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Structures of $[M(Ura\text{-}H)(Ura)]^+$ and $[M(Ura\text{-}H)(H_2O)_n]^+$ (M = Cu, Zn, Pb; n = 1–3) complexes in the gas phase by IRMPD spectroscopy in the fingerprint region and theoretical studies

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ABSTRACT

The gas-phase structures of the bare dimers, $[M(Ura\text{-}H)(Ura)]^+$, and hydrated monomers, $[M(Ura\text{-}H)(H_2O)_n]^+$, were examined using infrared multiple photon dissociation spectroscopy in the fingerprint region (1000 cm^{-1}–1900 cm^{-1}) for M = Cu, Zn, and Pb and n = 1–3. The experimental results were compared to those calculated using density functional methods The dimeric structures all show deprotonation of one uracil moiety at N3, and forms a tetracoordinate interaction with N3 and O4 of the deprotonated uracil, and N3 and O2 of the neutral uracil. The hydrated monomers, $[M(Ura\text{-}H)(H_2O)]^+$, all have rather different structures. Uracil is deprotonated at N3 for M = Zn and Pb, but for Cu, uracil is deprotonated at N1 and Cu^{2+} is bound to N1 and O2. Like the $[M(Ura\text{-}H)(Ura)]^+$ complexes, in $[Pb(Ura\text{-}H)(H_2O)]^+$ the metal is bound to N3 and O4. The Zn^{2+} complex actually better resembles $[M(Ura)(OH)]^+$ with a proton apparently transferred from water to O4 of uracil and the metal cation coordinated to O2. Unlike the singly hydrated complex, uracil is deprotonated at N3 in $[Cu(Ura\text{-}H)(H_2O)_2]^+$. In all singly, doubly, and triply solvated complexes studied, water is found to be coordinated to the metal cation.

1. Introduction

The sequencing of nucleobases in DNA and RNA forms the basis of our genetic code. The formation of proteins relies upon proper transcription of the DNA sequence to messenger RNA, through the Watson-Crick pairing of nucleobases [1]. This proper base pairing is dependent upon hydrogen bonding interactions. Should the configuration of a nucleobase be altered, resulting in changes to hydrogen bonding sites, disruption of proper Watson-Crick pairing can result, leading to errors in transcription and thus genetic mutations. Among other biological processes, metal ions play an important role in RNA stability and activity [2–4], but their presence also has the ability to affect the tautomerization of nucleobases [5], thus impacting the hydrogen bonding sites and potentially leading to mis-matched base pairs and genetic mutations [6]. Transition metal dications have shown an increased affinity towards nucleobases compared to their group 2 counterparts [7], with copper having the greatest affinity of the divalent cations [8]. Cu^{2+} is one of the metal ions of interest in this current work, along with Zn^{2+} and Pb^{2+}, and the impact they have on the structure of both bare and hydrated uracil complexes.

Each of these metals has been thoroughly explored in terms of their enhancement of or interference in biological processes. While copper is important to nucleotide stability, it can also reach toxic levels in cells, causing reduction of hydrogen peroxide in the mitochondria. As a result, this produces highly reactive hydroxyl radicals which can negatively impact DNA and cause membrane damage [9,10]. Zinc is one of the most abundant d-block elements found in cell cytoplasm, and has a role in gene regulation and protein folding [11,12], making its inclusion in this work particularly interesting. The toxic impact and detrimental effect Pb^{2+} has on human health has been well documented, in particular its disruption of biological homeostasis and its targeting of the heart, liver and kidneys [13].

While several stable tautomers of uracil exist, as well as its DNA replacement thymine, it is the diketo form that is favoured [14–18]. The diketo tautomer of uracil, along with the numbering scheme for uracil, is presented in Scheme 1. The interaction of the Cu^{2+}, Zn^{2+} and Pb^{2+} ions with both uracil and thymine have been explored both experimentally and computationally. Both Cu^{2+} and Zn^{2+} have been shown to stabilize the keto-enol tautomer of thymine [19]. When complexed with uracil, each of these dications will deprotonate uracil

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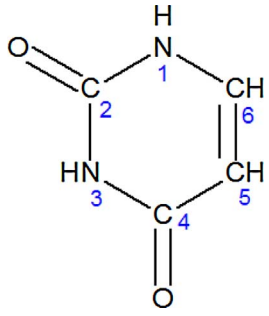

Scheme 1. Numbering scheme for uracil.

to form a singly charged ion of the form $[M(Ura\text{-}H)]^+$. However, the site of deprotonation is dependent upon the metal. Both Pb^{2+} [20] and Zn^{2+} [21] will deprotonate uracil from the N3 position, and form a bidentate interaction with uracil at N3 and O4. This binding is also characteristic of the $[M(Ura\text{-}H)]^+$ moiety in $[M(Ura\text{-}H)(Ura)]^+$ (loosely termed "dimeric complex") when M is Zn or Pb [22,23] or the group 2 cations [24–26]. By contrast, the $[Cu(Ura\text{-}H)]^+$ complex was shown to be deprotonated at the N1 position of uracil, with Cu bound to N1 and O2 [27,28]. However, the dimeric complex adopts a similar structure to the Pb and Zn dimers, where deprotonation occurs at N3 and metal binding is to N3 and O4 of the deprotonated moiety [23,29,30].

