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Carnosine complexes and binding energies to some biologically relevant metals and platinum containing anticancer drugs

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ABSTRACT

Pt-based anti-cancer drugs can form complexes with biological ligands other than their intended pharmacological targets. Such complexes are believed to be a major contributor to the reduction of the anti-cancer drugs' therapeutic potential and can act as potential causes of toxicity. Recently, the cytoplasmic ligand β-alanyl-L-histidine dipeptide (carnosine) was shown to act as a sequestering agent for oxaliplatin (OxPt) inhibiting its cytotoxic action most likely through the formation of complexes that are less cytotoxic than OxPt alone. In this paper, the calculated binding modes and binding energies of protonated carnosine as well as canosine complexes with various biologically relevant metal cations and some common Pt-based anti-cancer drugs both in the gas phase and in solution are presented. Theoretical evidence for the existence of protonated carnosine in a zwitterionic form is offered. Six calculated geometrical arrangements comprising general structural motifs of metal ion-carnosine complexes are presented. In all but one of these six conformers the metal ions were shown to form three bonds to each of the carnosine ligands. These six general binding motifs were found to cover the lowest energy structures of all species investigated here whether in the gas phase or in solution. The data presented increases our knowledge of the interactions of carnosine with different metals, either those naturally found inside the body or those that are up taken via foods, supplements or drugs.

1. Introduction

Carnosine, shown in Fig. 1, is a naturally occurring dipeptide found in different body organs such as the stomach, kidney and at elevated levels in skeletal and cardiac muscles as well as in brain tissue [1]. The concentration of carnosine in dry human skeletal muscles was reported to be 17.5 ± 4.8 mmol kg^{-1} in females and 21.3 ± 4.2 mmol kg^{-1} in males, while its concentration in mammalian brain and human cardiac muscles was reported to range from 0.7 to 2.0 mM and 2 to 10 mM, respectively [2–4]. The two amino acids that make up this dipeptide are β-alanine and L-histidine bound together by means of a peptide linkage [5,6]. Carnosine is usually biologically present in the levorotatory form as L-carnosine. Owing to its water solubility it was found to be concentrated in the cell cytosol [6].

Due to its interaction with several highly reactive species, such as hydroxyl, super oxide and molecular oxygen free radicals, especially in the water rich environment inside the body, carnosine is reported to have unique antioxidant abilities [7–10]. These antioxidant properties are prominent in the ability of carnosine to hinder lipid peroxidation which helps in preserving the integrity of body membranes [7,11]. Carnosine is also known to promote the effects of lipid soluble antioxidants such as alpha tocopherol [12,13] and for its buffering capability, being able to buffer the increased acidity generated by lactic acid formation inside muscle tissue during muscle stress [14]. This natural dipeptide has also been reported to have significant anti-glycation, anti-inflammatory, antihypertensive, anti-aging, wound healing and neurological effects [15]. These wound healing properties of carnosine particularly in cases of gastric ulcers [12] led to the development of polaprezinc, a commercially available carnosine-zinc drug complex, with effective antiulcer properties and the ability to improve gastric health [16–18]. This biologically active β-alanine-L-histidine dipeptide has recently been reported to have an effective metal chelating ability allowing it to interact with free circulating metals ions within the body such as copper, zinc, iron and calcium as well as with metal containing enzymes [19].

Several electron rich sites within this dipeptide can act as potential binding sites to various metal cations such as the carboxylic, amino, and amide groups as well as the imidazole moiety of

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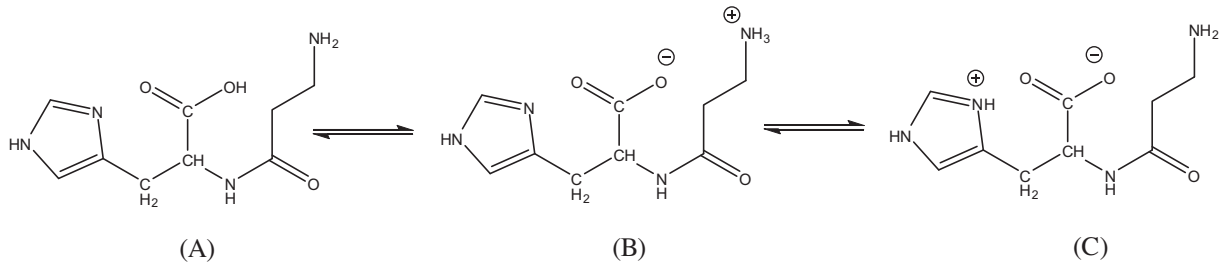

Fig. 1. Three different tautomers of carnosine.

