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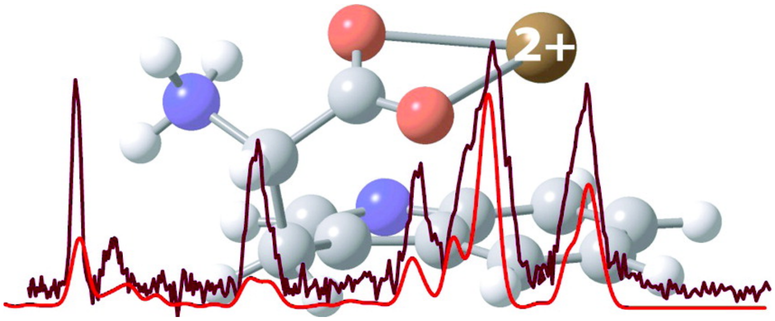

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Gas-Phase Zwitterion Stabilization by a Metal Dication

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There is widespread interest in understanding the effects of solvation and metal chelation on the structure of biomolecules. Gas-phase measurements give detailed insights into these effects, as the complexes can be studied in complete isolation, unperturbed by other factors. Solution- and gas-phase structures can be very different. Whereas all amino acids are known to exist as zwitterions in aqueous solution, even the most basic amino acid arginine is nonzwitterionic in the gas phase.[1] The zwitterionic form of amino acids can be stabilized by attachment of sufficient polar solvent molecules[2] or alternatively by formation of a metal cation complex in a salt-bridge (SB) structure.[3] However, only high-basicity amino acids, such as proline,[4a,b] arginine,[4c,d] and lysine,[4e] have been shown to adopt SB conformations. It is clear that the proton affinity of the proton-accepting site significantly affects the stability of the zwitterionic form.[5] For the 16 “normal” (i.e., nonbasic) amino acids, the zwitterion is formed by proton transfer from the acid to the amino group. This is mostly unfavorable energetically, so that only nonzwitterionic (i.e., charge solvation, CS) complexes have been observed, for both metalated[4a,b,6] and even metalated partially solvated[7] complexes. There is evidence, however, that zwitterions can be formed following gas-phase H/D exchange with a polar solvent molecule (CH_3OD).[8]

The present study is inspired by computational suggestions that increasing the metal ion charge to +2 has a stabilizing effect on the SB form,[9] offering a promising route to stable gas-phase zwitterions of metal-complexed normal amino acids. The energy differences between CS and SB structures are small compared with the binding energies of the metal ions, and it is not a priori clear why one or the other should be favored by particular features of the ligand or the metal ion. Computations of Trp complexes were performed to gain further insight into the effect of metal-ion charge. Previous plotting of SB stability versus metal ion size gave some degree of correlation for singly charged Arg complexes[3a] and singly and doubly charged Gly complexes,[9c] but a plot of the relative SB stability from the present computations versus metal ion size (measured as the O-metal distance) gave poor results. An alternative plot of CS/SB preference versus complex binding energy gives surprisingly good correlations (Figure 1) and divides the complexes into two families of singly and doubly charged ions. The empirical prediction from this plot is that the zwitterionic form is favored by chelation of Trp to doubly charged metals that bind relatively weakly. The alkaline earth metals Ba^{2+}, Sr^{2+}, and Ca^{2+} are all promising candidates, and experimental results for Ba^{2+} are presented here.

The calculations suggest that the three main low-energy structural families shown here have to be considered, in analogy to singly charged M^+Trp complexes.[6] However, there are some significant differences compared to those previous structures.

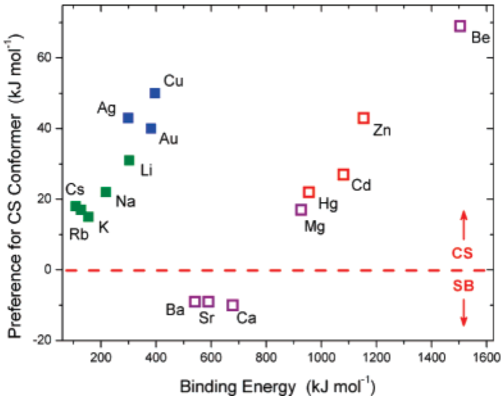
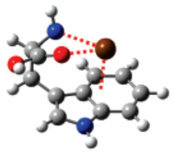
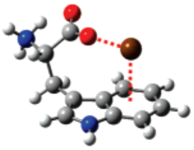


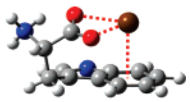
Figure 1. Metal-ion/Trp complexes. Calculated enthalpy preference for the most stable charge-solvation (CS) conformer relative to the zwitterionic salt bridge (SB) conformation, plotted against the binding energy of the most stable conformer. Solid symbols are singly charged complexes; open symbols are doubly charged. Green and purple symbols are alkalis and alkaline earths, respectively; blue and red symbols are transition metals.



CS N/O/Ring



SB O/Ring



SB O/O/Ring

The threefold chelated CS conformation labeled CS N/O/Ring is similar to that in the singly charged alkali systems.[6b] However, the CS O/Ring structure that was found for singly charged systems is not stable here but rearranges spontaneously by hydroxyl proton migration to the nitrogen, giving rise to the twofold chelated SB O/Ring structure shown. SB O/O/Ring, with both oxygens chelated, is the most stable structure; in contrast to the singly charged case it is found that this ring-chelated zwitterion is substantially more stable (by more than 50 kJ mol^{-1}) than the extended (ring-unchelated) zwitterion previously found.[6b] This preference for the ring-chelated zwitterion conformation reflects the larger energy advantage of microsolvation of the doubly charged metal ion by the proximity of the ring, compared with the singly charged metal ions.

