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A structural and free energy analysis of Ag^+ complexes to five small peptides

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ABSTRACT

The complexes of Ag^+ with the peptides MetGly, ProGly, GlyPro, GlyHis and GlyProAla were investigated using hybrid density functional theory at the B3LYP/DZVP level. The silver ion binding free energies at 298 K to each of these peptides was calculated to be 60.8, 52.0, 54.3, 71.2 and 63.3 kcal mol^{-1}, respectively. Structural information and relative free energies are presented for several isomers for each of the five complexes. Each of the global minima found for the five complexes is a charge-solvated ion. An important finding is that the Ag^+–ProGly is the only complex where a salt bridge structure is energetically favored occurring at 4.0 kcal mol^{-1} higher in free energy than the global minimum. The Ag^+ ion in this salt bridge structure is attached to the carboxylate anion of zwitterionic ProGly in which the terminal amino nitrogen is protonated. For all the other complexes studied, the salt bridge structure occurs at much higher energies. All the dipeptide complexes with Ag^+, but one, exhibit a di- or tri-coordinate metal where the sites of attachment are amino and carbonyl groups. However, the highest coordination numbers are not always the global minima due to steric costs. The global minimum of the Ag^+–GlyProAla complex is the only structure found in this study where the metal is tetra-coordinated, binding to the terminal amino nitrogen and all three carbonyl oxygen atoms. Silver binding to sulphur and imidazole nitrogen atoms of MetGly and GlyHis, respectively, are present in the three most energetically favored species in each of these cases.

1. Introduction

Metallothioneins which are small cysteine-rich proteins, that are believed to be involved in heavy-metal detoxification, exhibit very high affinities for Ag^+ [1–3]. The secondary or three-dimensional structures of nucleic acids and metallothioneins [4] that are complexed with Ag^+ are entirely dictated by the metal ligation. Silver ions also bind strongly to amino acids [5,6] and oligopeptides [7,8] in the gas phase. The collision-induced dissociation (CID) of Ag^+ complexes with α-amino acids leads to several common fragment ions and neutral loss species generated by common fragmentation pathways [6,9,10]. The formation of radical cations from the CID of several Ag^+ complexes with aromatic α-amino acids was also observed [9,10]. The CID of peptide complexes of Ag^+ was shown to be useful for obtaining sequencing information [11]. The nearly equal isotopic distribution of ^{107}Ag and ^{109}Ag greatly reduces the possibility of isobaric interference with ions that are indicative of the residue sequence. However, the fragmentation of silver-containing peptides was also shown to produce several unassigned ions [11,12] which hindered the application of this method, highlighting the importance of the detailed characterisation of such dissociation products.

A recent study of Ag^+ complexes with larger peptides provided evidence that the fragments observed were charge proximal and depended on the site(s) of the silver ion attachment [12]. This suggest either a heterogeneous precursor ion structure in which the silver ion is "mobile" or a distribution of several, non-interconverting, silver-containing ion structures. The global minima of the Ag^+–proline [13] and the Ag^+–phenylalanine [9] complexes were shown not lead to all of the experimentally observed fragments for these systems, while conformers lying within 10 kcal mol^{-1} of these global minima were shown to lead to several of the observed fragments. These low lying conformers have low barriers for inter-conversion with each other and with their respective global minimum structures [9,13]. These calculated barriers were all accessible since they were lower than the energy available during the experiments. This exemplifies the importance of optimising all the low energy conformers, which are those that lie within about 20 kcal mol^{-1} of each of their respective global minima. Theoretical studies have showed that Ag^+ in these complexes is often di- and tri-coordinated to electron rich sites such as carbonyl oxygen atoms and terminal amino nitrogen atoms while tetra-coordination is seen with tripeptides [6,8,9]. The structures of Ag^+ complexes with all 20 α-amino acids and with di-, and tri-glycine have been examined in detail by means of density functional

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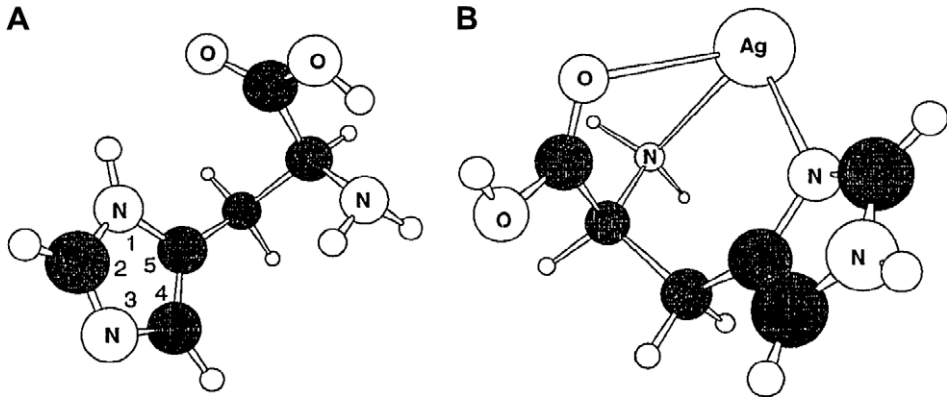
theory [6,8]. The structures were found to fall into three major categories: (a) five-membered cyclic structures in which the silver ion is di-coordinated by the amino nitrogen and the carbonyl oxygen atom of the first residue; (b) multiple ring structures in which the silver ion is chelated by three or four atoms; and (c) silver salts in which the silver ion is bound to the carboxylate anion of the zwitterionic amino acid or peptide. Structures (a) and (b) have been described as "charge-solvated" since the amino acid or peptide effectively solvate the silver ion in the gas phase.