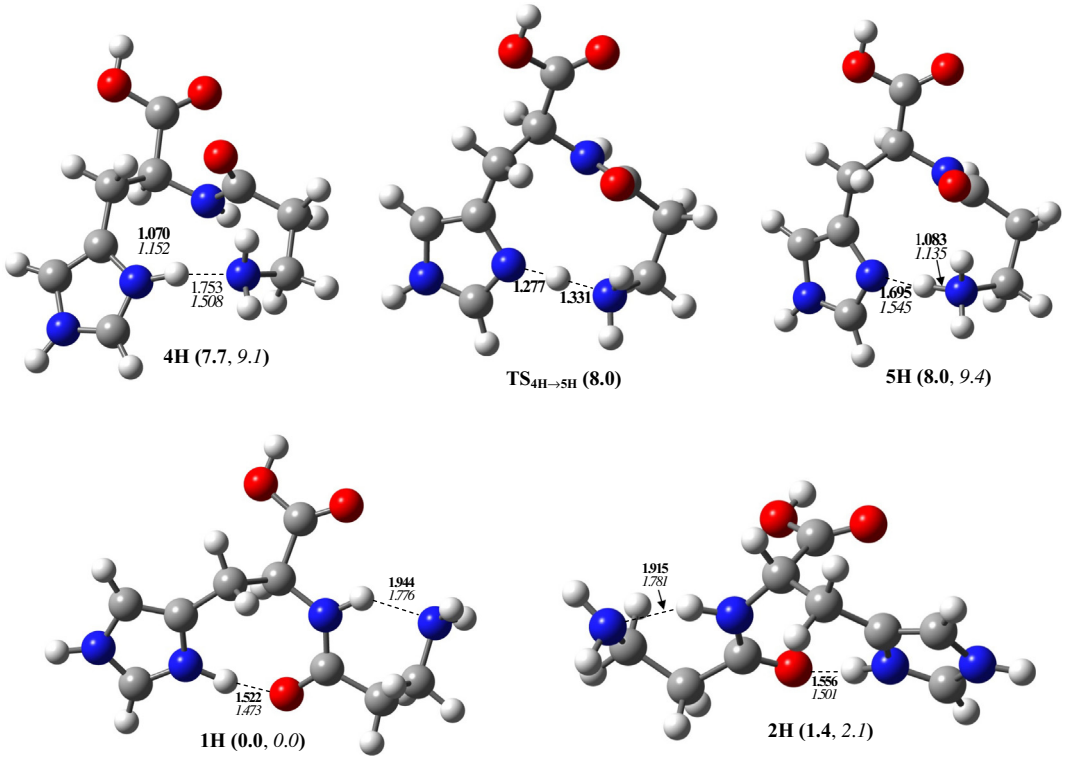

Fig. 2. Structures for [Carnosine + H]$^+$ ions as calculated at the B3LYP/6-311++G(2d,2p) (bold values) and the B3LYP/LANL2DZ (italicised values) levels of theory. Bond lengths are in Angstroms, relative free energies are indicated in parenthesis.

histidine. The average p*K* values of these groups are 2.64 for the carboxylic, 6.77 for the *tele* nitrogen of imidazole and 9.37 for the amino group. This large range can explain the fact that carnosine can exist in several different tautomeric forms as shown in Fig. 1 [20]. In fact, most recently, the very first hypothesis driven investigation of the role of carnosine in oxaliplatin detoxification showed that carnosine may inhibit the cytotoxic action of oxaliplatin being one of the most commonly used Pt-anticancer chemotherapeutic agents. [21]. In that study, it was shown that complexes formed between carnosine and oxaliplatin reduced the efficacy of the Pt-drug causing increased viability of cancer cells [21]. These complexes and the consequences of their formation thus increase the relevance of the interaction of carnosine to metals of biological relevance as a topic to address. This is most especially important since due to the many beneficial physiological effects of carnosine, it is available as an over the counter supplement in the form of oral tablets. The acetylated form of this dipeptide, N-Acetyl L-carnosine is also sold as an eye drop for corneal erosion treatment [22]. Several previous reports on carnosine and its metal complexes employed techniques such as NMR, IR, ESR and MS [21,23–26]. However, the available literature employing computational chemistry tools to study these complexes is very sparse [21,24,25,27].

The conformers of carnosine were the subject of an investigation employing semi-empirical potentials and PM3 approximations [27]. Such semi-empirical models were also recently employed to estimate structural and energy parameters of monomeric and dimeric carnosine complexes in two of its tautomeric forms to Zn^{+2} [28]. Several studies have attempted to characterise carnosine complexes with vanadium, cobalt and ruthenium [29–31]. A recent report on carnosine employed the B3LYP/cc-pVDZ level of theory to investigate protonated carnosine as well as the interaction of the neutral dipeptide with several alkali metals including lithium, sodium, potassium, rubidium and cesium [25]. The most recent report on carnosine complexes with oxaliplatin employed density functional theory at the B3LYP/LANL2DZ level to obtain structural information and relative free energies of different isomers of these observed complexes both in the gas phase and in solution as well as to probe their fragmentation and highlighting plausible dissociation mechanisms that account for all the experimental results presented [21].

In this paper, molecular orbital calculations are used to investigate the binding modes and binding energies of carnosine to various biologically relevant metal cations as well as to some Pt based anticancer drugs. General structural motifs of metal ion-carnosine complexes will also be presented.