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Infrared Multiple-Photon Dissociation Spectroscopy of Tripositive Ions: Lanthanum−Tryptophan Complexes

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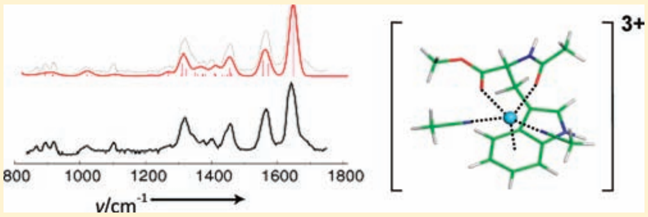
S *Supporting Information*



ABSTRACT: Collision-induced charge disproportionation limits the stability of triply charged metal ion complexes and has thus far prevented successful acquisition of their gas-phase IR spectra. This has curtailed our understanding of the structures of triply charged metal complexes in the gas phase and in biological environments. Herein we report the first gas-phase IR spectra of triply charged La^{III} complexes with a derivative of tryptophan (*N*-acetyl tryptophan methyl ester), and an unusual dissociation product, a lanthanum amidate. These spectra are compared with those predicted using density functional theory. The best structures are those of the lowest energies that differ by details in the π-interaction between La^{3+} and the indole rings. Other binding sites on the tryptophan derivative are the carbonyl oxygens. In the lanthanum amidate, La^{3+} replaces an H^+ in the amide bond of the tryptophan derivative.

■ INTRODUCTION

It is now recognized, as a result of insight gained from gas-phase studies,[1] that binding of metal ions to the π-systems of aromatic amino acids such as tryptophan plays a crucial role in the functioning of ion channels.[2−4] In the absence of solvent, structures and energetics of ionized biomolecular models can accurately be calculated using computational methods. Thus, the combination of infrared multiple-photon dissociation (IRMPD) spectroscopy and computational methods has emerged as an indispensable tool for structure elucidation of gas-phase ions.[5,6] Research has focused on salt bridge and charge-solvated coordination of monovalent alkali and divalent alkaline earth metal cations to amino acids and small peptides.[7−11] Extension to interactions of triply charged metal ions with peptides are of interest because of the limited knowledge on structural characteristics of their binding sites in proteins and peptides,[12−15] as well as their gas-phase fragmentation chemistry.[16,17] Furthermore, lanthanides have found increasing use as contrast agents, protein−metal binding probes, and luminescent tags for measuring protein−peptide interactions,[12−15] each of which requires a fundamental understanding of binding interactions. Vibrational spectra of gas-phase ions can be acquired as action spectra by measuring the intensities of precursor and fragment ions as a function of the wavelength of an intense, tunable IR excitation source; the IRMPD spectrum is obtained by plotting $\Sigma I_{\text{fragment}}/(I_{\text{parent}} + \Sigma I_{\text{fragment}})$ versus the wavenumber. For the experiments described here, the FELIX free electron IR laser coupled to a Fourier-transform ion cyclotron mass spectrometer was used.[18,19] Although the IRMPD spectrum is the result of a multiphoton process and dissociation kinetics, the spectrum reflects to a large extent a linear (single-photon) absorption spectrum allowing a comparison with calculated IR transitions.[20,21] IRMPD and density functional theory (DFT) literature has shown that metal-cation binding by model peptides (P) tends to be multicoordinate in order to alleviate the electron deficiency of the ion in the absence of solvent (S) molecules.[22−24]For multiply charged metal cation complexes, removal of electron-donating ligands through collisional activation results in charge disproportionation.[25−27]

$$[La^{III}(P)(S)_2]^{3+} \xrightarrow{CID} [La^{III}(P - H)(S)]^{2+} + HS^+$$

Such loss of a single positive charge by the metal complex, through interligand proton transfer, has severely curtailed studies of the interactions between small ligands, and triply and higher charged metal ions.[28,29] Two of the smallest peptides that have been successfully employed to ligate triply charged La^{3+} are triglycine and diproline.[16,17] Both peptides bind with multiple coordination sites, but the stabilities of the complexes were insufficient to allow IRMPD spectroscopy.

Herein we report the first IRMPD spectra of triply charged metal−peptide complexes between La^{3+} and derivatized tryptophan (Trp), and the charge disproportionation product,

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a lanthanum amidate. Removal of latent mobile protons, by *N*-acetylation (Ac) of the amino group and esterification of the carboxylic acid group (OMe), was essential to discourage dissociative proton transfer and secure a sufficiently large population of $[La^{III}(Ac\text{-}Trp\text{-}OMe)(CH_3CN)_2]^{3+}$ and $[La^{III}(Ac\text{-}Trp\text{-}OMe)_2]^{3+}$ for IRMPD.