The current work uses IRMPD spectroscopy in the fingerprint region (1000–1900 cm^{-1}) to explore the structures of bare dimeric $[M(Ura\text{-}H)(Ura)]^+$ complexes, as well as hydrated monomers $[M(Ura\text{-}H)(H_2O)]^+$, where M = Cu, Zn, and Pb. The doubly hydrated monomers of Cu and Zn are also examined, along with the triply hydrated Zn monomer. The chief feature in the fingerprint region is carbonyl stretching, which is then compared to the computed spectra for several lowest energy isomers for each complex.

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) [31,32]. 0.01 mmol L^{-1} solutions of the chloride salts of each metal ion were prepared using 18 MΩ-cm water (Millipore). Uracil solutions were prepared to 1 mmol L^{-1} in 18 MΩ-cm water (Millipore). Mixtures were then prepared in a 1–10 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^{-1}. The ions were mass selected with a quadrupole mass filter and introduced in to the ICR cell, where they are then isolated and irradiated with the free electron laser. To accomplish hydration, bare $[M(Ura\text{-}H)]^+$ ions were mass selected in the quadrupole mass filter and stored in the hexapole storage cell, where water vapour had been introduced [33]. Irradiation times varied from 0.1 to 3 s, with the shorter irradiation times corresponding to the more weakly bound hydrated ions. Areas of the IRMPD spectra which experienced saturation 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 [34]. Each structure was optimized, and infrared spectra computed, using B3LYP density functional theory. For the complexes of Cu and Zn, the 6–31 + G(d,p) basis set was applied to all atoms. For complexes of Pb, the LANL2DZ basis set with relativistic core potential was applied to the Pb atom 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 Pb, 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 [35,36] 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 the optimization geometries.

The bonding within the individual equilibrium structures was also explored by locating the bond critical points (BCPs) using atoms-in-molecules (AIM) theory [37], which is based on a topological analysis of the electronic density at the BCPs, and is a good descriptor of the bond character; electrostatic or covalent. This analysis was conducted using optimized structures from method 2 using the AIMAll software [38]. Data from the topological analysis are given collectively in the Supporting information as Fig. S13.

Due to errors with the computational method and basis set as well as errors with the harmonic approximation, when comparing the calculated IR spectra to the experimental IRMPD spectra, it is typical that a scaling of the computed spectra to better match the experimental spectra is done. In this work, for comparison with the experimental spectra, the computed infrared spectra were all scaled by a factor of 0.97, consistent with other molecules of this type in this region of the infrared [25,26,30]. Further the computed spectra were convoluted with a Lorentzian profile with a width (FWHM) of 15 cm^{-1}.

3. Results and discussion

3.1. Examination of the IRMPD spectra

For the hydrated monomers of all metals, the primary fragmentation pathway results from the sequential loss of water solvent molecules. For the case of the bare dimer complexes, the primary fragmentation pathway is dependent upon the identity of the metal center [22,23,29]. For M = Cu and Zn,

$$[M(Ura\text{-}H)(Ura)]^+ \xrightarrow{IRMPD} [M(Ura\text{-}H)(Ura)\text{-}HNCO]^+ + HNCO$$

$$[M(Ura\text{-}H)(Ura)\text{-}HNCO]^+ \xrightarrow{IRMPD} [M(Ura\text{-}H)(Ura)\text{-}HNCO\text{-}HCN]^+ + HCN$$

where the identity of the fragment ions for the Cu^{2+} complex was explored previously [29]. $[Pb(Ura\text{-}H)(Ura)]^+$ simply loses uracil upon IRMPD activation. The hydrated complexes were found to simply lose solvent.

Fig. 1 is a comparison of the experimental spectra for all $[M(Ura\text{-}H)(Ura)]^+$ complexes in the 1000–1900 cm^{-1} region. All three complexes exhibit similar features in the 1517–1553 cm^{-1} region, corresponding to an enolic C—OH stretch, characteristic of the lowest energy structures of each which will be discussed later. Above 1600 cm^{-1}, only one band is observed for the Zn and Pb complexes, while two major bands are observed in the Cu complex. For the Cu complex, blue shifting of the C=O stretch, by approximately 60–70 cm^{-1} in comparison to the other metals, allows the intense C=C stretch (1626 cm^{-1}), and the carbonyl stretches centered at 1678 cm^{-1} to be resolved. This separation is not seen in the Zn and Pb complexes, as one broad band