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Theoretical study of the complexes of tyrosine and tryptophan with biologically important metal cations in aqueous solutions

Agnieszka Kowalska-Baron *

Institute of General Food Chemistry, Faculty of Biotechnology and Food Sciences, Technical University of Lodz, ul. Stefanowskiego 4/10, 90-924 Lodz, Poland

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ABSTRACT

In this study geometrical parameters and thermodynamical stability of the complexes formed between zwitterionic tyrosine/tryptophan and some biologically relevant monovalent alkali metal cations (Na^+, K^+) and divalent alkaline earth metal cations (Mg^{2+}, Ca^{2+}) have been determined on the bases of the new and yet unpublished theoretical calculations performed at the DFT(B3LYP-CAM)/6-31+G(d,p) level in the hydrated environment with the use of the polarizable continuum model (PCM). The obtained results of calculations in aqueous solution indicated that the tyrosine–metal cation and tryptophan–metal cation complexes studied adopted salt bridged (SB) structures involving bidentate coordination of the metal cation (M^{n+}, $n = 1, 2$) to the carboxylate moiety. In these structures, as inferred from the $M^{n+}\cdots O$ separation range, the metal cation is oriented almost symmetrically to two oxygen atoms of the functional group. It is believed that the theoretical results obtained in this study may be used to gain a better understanding of the interactions between biologically important metal cations and large biological molecules such as proteins.

1. Introduction

Interactions between metal ions and amino acids (AAs) are common both in solution and in the gas phase. In particular, complexes of natural amino acids and/or oligopeptides with different biologically important metal cations in the gas phase have been systematically studied both experimentally and theoretically [1–12]. In general, two possible structures have been proposed for the amino acid–metal cation complexes: the charge solvated (CS) structure (in which the AA (in the form of a free acid) coordinates the metal ion by the carbonyl oxygen, amino nitrogen and, if present, side chain functional group of AA) and the salt-bridged (SB) one (in which the metal cation is bound between the oxygen atoms of the zwitterionic carboxylate group, while carboxylate and ammonium centers interact through a hydrogen bond) [1]. Previously reported literature data provided ample evidence for the general trend that the formation of gas-phase salt bridges is explicitly favoured with increasing size and charge of the metal ion [3,4].

Among the AA/metal cation interactions, those involved in the complexes formation between alkali or alkaline earth metal cations and aromatic amino acids (AAAs) (in particular tyrosine and tryptophan) are of the great importance for a few reasons. First of all, the binding of alkali metal cations to the exposed π faces of aromatic amino acids that lie along the interior surfaces of ionic channels is thought to play a role in the selective transport of these metal cations through the ion channel [13,14]. Secondly, other studies have indicated that gating of the Ca^{2+} channel in N-methyl-D-aspartate receptors involves participation of a tryptophan residue [15]. Moreover, the formation of the salt bridged complexes with the zwitterionic forms of amino acids has been suggested to play a crucial role in the fragmentations promoted by alkali metal ion binding of peptides [5], in the assembly of some protein multimers [16] as well as in enzyme-receptor recognition [17].

Thus, the detailed knowledge of the nature of interactions involved in the model AAA/metal cation complexes may shed light into the binding of metal ions to peptides and proteins in the real biological systems. Theoretical predictions of the above mentioned AAA/metal cation complexes are extremely important since only by computation can we readily examine the different possible binding sites and geometries of the complexes and compare their energetics.

A number of gaseous complexes in which neutral aromatic amino acid (AAA) molecule binds metal cation through its π electrons has been previously widely studied both experimentally and theoretically [2,6,8]. It has been generally agreed that *in vacuo*

* Tel.: +48 (42) 631 34 26; fax: +48 (42) 636 28 60.
E-mail address: agnieszka.kowalska-baron@p.lodz.pl

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the cation–π interactions are the major interactions involving the side chain of the aromatic AAs in these systems [2,6].

A detailed and systematic study on the nature of the cation/π interactions has been previously reported by Dougherty and coworkers [18]. It has been postulated that the electrostatic forces play a prominent role in the cation/π interactions involved in alkali metal/model π system complexes, but nonelectrostatic terms (the most likely the induction (polarization) terms) make also an important contribution to the attractive cation/π interactions. The study of Tsuzuki et al. [19] strengthened the hypothesis that induction (polarization) and electrostatic interactions are the major source of the attraction in the M^+/π ($M^+ = Li^+$, Na^+, K^+) complexes. Unfortunately, it is still not clear how largely the induction contributes to the attraction.

Previously Dunbar [6] have found several gaseous low-energy conformers of the AAAs/$Na^+(K^+)$ complexes at the DFT (B3LYP)/6-31+G(d) level. The most favorable binding geometry of the AAA-$Na^+(K^+)$ systems studied, with only one exception, was the tridentate N/O/ring chelate in which the metal ion is placed in a favorable position for cation–π interactions. Zwitterionic forms of the complexes *in vacuo* were not unreasonable, but were less stable than the normal forms by ~5 kcal/mol. Cation–π stabilization energies, estimated by the authors from the examination of conformers in which the side chain was rotated out of chelation, were ~5 kcal/mol. According to the gas-phase calculations performed by Dunbar [6] it seems unlikely that the zwitterions form an important fraction of the gas-phase thermal populations of any of the complexes studied. The tridentate N/O/ring structure of the gaseous AAA/K^+ complex was also postulated by the studies of Polfer et al. [7].