■ EXPERIMENTAL AND THEORETICAL METHODS

Experimental Details. IRMPD spectroscopy experiments were performed at the FOM-Institute for Plasma Physics "Rijnhuizen" in Nieuwegein, The Netherlands. A 1-mM solution of commercially available *N*-acetylated tryptophan methyl ester and lanthanum(III) nitrate in acetonitrile/water (50/50) was used to form the lanthanum complexes by electrospray (via a Z-spray interface). Gas-phase ions were sampled into a hexapole ion trap and transferred into an FTICR cavity for irradiation by the IR laser beam. For the IRMPD spectrum of $[La^{III}(Ac\text{-}Trp\text{-}OMe)(CH_3CN)_2]^{3+}$ (*m/z* 160.3), fragment ions at *m/z* 199 $[Precursor - H(CH_3CN)_2]^{2+}$, *m/z* 208 $[Precursor - H(CH_3CN)_2 + H_2O]^{2+}$, and *m/z* 219.6 $[Precursor - H(CH_3CN)]^{2+}$ were used. For the spectrum of $[La^{III}(Ac\text{-}Trp\text{-}OMe)_2]^{3+}$ (*m/z* 219.6), fragment ions at *m/z* 130, $C_9H_8N^+$ or protonated 3-methylene indolenine, *m/z* 199 $[Precursor - H(Ac\text{-}Trp\text{-}OMe)]^{2+}$, *m/z* 248 $[Precursor - C_9H_8N + CH_3OH]^{2+}$, and *m/z* 264 $[Precursor - C_9H_8N]^{2+}$ were monitored. For that of $[La^{III}(Ac\text{-}Trp\text{-}OMe) - H]^{2+}$ (*m/z* 199), fragments ions at *m/z* 170 $[Precursor - CO - H_2CO]^{2+}$ and *m/z* 185 $[Precursor - CO]^{2+}$ were used.

DFT Calculations. All calculations reported here were carried out using the Gaussian 03 suite of programs.[30] The B3LYP hybrid exchange-correlation functional along with the sdd relativistic effective core potential/standard 6-31++G(d,p) basis set combination for La/C, N, O, and H atoms were employed in determination of the optimized structures and vibrational frequencies for all La complexes. Previous extensive experimental and theoretical studies on cation−π interactions have proven that B3LYP permits a very good compromise between accuracy and computational efficiency;[7,16,23,29,31−33] in particular, DFT force field calculated using the B3LYP density functional yields mid-IR absorption spectra in excellent agreement with experiment.[31] All B3LYP/sdd/6-31++G(d,p) structures were found to have all real vibrational frequencies, indicating that they are at minima on the potential energy surface. Calculated IR spectra were plotted with wavenumbers scaled by 0.982, which is comparable to scaling factors that have been used in previous simulations of IRMPD spectra of metal complexes.[7,33] The predicted IR absorption peaks were convoluted using a bandwidth of 30 cm^{-1} fwhm (Lorentzian profile) to simulate experimental resolution.

Conventional DFT techniques are known to treat dispersion effects inadequately; to further evaluate performance of the B3LYP functional, we also performed calculations on a representative structure, $[La^{III}(Ac\text{-}Trp\text{-}OMe) - H]^{2+}$, using the recently developed DFT-D strategies that involve the treatment of dispersion interactions. The models that we used included the double hybrid functional B2PLYP[34] and the exchange-correlation functional provided by BMK.[35] Our calculations show that B2PLYP and BMK give geometric parameters and relative energies very similar to those from B3LYP (Supporting Information, Figure S4). However, the calculated IR spectra at the B2PLYP/sdd/6-31++G(d,p) and BMK/sdd/6-31++G(d,p) levels of theory are both poor matches to the experimental IRMPD spectrum, despite higher computational cost (Supporting Information, Figure S5).

■ RESULTS AND DISCUSSION

Figure 1 shows the IRMPD spectrum of $[La^{III}(Ac\text{-}Trp\text{-}OMe)(CH_3CN)_2]^{3+}$ and the calculated spectra of the two lowest-energy structures, **I** and **II**. The match between theory and experiment is excellent at the B3LYP/sdd/6-31++G(d,p) level of theory with ≤10 cm^{-1} difference between observed and calculated band positions over the full range of the spectrum. The most intense band in the IRMPD spectrum at $\tilde{\nu}$ = 1642 (calculated for **I**: 1652) cm^{-1} is due to the ester C═O stretch (str) vibration. The intense IRMPD band at $\tilde{\nu}$ = 1566 cm^{-1} is assigned to the combined bands of the *N*-acetyl amide C—N (str) and C═O (str) vibrations at 1575 and 1560 cm^{-1}, respectively. The lanthanum ion is pentacoordinate with two acetonitrile ligands and the tryptophan occupying a distorted square pyramidal geometry for structure **I** and a trigonal bipyramidal geometry for structure **II**; the indole π-system occupies an apical site in both structures, see Figure 1.