The experimental infrared spectrum of the gas-phase complex is obtained by infrared multiple photon dissociation (IRMPD) spectroscopy.[10] A Fourier-transform ion cyclotron resonance (FT-ICR) mass spectrometer interfaced to the FELIX free electron laser light source was used in these experiments, as recently described for singly charged metal ion complexes of Trp.[6] The Ba^{2+}Trp complex was formed by electrospray ionization (ESI) under conditions similar to those of the previous work. The IR spectrum

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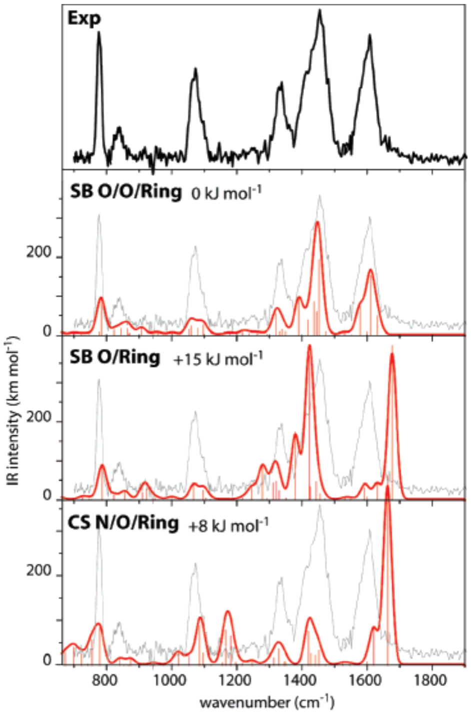

Figure 2. Experimental IRMPD spectrum of Ba^{2+}Trp, compared to calculated spectra and free energies for three low-energy conformers.

of Ba^{2+}Trp (*m*/*z* 171) was recorded by monitoring the wavelength-dependent photodissociation yield at *m*/*z* 162.5, 140.5, 132, 210, and 324. Computations (Gaussian03[11]) were performed at the B3LYP/6-311+g(d,p) (SDD effective core potential on Ba) level for vibrational spectra (frequencies scaled by 0.975) and at the MPW1PW91/6-311+g(d,p)(SDD) level for energy comparisons, because of the higher accuracy of the latter functional for modeling cation-pi interactions.[12]

The mid-IR spectrum, in particular the CO stretch mode, has been found to be a reliable and predictable test of CS versus SB structure of metal-ion-complexed amino acids.[4a,b,d,e,6] In CS complexes for singly charged metals, the $\mathrm{C{=}O}$ stretch appears as an intense peak between 1700 and 1800 cm^{-1}. In SB structures a corresponding characteristic peak is observed between 1650 and 1700 cm^{-1}, which has antisymmetric $\mathrm{CO_2^-}$ stretching and $\mathrm{NH_3^+}$ bending character. (This latter peak is found to be split into two closely spaced components in the computed spectra.) The conformations deduced spectroscopically based on this distinction consistently agree with the predicted ground state from thermochemical calculations, and the positions of these peaks agree well with scaled DFT or MP2 frequency calculations. Agreement of intensities is generally not as good.

In the present case, which is the first doubly charged complex to be studied spectroscopically, computation indicates that the diagnostic $\mathrm{C{=}O}$ feature is shifted to lower energy in both SB and CS forms compared with singly charged complexes. Thus, as Figure 2 shows, the peak is predicted near 1660 cm^{-1} for CS and 1600 cm^{-1} (with splitting) for SB O/O/Ring. Experimentally, little or no intensity is observed at 1660 cm^{-1}, whereas a strong peak is seen around 1600 cm^{-1}, which is clearly consistent with SB O/O/Ring but not with a CS structure. Moreover, the absence of a CO stretch mode at 1660 cm^{-1} rules out a significant contribution of the twofold chelated SB O/Ring zwitterion conformation.

In light of the shifting of the CO stretch mode due to chelation of the metal ion and the uncertainty attending the empirical frequency scaling factor in the calculations, further characteristic spectroscopic differences between ZW and CS conformations are important in confirming the structural assignment. The most intense peak in the spectrum at around 1450 cm^{-1} matches well to the predicted $\mathrm{NH_3^+}$ umbrella mode of SB O/O/Ring. This mode is generally characteristic of the presence of zwitterions. Furthermore, the absence of a double peak structure in the spectral range 1000−1200 cm^{-1} gives additional support for the presence of only SB structures. Finally, the overall agreement with the predicted SB spectrum is excellent and is far better than other low-energy alternatives.

In summary, the observed spectrum is in excellent agreement with the expectation for the lowest-energy SB O/O/Ring zwitterion with respect to the positions of all the expected major peaks and rules out any substantial contribution (that is, more than a few percent) of the likely alternative conformations. In fact, this spectrum can be considered to be a signature IR spectrum of a gas-phase zwitterion for “normal” amino acids that are chelated to a divalent metal cation, as both SB diagnostic modes, the $\mathrm{CO_2^-}$ stretch and $\mathrm{NH_3^+}$ umbrella vibrations, are observed as intense peaks. Although prior computational results have suggested that increasing the metal ion charge is a route to stabilization of the zwitterions, the present results are the first experimental confirmation of this effect. Further exploration of the boundary between SB and CS conformations for multiply charged ions will focus on the influence of metal ion size, proton affinity of the amino acid, and addition of solvent molecules.

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Supporting Information Available: Full citation for ref 11. This material is available free of charge via the Internet at http://pubs.acs.org.

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