

Structures of bare and singly hydrated $[M(\text{Ura}-\text{H})(\text{Ura})]^+$ ($M = \text{Mg}, \text{Ca}, \text{Sr}, \text{Ba}$) complexes in the gas phase by IRMPD spectroscopy in the fingerprint region



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ABSTRACT

The structures of deprotonated group 2 metal dication bound uracil dimers as well as the singly hydrated dimers were explored in the gas phase using infrared multiple photon dissociation (IRMPD) spectroscopy (1000–1900 cm⁻¹) in a Fourier transform ion cyclotron resonance mass spectrometer (FTICR-MS). The IRMPD spectra were then compared to computed IR spectra for various isomers. Calculations were performed using B3LYP with the 6-31+G(d,p) basis set for all atoms except Ba²⁺ and Sr²⁺, for which the LANL2DZ or the def2-TZVPP basis sets with relativistic core potentials were used. The lowest energy structures are those in which the one uracil is deprotonated at the N3 position while the neutral uracil is a tautomer where the N3 hydrogen is at the O4 or O2 carbonyl oxygen and the metal is tetracoordinate interacting with N3 and O4 of deprotonated uracil and either N3 and O2 or N3 and O4 of neutral uracil. In the solvated complexes, the water molecule is also coordinated to the metal ion.

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1. Introduction

Metal cations are known to play a central role in many biological systems. In particular, divalent cations have been shown to be crucial in the stability and activity of nucleic acids, as well as the folding of RNA structures [1–4]. These ions provide their stabilizing effect to the structure of DNA [5,6] and RNA [1], through both charge neutralization and noncovalent interactions with the phosphate backbone of the nucleic acids. Even in trace amounts, the interaction of metal cations with nucleic acids has a vital role in setting the course for the functionality of various biological molecules [7,8], however, striking a balance is critical. Even though these metal ions play essential roles, the influence they hold over the behaviour of nucleic acids can often be detrimental. Unwanted conformational changes can result from an excess of metal dications, and through interaction of the ions with nucleobases themselves [2,6,9–13]. In particular, if nucleobases deviate from their canonical tautomer,

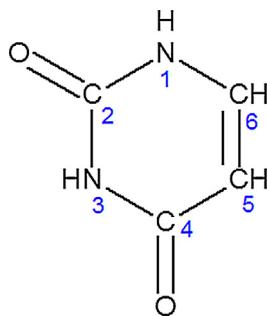
improper base pairings and mutations are likely to result [14–17]. The interaction of metal ions with nucleobases has been the subject of many studies through a variety of techniques [18–32]. A major obstacle is the difficulty to replicate a cellular environment in condensed phase analysis. Rather, gas-phase conditions are desired to allow for direct structural examination without the hindrance of bulk solvents, which may otherwise alter the complex structure. To accomplish this, action or consequence spectroscopy has been employed recently. In particular, infrared multiple photon dissociation (IRMPD) is a technique that has been successfully applied in many of these studies, and is the method of choice for this research.

The conventional numbering scheme for uracil is presented in Scheme 1. The most stable form of neutral uracil is the canonical, 2–4 diketo tautomer, in both the solid and gas phases [33–51]. However, metal ions have the ability to stabilize the keto-enol tautomer. Even though alkaline earth dications do not have as strong an affinity towards nucleobases as transition metal dications [52], similar effects are observed. Trujillo and coworkers determined that in $[\text{Ca}(\text{Ura})]^2+$, uracil tautomerizes to the 4-enol form, and the calcium ion bridges the O2 and dehydrogenated N3 atoms [53]. While such complexes having the form $[\text{M}(\text{Ura})]^2+$ are stable in the case of alkaline-earth metals like Ca, the Pb²⁺ ion or transition dications such as Ni²⁺ and Cu²⁺, will lead to deprotonation of the uracil moiety. For example, the lead(II)-uracil complex, $[\text{Pb}(\text{Ura}-\text{H})]^+$, shows a

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Scheme 1. Numbering scheme for uracil.

preference towards the canonical, 2,4-diketo conformation of uracil [18] but it is deprotonated at N3. Although the monomeric complexes formed may differ based upon the interaction between the ion and uracil (electrostatic vs. covalent), the dimeric complexes $[M(Ura-H)(Ura)]^+$ all behave similarly in the fact that one uracil is deprotonated, and the other remains neutral. The $[M(Ura)_2]^{2+}$ complex is generally not observed in the gas phase.

Previous works have determined that in these dimeric complexes the dication is tetracoordinate regardless of whether it is a transition metal [22,27] or alkaline earth metal [31]. The neutral uracil in the lowest energy complex is an enol, which participates in a hydrogen bond with a carbonyl of the neighbouring deprotonated uracil. Although good agreement was obtained between the computed lowest energy structures and the experimental spectra in each case, spectroscopically the exact placement of metal ion coordination could not be determined. In the N–H/O–H stretching region which was used to examine these complexes, no distinction could be made between those where the neutral uracil was the O2 or O4 enol resulting in the metal binding to N3 and O4 or N3 and O2, respectively. Even though the general structures of these dimeric complexes are expected to be similar for all dications, the pathway of fragmentation differs. Within the alkaline earth group, Ba²⁺ and Sr²⁺ complexes fragment by loss of uracil, while Ca²⁺ and Mg²⁺ complexes lose an HNCO unit upon IRMPD or CID activation [30].