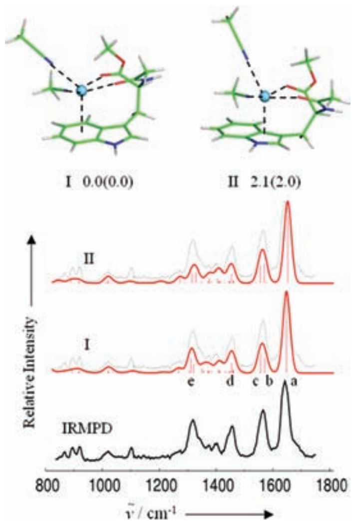

Figure 1. IRMPD spectrum of the $[La(Ac\text{-}Trp\text{-}OMe)(CH_3CN)_2]^{3+}$ ion and predicted IR absorption spectra for structures **I** and **II**. Band assignments for **I**: (a) $\tilde{\nu}$ = 1652 cm^{-1} ester C═O (str); (**b**) $\tilde{\nu}$ = 1575 cm^{-1} amide C−N (str); (**c**) $\tilde{\nu}$ = 1560 cm^{-1} amide C═O (str); (**d**) $\tilde{\nu}$ = 1457 cm^{-1} *N*-acetyl CH_3 (scissoring, scr) and ester CH_3 (bend); (**e**) $\tilde{\nu}$ = 1315 cm^{-1}/1324 cm^{-1} (sync/async) C_α−H and *N*-acetyl amide N−H (wag). Indicated under the structures are ΔH_0^o (ΔG_{298}^o) in kcal mol^{-1}.

The tryptophan ligand in structures **I** and **II** coordinates to La^{3+} by the two carbonyl oxygens and the tryptophan π-system, analogous to the "N/O/Ring" binding motif reported by Polfer et al. for singly charged metal ions.[8] The two lowest-energy structures differ essentially only in the La^{3+}−π interaction, with **I** being on the aryl ring and **II** on the pyrrole ring of the indole group. A slight preference for the aryl π-interaction is apparent, in accordance with DFT calculations on indole and tryptophan interacting with alkali metal ions that revealed limited π-electron donation by the pyrrole ring.[36,37] In **I** and **II**, both C−O distances are elongated (by 0.030 to 0.042 Å) and the C−N distance is shortened by ∼0.030 Å relative to the neutral ligand; for structure **I**, C−C distances in the aryl ring are all elongated in the complex (by 0.007 to 0.015 Å). These structural changes are all consistent with electron donation to La^{3+}.

According to the DFT studies by Rezabal et al.,[32] Al^{3+}−tryptophan complexation has as the most stable configuration an N/O/covalent bond motif instead of an indole π-interaction. Attempts to reproduce this binding motif were unsuccessful for La^{3+} and instead produced an indole π-interaction as a local minimum. Conversion from **I** to **II** has an enthalpic barrier of only 2.5 kcal mol^{-1}; a binding preference for the two distinct π-interactions cannot be determined as the predicted IR spectra of the two structures are virtually identical and in excellent agreement with the IRMPD spectrum.

In $[La^{III}(Ac\text{-}Trp\text{-}OMe)_2]^{3+}$, a second derivatized Trp replaces the acetonitrile molecules of **I** in completing the ligation of La^{3+} (see Figure 2). The three lowest-energy structures (**III**−**V**) as determined by DFT have La^{3+} hexacoordinated by the two Trp ligands. The major difference among the three structures lies in permutations of the $La^{3+}-\pi$ interaction with the indole group of the tryptophan (pyrrole/pyrrole, **III**; aryl/pyrrole, **IV**; and aryl/aryl, **V**). The differences in enthalpy among the three structures are small. The predicted IR spectrum of **III**, the structure at the global minimum, provides the best match to the IRMPD spectrum. The differences among **III**−**V**, in terms of spectral features, however, are small. In addition, the small differences in energy make the presence of a mixture of **III**−**V** likely.