The five small peptides in this study were chosen to contain methionine, proline and histidine residues. Methionine is one of the four common sulphur-containing amino acids (the other three are cysteine, homocysteine, and taurine), however, it is one of two among these four that gets incorporated into proteins. Methionine is generally considered non-polar and hydrophobic. These distinctive properties are accounted for by sulphur being much less electronegative than oxygen even though both atoms belong to the same group in the periodic table. This makes sulphur have a much lower propensity to hydrogen bonding relative to oxygen. One of the consequences of this fact can be seen in H_2S being a gas while H_2O is a liquid under the same conditions and in methionine being almost always found on the interior of proteins. Methionine, however, does have one of the highest silver ion affinities among the α-amino acids at 62.7 kcal mol^{-1} [6]. This scale begins at 49.3 kcal mol^{-1} for glycine and ends with arginine which possesses the highest silver ion affinity of any α-amino acids at 80.5 kcal mol^{-1} [6]. It is therefore not surprising that methionine containing peptides were reported to produce comparatively more intense Ag^+–peptide complexes than their non-methionine containing analogs [7]. This apparent selective binding of Ag^+ to methionine, however, was not evident in a comparison of the collision-induced dissociation of these argentinated complexes. That is to say that most silver-containing fragment ions generated from these complexes did not contain the methionine residue. This led Li et al. [7] to postulate that some rearrangements must have occurred in the gas phase resulting in self-solvation of the amidic carbonyl and amino nitrogen groups around the silver ion thus leading to weakening of the silver–methionine bond.

Proline is unusual in that it is the only naturally occurring amino acid with a secondary α-amino group. This cyclic feature gives proline an exceptional conformational rigidity compared to other amino acids. Hence, proline loses less conformational entropy upon folding, which may account for its critical role in protein conformation and the fact that it is commonly found in the turns of folded protein chains. This may be partially responsible for proline being usually solvent-exposed, despite having a completely aliphatic side chain. The unique secondary amino nitrogen also makes proline more basic than many other α-amino acids having a silver ion affinity of 56.1 kcal mol^{-1} [6]. As silver ion affinities of amino groups are lower than their corresponding proton ion affinities but follow the same relative order, the larger binding energy of the secondary amine helps to stabilise the silver salt structure of proline, making it about 2 kcal mol^{-1} lower in energy than the charge-solvated form of the complex in the gas phase [6].

Histidine is the amino acid with the highest silver ion affinity of the ones chosen in this study at 68.0 kcal mol^{-1} [6]. The nitrogen atoms of the imidazole ring of histidine are denoted by *pros* (near) and *tele* (far) to show their position relative to the side chain. Histidine contains an aromatic ring in its side chain, in its un-complexed form, the *pros* nitrogen is protonated, that is to say the NH group in the ring is adjacent to the side chain (structure **A**), i.e. the hydrogen is on atom 1, while in the argentinated ion the hydrogen migrates to the *tele* nitrogen which is the other nitrogen in the ring, N3, thereby permitting the *pros* nitrogen, N1, to coordinate to silver (structure **B**) creating the shortest, and presumably strongest bond to the tri-coordinate silver [6]. The native yeast *Saccharomyces cerevisiae* metallothionine contains a single histidine residue and binds Ag^+ [4]. Despite its high silver ion affinity, the histidine residue in this identified yeast metallothionine was shown not to be involved in silver binding [4]. This rather surprising finding has led us to include this residue in our investigation.



Here we use theory to obtain structural information and relative free energies for the Ag^+ complexes with five small peptides (MetGly, ProGly, GlyPro, GlyHis and GlyProAla). Each of these five peptides contains several electron rich sites for metal attachment including terminal amino nitrogen atoms, carbonyl oxygen atoms, as well as side chain groups such as a sulphur atom in the case of MethGly or an imidazole ring in GlyHis. Several conformers for these Ag^+ complexes are therefore possible. To our knowledge, this work is the first report on these five complexes in the literature. This paper will be instrumental in the interpretation of the gas-phase collision-induced dissociation of these complexes, the topic of an upcoming report, and will also contribute to the understanding of the fundamental fragmentation pathways of silver-containing peptides in more general terms which is essential to the wider applicability of this method for proteome analysis.