classic and unconventional Pt(II) and Pt(IV) complexes have been introduced in therapy or are presently in advanced clinical trials. Moreover, innovative non-platinum metal-based antitumor agents, whose activity do

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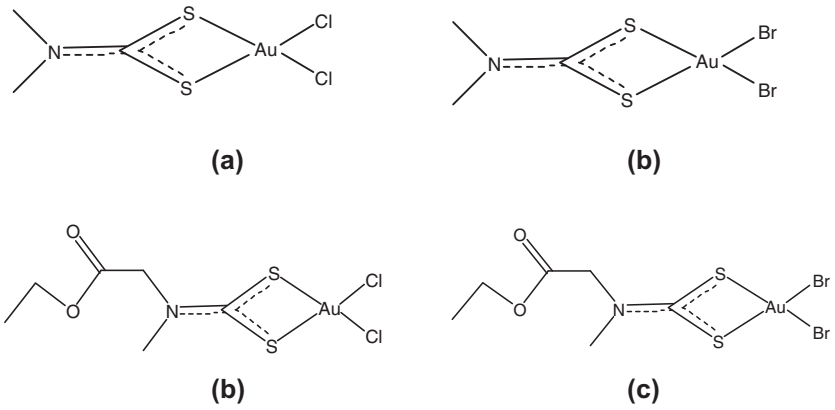

Figure 1 Gold(III) complexes with Au–S bonds (a) [DMDT(Au)Cl_2], (b) [DMDT(Au) Br_2], (c) [ESDT(Au)Cl_2] and (d) [ESDT(Au)Br_2].

not rely on direct DNA damage and may involve proteins and enzymes, have been developed (Alama1 et al., 2009). Of the non-platinum metal compounds with antitumor activity, particular interest has been focused on gold and tin derivatives, which have a common activity on mitochondria and a strong affinity to thiol groups of proteins and enzymes (Louie and Meade, 1999; Robertson and Orrenius, 2002).

Based on their structural and electronic similarity to cisplatin and cisplatin-related antitumor drugs gold(III) species represent a promising class of potential anticancer agents. However, the development of gold(III) complexes as therapeutic drugs has been hampered by their low stability under physiological conditions which remains a critical parameter in the drug development of these species. Gold(III) complexes with various ligands have been prepared and biologically investigated (Gabbiani et al., 2007; Marzano et al., 2011). Most of them are complexes with Au–N bonds (eventually containing additional Au–O and Au–Cl bonds) but also some species with Au–S or Au–C bonds and their bioactivities have been described (Ott, 2009). Gold(III) complexes (see Fig. 1 for some relevant examples) exhibited superior cytotoxic effects to cisplatin, being also active in resistant cells and induced apoptosis (Giovagnini et al., 2005; Ronconi et al., 2005). The compounds showed good stability under physiological conditions, bind readily to the DNA, inhibit both DNA and RNA synthesis and induce fast DNA lesions. Experiments on red blood cells indicated that hemolytic properties might contribute significantly to the bioactivity of the agents (Ronconi et al., 2006).

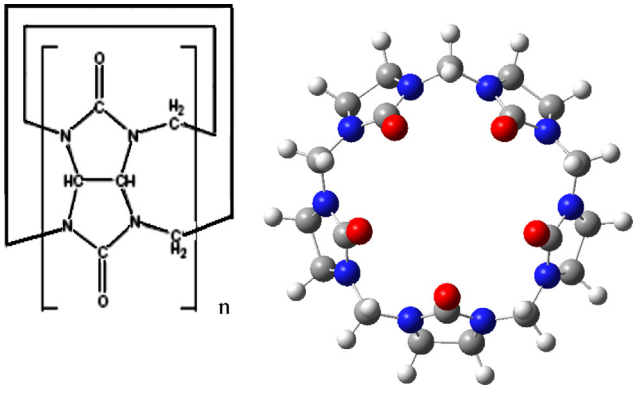

Figure 2 General structures of cucurbit[n]urils.

Cucurbit[*n*]urils (CB[*n*]), a family of pumpkin-like molecular containers, are cyclic methylene-bridged glycoluril oligomers with two portals lined by ureido carbonyl groups (Fig. 2) that provide entry to their hydrophobic cavity (Lei et al., 2010). While Cucurbit[6]uril (CB[6]) was first discovered in 1905 (Behrend et al., 1905) and its macrocyclic structure was not determined until 1981 in 2000, CB[6] was the one of the only cucurbit[*n*]uril to receive any attention as a molecule useful in the host–guest chemistry (Freeman et al., 1981). This changed upon the discovery of different sized cucurbit[*n*]urils: CB[5], CB[7], CB[8] and the isolation of free CB[10] (Kim et al., 2000; Liu et al., 2005). Their discovery has led to a rapid increase in the interest in the use of, CB[*n*] in a variety of fields including: nano machines, chromatography, and drug delivery (Wyman and Macartney, 2010).

There has been an increasing interest recently in using cyclodextrins and cucurbit[*n*]urils to aid in the delivery of molecules of biological and medicinal interest, through host–guest formation (Bali et al., 2006; Lagona et al., 2005; Faustino et al., 2011; Sancho et al., 2011). Cucurbit[*n*]urils can encapsulate a variety of molecules within their hydrophobic cavity, with the binding potentially further stabilized by favorable electrostatic and hydrogen bonding interactions with the carbonyl rimmed portals (Bali et al., 2006). Encapsulation of drugs inside a cucurbit[*n*]uril provides two benefits. Protects the drugs from degradation and increases the specificity of the drugs, and uptake into cancerous cells. Consequently, encapsulation in cucurbit[*n*]uril would protect the metal complexes such as platinum complex from reactions with plasma proteins in the bloodstream, but would not affect the reaction of the metal complex with DNA inside the cell (Bali et al., 2006). There has been increasing interest recently in using cucurbit[*n*]urils to aid in the delivery of molecules of biological and medicinal interest, through host–guest formation. Cucurbit[7]uril and cucurbit[8]uril molecules have been used to form host–guest complexes with mononuclear, dinuclear and trinuclear platinum(II) complexes (Wheate et al., 2004; Wheate, 2008; Wang and Macartney, 2008; Anconi et al., 2011). There are many reports on the theoretical studies of CB[*n*] (Marquez et al., 2004; Pichierri, 2006; Buschmann et al., 2006; Bakovets et al., 2008; Suvitha et al., 2010). Kim and coworkers have shown that the inclusion complex formation of oxaliplatin with cucurbit[7]uril has moderate cytotoxicity with a larger decrease in reactivity toward guanosine and L-methionine, respectively (Jeon et al., 2005). Gejji and coworkers, made an