Previously reported computational suggestions [20] that increasing the metal ion charge to +2 has a stabilizing effect on the salt bridged forms offered a promising route to stable gas-phase zwitterions of metal-complexed amino acids. Moreover, a recent comparison of the Phe-Na^+ complex with the Ala-Na^+ counterpart suggested only a small contribution of the phenyl ring interaction to binding which cast doubt on the extent of the cation–π effect [8]. The reported observation of electrosprayed tryptophan/barium complexes in the +2 charge state [9] provided the first experimental demonstration that in the gas phase the amino acids can bind in the zwitterionic form, which gives rise to a salt bridged form when complexed to a higher metal-ion charge. After the work of Dunbar et al. [9] the following study indicated that arginine, glutamine, proline, serine and valine all adopt zwitterionic structures when complexed with divalent barium [10]. In the previously reported study of Dunbar et al. [21] on the complexes of di- and tripeptides with singly and doubly charged metal ions it has been concluded that charge solvated (CS) conformation of the peptide in the complex with metal ions is favoured for small metal ions with high charge density and extensive microsolvation of the charge by Lewis-basic groups, while zwitterionic salt-bridged conformations are favoured by metal ions of high charge but low charge density [21].

Although many experimental and theoretical studies have been devoted to the complexation of metal cations to natural amino acids in the gas phase, only few works [4] have attempted to investigate the binding role of different metal cations in their interaction with the non-zwitterionic and zwitterionic forms of amino acids in solution. In particular, information on the geometries and energetics of the aromatic amino acids/metal cation complexes in aqueous medium is lacking. The importance of the theoretical studies in aqueous media is evident since the solvent effects are expected to have profound effect on the geometries and stabilities of the AAAs and their complexes with metal cations. This hypothesis may be strengthen by the previously reported theoretical studies [22] which have indicated that the side chain of aromatic amino acids can sweep a large space, rendering their interactions with the environment. Especially water molecules, through their interactions with these amino acids, seem to facilitate the side chain conformational transitions by lowering the energy barriers separating different conformers [22]. Moreover, it has been previously found that explicit addition of two and five water molecules leads to considerable changes in the relative stability of the hydrated $Gly{\cdot}M^{n+}(H_2O)_m$ and $GlyZwitt{\cdot}M^{n+}(H_2O)_m$ ($m = 0, 2, 5$) ($M^{n+} = Li^+$, Na^+, K^+, Mg^{2+}, Ca^{2+}, Ni^{2+}, Cu^{2+}, Zn^{2+}) systems [4].

The aim of the present report is to study geometrical features and thermodynamical stability of the complexes formed between zwitterionic tyrosine/tryptophan and some biologically important monovalent alkali (Na^+, K^+) and divalent alkaline earth (Mg^{2+}, Ca^{2+}) metal cations on the bases of the new and yet unpublished theoretical calculations performed at the DFT(B3LYP-CAM)/6-31+G(d,p) level in the hydrated environment (with the use of the polarizable continuum model (PCM)). Firstly, the preferred geometries of metal ion binding sites in the above mentioned complexes will be explored. Next, the thermodynamical parameters (the binding energies, binding enthalpies) of the AAA–metal cation complexes will be estimated in aqueous solution applying the supermolecule approach. It is believed that the theoretical results obtained in this study may be used to gain a better understanding of the interactions between biologically important metal cations and large biological molecules such as proteins.

2. Quantum chemical calculations

Geometry optimization and the subsequent vibrational frequencies calculations of Na^+, K^+, Ca^{2+}, Mg^{2+} cations, tyrosine, tryptophan and their complexes with the above mentioned ions have been performed using Gaussian 09 [23] and GaussView 5 [24] suite of programs.

The calculations have been carried out at the density functional theory (DFT) level with the use of the hybrid exchange–correlation functional applying the Coulomb-attenuating method (CAM-B3LYP) [25] and 6-31+G(d,p) basis set in aqueous phase. Tyrosine, tryptophan, metal cations and their complexes were hydrated by means of a polarizable continuum model (PCM) capable of mimicking a bulk water environment around the molecule. Analyzing the calculated vibrational frequencies, no imaginary frequencies have been found, which indicated that the optimized structures corresponded to the local minima on the potential energy hypersurface.

The ground state binding energies (ΔE_{bind}) of the interacting systems have been calculated using the supermolecule approach [26] as the electronic energy difference between the complex and the isolated molecules (tyrosine, tryptophan, cations), then corrected for the basis set superposition error (BSSE) and the zero point vibrational energy (ΔZPVE).

$$\Delta E_{bind} = E_{complex} - (E_{tyrosine(tryptophan)} + E_{cation}) + \mathrm{BSSE} + \Delta\mathrm{ZPVE}$$

The basis set superposition error (BSSE) was estimated applying the counterpoise method [27]. The zero-point vibrational energy (ΔZPVE) correction was estimated as the difference in zero-point vibrational energies between the complex and the isolated molecules [28]:

$$\Delta\mathrm{ZPVE} = \mathrm{ZPVE}_{complex} - (\mathrm{ZPVE}_{tyrosine(tryptophan)} + \mathrm{ZPVE}_{cation})$$

The binding enthalpy (ΔH_{bind}) and the Gibbs free energy of binding (association) (ΔG_{bind}) at 298 K were calculated from the data listed in the output of Gaussian calculation without scaling their values.

$$\Delta H_{bind} = H_{complex} - (H_{tyrosine(tryptophan)} + H_{cation}) + \mathrm{BSSE}$$

$$\Delta G_{bind} = G_{complex} - (G_{tyrosine(tryptophan)} + G_{cation}) + \mathrm{BSSE}$$