



MSc Departmental Seminar 6001

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Title: Mass Spectrometric and Computational Study of Gaseous L-Glutathione Non-Covalent Complexes

L-glutathione (GSH) is a tripeptide composed of glutamic acid, cysteine, and glycine. GSH serves a variety of important physiological functions in the cells such as detoxification by helping transport metal cations from the cell,¹ and antioxidation by controlling the redox status as a reducing agent and preventing the accumulation of reactive oxygen species within cells.²⁻⁴ The motivation behind experiments stems from the important bioactivity role and the potential pharmaceutical application of GSH adducts in biological systems.⁵ The main scope of this research is to study the intrinsic properties of charged GSH adducts with alkali metal, alkaline earth metals, transition metals, some heavy metals and seven amino acids in the gas phase by using tandem mass spectrometry along with computational chemistry. In the first project, we explore the unimolecular chemistry and the structures of gas-phase complexes of alkali metal cations with GSH. Sustained off-resonance irradiation collision-induced dissociation (SORI-CID) shows extensive dissociation of GSH when $M=Li^+$, Na^+ , and K^+ , whereas the main dissociation pathway is loss of GSH for $M=Rb^+$ and Cs^+ . Infrared multiphoton dissociation (IRMPD) spectroscopy and computational techniques reveal tetracoordinated structures where the ion is bound to three carbonyls as well as the amine nitrogen with an additional S-H—O=C interactions. The experimental spectra in the 1000-1800 cm^{-1} region matched computed spectra, confirming the lowest computed Gibbs energy structures. In the next study, the structures, energetics, and unimolecular reactivity of deprotonated GSH complexes with various doubly charged metal cations including alkaline earth metals, transition metals, and heavy metals are discussed. Employing SORI-CID and IRMPD spectroscopy, combined with computational methods, the research explores the coordination chemistry of these metal-GSH complexes. Results indicate that the dissociation pathways and binding energies vary significantly among different metal cations. The study identifies the common primary fragmentation pathways involved the loss of water in most $M(GSH-H)^+$ complexes with doubly charged metals (excluding Ni^{2+} , Cu^{2+} , and Hg^{2+}). However, $Ni(GSH-H)^+$ and $Cu(GSH-H)^+$ SORI mass spectra showed the loss of NH_3 . Additionally, all metals except Mn, Zn, and Hg experienced the loss of pyroglutamic acid. This study compares IRMPD spectra of protonated GSH complexes with alkaline earth metals (Mg^{2+} , Ca^{2+} , Sr^{2+} , Ba^{2+}) to computed spectra of their lowest energy conformations. The metal cations coordinate to the amine group and four carbonyl

oxygens, with additional S-H—O=C interactions. Experimental spectra in the 1000-1800 cm^{-1} region show characteristic bands that align with computed spectra. In the third study blackbody infrared radiative dissociation (BIRD) kinetic measurements were used to study the gas-phase gas basicity and stabilities of protonated GSH-amino acid complexes (arginine, histidine, lysine, glutamine, asparagine, glutamic acid and aspartic acid) cations in the gas phase. The results show that Arginine demonstrates the highest gas basicity, significantly contributing to the dissociation of protonated amino acids, while in other complexes, protonated GSH tends to be the primary product. The arginine side chain's strong basicity results from the stabilization of its positive charge through resonance. Histidine's side chain, with its two nitrogens, has a relatively moderate affinity for an additional proton (H^+). Lysine's overall basic nature is due to its possession of two amine groups, particularly the second isolated amine group. Also, we determined Arrhenius activation energies by examining the temperature-dependent dissociation rate constants.

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- (2) Li, Y.; Wei, G.; Chen, J. Glutathione: a review on biotechnological production. *Applied microbiology and biotechnology* **2004**, *66* (3), 233-242.
- (3) Forman, H. J.; Zhang, H.; Rinna, A. Glutathione: overview of its protective roles, measurement, and biosynthesis. *Molecular aspects of medicine* **2009**, *30* (1-2), 1-12.
- (4) Banu, L.; Blagojevic, V.; Bohme, D. K. Dissociations of gas-phase complexes of deprotonated glutathione with Co^{2+} , Ni^{2+} , Cu^{2+} and Zn^{2+} : The importance of metal ion reduction. *International Journal of Mass Spectrometry* **2013**, *345*, 142-152.
- (5) Liu, J.; Xia, X.; Li, Y.; Wang, H.; Li, Z. Theoretical study on the interaction of glutathione with group IA (Li^+ , Na^+ , K^+), IIA (Be^{2+} , Mg^{2+} , Ca^{2+}), and IIIA (Al^{3+}) metal cations. *Structural Chemistry* **2013**, *24* (1), 251-261.