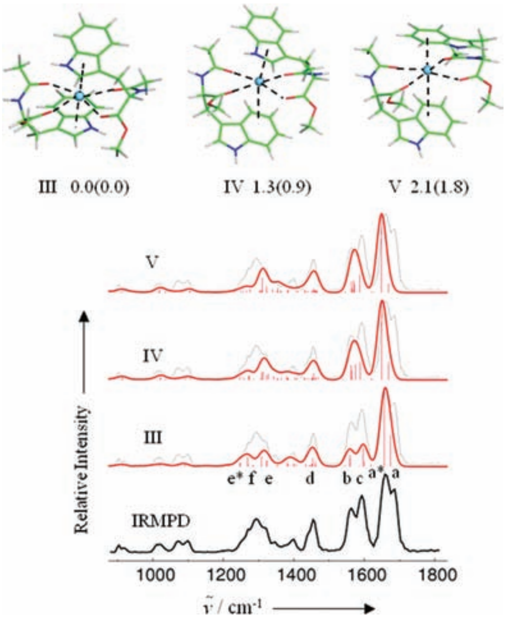

Figure 2. IRMPD spectrum of the $[La(Ac\text{-}Trp\text{-}OMe)_2]^{3+}$ ion and predicted IR absorption spectra for structures **III**−**V**. Band assignment for **III**: (**a**) $\tilde{\nu}_{\text{sym}}$ = 1678 cm^{-1} ester C═O (str); (**a***) $\tilde{\nu}_{\text{anti}}$ = 1660 cm^{-1} ester C═O (str); (**b**) $\tilde{\nu}_{\text{sym,anti}}$ = 1563/1562 cm^{-1} amide C−N (str); (**c**) $\tilde{\nu}_{\text{sym,anti}}$ = 1603/1599 cm^{-1} *N*-acetyl amide C═O (str); (**d**) $\tilde{\nu}$ = 1457 cm^{-1} $C_\beta-CH_2$ (scr); (**e**) $\tilde{\nu}$ = 1325 cm^{-1} $C_\alpha-H/C_\beta-CH_2$ (bend) and 1311 cm^{-1} *N*-acetyl amide N−H (wag); (**e***) $\tilde{\nu}$ = 1272 cm^{-1} $C_\alpha-H/C_\beta-H$ (bend); (**f**) $\tilde{\nu}$ = 1288 cm^{-1} pyrrole C−H (wag). Indicated under the structures are $\Delta H_0{}^{\circ}$ ($\Delta G_{298}{}^{\circ}$) in kcal mol^{-1}.

A cursory comparison of the spectra of the mono- and bis-tryptophan−La^{III} complex shows a doubling of bands in the region 1500−1700 cm^{-1} for the latter that reflects the in-phase, symmetric ($\tilde{\nu}_{\text{sym}}$) and out-of-phase, antisymmetric ($\tilde{\nu}_{\text{anti}}$) C═O (str) vibrations. For the ester OC═O group, the former normal mode occurs at slightly higher wavenumbers ($\tilde{\nu}_{\text{sym}}$ = 1683, calcd 1678 cm^{-1}) than the latter ($\tilde{\nu}_{\text{anti}}$ = 1661, calcd 1660 cm^{-1}). The differences between symmetric and antisymmetric combinations of the other vibrational modes are smaller and are not resolved; the doublet around 1580 cm^{-1} is due to the *N*-acetyl amide C═O (sym/anti str) and C—N (sym/anti str) vibrations.

The electron-density demand on individual ligands is diminished in the bis-tryptophan complex, resulting in diagnostic band position reversals when compared with the mono-tryptophan complex. The band at 1566 cm^{-1} for the mono-tryptophan complex consisting of the amide C—N (str) and *N*-acetyl amide C═O (str) vibrations splits for the bis-tryptophan complex **III** into bands at 1593 cm^{-1} for the amide C═O (str, calcd $\tilde{\nu}_{\text{anti}}$ = 1599/$\tilde{\nu}_{\text{sym}}$ = 1603 cm^{-1}) and 1563 cm^{-1} for the amide C—N (str, calcd $\tilde{\nu}_{\text{anti}}$ = 1563/$\tilde{\nu}_{\text{sym}}$ = 1562 cm^{-1}). The small red shift of the amide C—N stretch vibration (Δ ~3 cm^{-1}) and the blue shift of the amide C═O (str) (Δ ~20 cm^{-1}) indicate less donation of electron density to the La^{3+} ion in the bis complex. This is also reflected in the blue shift (Δ ~40 cm^{-1}) of the ester C═O (str) vibrations in the mono complex versus the bis complex.