The current work aims to provide further insight into the previously examined [31] alkaline earth metal dimeric complexes, $[M(Ura-H)(Ura)]^+$, using IRMPD spectroscopy in the mid-infrared region, 1000–1900 cm⁻¹. In this fingerprint region, carbonyl stretching frequencies are obtained and distinguishing features between the N3O4 and N3 O2 coordinated complexes are exposed. Along with the bare dimeric complexes, $[M(Ura-H)(Ura)]^+$, we also probe the singly hydrated complexes, $[M(Ura-H)(Ura)(H_2O)]^+$. The experimental spectra are compared to those computed using electronic structure calculations. A comparison of spectra and energies computed through different methods is also offered.

2. Methods

2.1. Experimental

All experiments were performed using a Fourier-transform ion cyclotron resonance mass spectrometer (FT-ICR-MS) coupled to a mid-infrared free electron laser (FEL) at the Centre Laser Infrarouge d'Orsay (CLIO) [54,55]. 0.01 M solutions of the chloride salts of each of the metal ions were prepared 18 MΩ water (Millipore). Uracil solutions were prepared to 1 mM in 18 MΩ water (Millipore). Mixtures were then prepared in a 1 to 10 ratio of metal solution to uracil solution, and introduced via syringe injection to the electrospray ion source at a flow rate of 75 μL/h. The ions were mass selected with a quadrupole mass filter and irradiated with the free electron laser following introduction and isolation into the ICR cell. Hydrated ions were prepared by first mass selecting the bare

$[M(Ura)(Ura-H)]^+$ ion in the quadrupole filter and storing them in the hexapole storage cell into which water vapour had been leaked [56]. Irradiation times varied from 0.1 to 3 s, with the more weakly bound and, therefore, faster dissociating hydrated ions being irradiated for the shortest time. Certain areas of the IRMPD spectra which were saturated were scanned after attenuation of the FEL. The laser was scanned at 5 cm⁻¹ intervals from ~1000 to 1900 cm⁻¹. The IRMPD efficiency is the negative of the natural logarithm of parent ion intensity divided by the sum of parent and fragment ion signals.

2.2. Computational

Calculations for all structures were conducted using the Gaussian 09 suite of programs [57]. Each structure was optimized and infrared spectra computed using B3LYP density functional theory. In the cases of $[M(Ura-H)(Ura)]^+$ and $[M(Ura-H)(Ura)(H_2O)]^+$, where M = Ca²⁺ or Mg²⁺, the 6-31+G(d,p) basis set was used for all atoms. For the $[M(Ura-H)(Ura)]^+$ and $[M(Ura-H)(Ura)(H_2O)]^+$ complexes, where M = Ba²⁺ and Sr²⁺, the LANL2DZ basis set with relativistic core potential was used for strontium and barium atoms and the 6-31+G(d,p) basis was used for all other atoms. Single point energy calculations were then carried out using B3LYP with the 6-311+G(3df,3pd) basis set on all atoms except Sr and Ba for which the LANL2DZ basis set with relativistic core potential was used. This computational method will be referred to as method 1.

All calculations were then repeated, for the five lowest energy structures, with the def2-TZVPP basis set which has been found to work better for metal-cation amino acid complexes than the LANL2DZ [58,59] for all metals during both the optimization and single point energy calculations. The def2-TZVPP basis set contains polarization functions, which are not included in the LANL2DZ basis set. The 6-31+G(d,p) basis set was again used for all other atoms (C, H, N and O) during optimization, followed by the 6-311+G(3df,3pd) basis set for single point energy calculations. This computational method will be referred to as method 2.

These single-point electronic energies, using methods 1 and 2 were used to compute the enthalpies and Gibbs energies of isomeric species at 298 K, using the unscaled harmonic vibrational frequencies calculated for optimization geometry.

The bonding within the individual equilibrium structures was also analysed by locating the bond critical points (BCPs) using atoms-in-molecules (AIM) theory [60], which is based on a topological analysis of the electronic density at the BCPs, and is a good descriptor of the bond strength or weakness. This analysis was conducted using optimized structures from method 2. Data from the topological analysis are given collectively in the Supporting information as Fig. S26.

For comparison with the experimental spectra, the computed infrared spectra were all scaled by a factor of 0.97 and convoluted with a Lorentzian profile with a width (FWHM) of 15 cm⁻¹.

3. Results and discussion

3.1. Examination of the IRMPD spectra

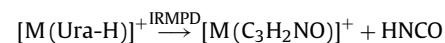
When complexes were irradiated with the FEL, the following dissociation pathways were observed:

All M except Mg



Following the loss of neutral Ura:

M = Sr²⁺



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