Subjecting $[La^{III}(Ac\text{-}Trp\text{-}OMe)(CH_3CN)]^{2+}$, formed by front-end collisional activation and disproportionation of $[La(Ac\text{-}Trp\text{-}OMe)(CH_3CN)_2]^{3+}$, to IR heating using a 10.6 μm CO_2 laser resulted in formation of $[La^{III}(Ac\text{-}Trp\text{-}OMe) - H]^{2+}$, whose IRMPD spectrum is shown in Figure 3 together with the predicted IR spectra of the two lowest-energy structures, **VI** and **VII**. The most interesting feature in the structure of $[La^{III}(Ac\text{-}Trp\text{-}OMe) - H]^{2+}$ is the substitution of a proton by La^{3+} in the amide group. Such a substitution of the amide H^+ by an alkali or alkaline earth metal ion has been suggested to occur in peptides and proteins in the gas phase upon collisional activation.[38−41] La^{3+} is tetracoordinated in both structures by the carbonyl oxygen, the amidate oxygen/nitrogen combination, and the indole π-system. Structure **VI** (0.0 kcal mol^{-1}) is separated from **VII** (2.0 kcal mol^{-1}) by a small enthalpic barrier of 4.4 kcal mol^{-1}. According to the amide C−N (str) band at $\tilde{\nu}$ = 1523 cm^{-1} (calcd 1528 cm^{-1}) of **VII** and a shoulder at $\tilde{\nu}$ ~ 1567 cm^{-1} (calcd 1562 cm^{-1}) attributed to **VI**, a considerable population (≤70%) of **VI** may be present experimentally.[21] The amide band shows a small blue shift of ~27 cm^{-1} (calcd 34 cm^{-1}) switching from pyrrole- (**VII**) to aryl-ring coordination (**VI**), which reflects an increase in the C−N double bond character.

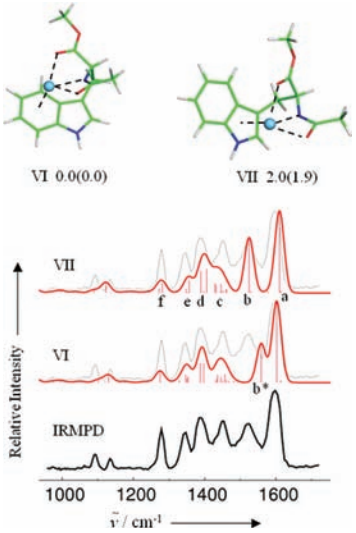

Figure 3. IRMPD spectrum of the $[La(Ac\text{-}Trp\text{-}OMe - H)]^{2+}$ ion and predicted IR absorption spectra for structures **VI** and **VII**. Band assignment for **VII**: (**a**) $\tilde{\nu}$ = 1612 cm^{-1} ester C═O (str); (**b**) $\tilde{\nu}$ = 1528 cm^{-1} [(**b***) 1562 cm^{-1} for **VI**)] amidate C−N (str); (**c**) $\tilde{\nu}$ = 1448 cm^{-1} ester CH_3 (bend), 1431 cm^{-1} acetyl CH_3 (scr); (**d**) $\tilde{\nu}$ = 1407 cm^{-1} amidate C═O (str)/CH_3 (asym inversion); 1391 cm^{-1} ester C═O (str)/CH_3 (bend); (**e**) $\tilde{\nu}$ = 1359 cm^{-1} amidate C═O (str)/CH_3 (syn. inv)/; (**f**) $\tilde{\nu}$ = 1283 cm^{-1} $C_\alpha-H/C_\beta-H$ (bend). Indicated under the structures are $\Delta H_0{}^{\circ}$ ($\Delta G_{298}{}^{\circ}$) in kcal mol^{-1}.

CONCLUSIONS

In summary, the first gas-phase IR spectra of small triply charged La^{III} complexes with an amino acid derivative and an unusual dissociation product, a lanthanum amidate, are reported here. Successful generation of similar triply charged complexes containing small peptide ligands will allow further spectroscopic exploration of metal ion−peptide coordination as well as novel collision-induced reactions and products.

ASSOCIATED CONTENT

Ⓢ Supporting Information

Tables for the total energies and Cartesian coordinates for structures **I−VII**; optimized structures and bond distances for structures **I−VII** optimized at the B3LYP/sdd/6-31++g(d,p) level; predicted IR spectra for additional structures (Figure **S1**, **S2**); optimized structure and predicted IR spectrum for the neutral ligand **Ac-Trp-OMe** (Figure **S3**); optimized structures, bond distances, and IR spectra for **VI** and **VII** using different functionals (Figures **S4**, **S5**). This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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