Thermochemistry of Non-Covalent Ion–Molecule Interactions

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The thermochemistry of non-covalent ion–molecule complexes has been examined by measuring quantitative bond dissociation energies using threshold collision-induced dissociation in guided ion beam tandem mass spectrometers (GIBMS). The methods used are briefly reviewed and several examples of the types of information and insight that can be obtained from such thermodynamic information are discussed. The hydration of metal cations, both singly and doubly charged, is reviewed and the trends elucidated, mainly on the basis of electrostatic contributions. The binding of alkali metal cations to amino acids has been examined for a range of systems, with both the overall polarizability of the amino acid and the local dipole moment of heteroatomic side-chains shown to be important contributors. The gas-phase interactions of the 12-crown-4 (12C4) polyether with alkali metal cations, classic molecular recognition systems in solution, have been newly compared to previous GIBMS work. These results validate the previous hypothesis that excited conformers were present for Rb⁺(12C4) and Cs⁺(12C4) and offer clues as to how and why they are formed.

Keywords: molecular recognition, collision-induced dissociation, bond dissociation energies

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INTRODUCTION

The use of mass spectrometry to study non-covalent interactions has a long history, as reviewed elsewhere,^{1–5} and pertains to phenomena ranging from ion solvation to host–guest complexes to protein folding. In all of these cases, electrostatic interactions often dominate the formation of the complexes of interest but more subtle interactions are also at play. These charge the acidities of metal ions and the probabilities that molecular recognition has selective interactions useful in environmental remediation, and that protein folding is directed and not stochastic.

Clearly, the strength of these non-covalent interactions is a key metric for how influential they can be. Energy-resolved collision-induced dissociation in a guided ion beam tandem mass spectrometer (GIBMS) is a method developed over the past years that permits the measurement of the energetics for a variety of non-covalent interactions.⁵ Such experiments involve measuring the probability for dissociation of an appropriate complex induced by collisions with an inert gas as a function of the kinetic energy of the ion, which can be varied over a wide range (four orders of magnitude). Analysis of such absolute cross section data, taking into account multiple collisions, the lifetimes for dissociation, and the energy distributions of the reagents, allows the extraction of the intrinsic affinity between the ion and various ligands, both simple and complex. Such absolute energetic data can generally be compared with quantum chemical reactions, thereby validating the energetic information (while simultaneously helping to benchmark theory), identifying the structures of the reactant complexes and their products, and determining the mechanisms for their dissociation.

In this presentation, examples of such energetic

measurements are applied to several case studies. The hydration of metal cations is of interest from both a biological and environmental point of view. Certainly, metal cations will confront aqueous media in the environment, in some cases including issues associated with contamination of aquifers, and their delivery in such media is important physiologically. This then leads to how strongly such metal cations interact with biological molecules, for which we have quantitatively measured bond energies with amino acids (discussed below) as well as nucleic acids,^{6–11} sugars,¹² and phosphates.^{13–15} These systems act as a starting place for establishing a thermodynamic “vocabulary,”¹⁶ a quantitative assessment of the pairwise interactions between metal cations and the components of biological molecules that allows the possibility of detailed insight into the thermochemistry of more complex systems. Finally, a classic example of how alkali metal cations interact with crown ethers has been revisited, with additional insight provided by the newly acquired thermodynamic data. Exploration of how other ions interact with crown ethers has also been pursued.^{17–19} Trends in all these data reveal some of the complexities that control the energetics of these non-covalent interactions.

EXPERIMENTAL AND COMPUTATIONAL METHODS

General experimental procedures and data analysis

The experiments were conducted using either the University of Utah GIBMS^{20,21} or the Wayne State University GIBMS.²² A schematic of the Utah instrument is shown in Fig. 1. All ions discussed here were generated using an electrospray ionization (ESI) source under conditions similar to those described previously²³ and detailed in the appropriate papers for each system. Notably the ESI/ion funnel/radio frequency (rf) hexapole source arrangement used has been shown to produce ions thermalized to 300 K.^{17,18,23–26} In both instruments, ions are extracted from the source,

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Fig. 1. The guided ion beam tandem mass spectrometer at the University of Utah. Key components are labeled.

focused, accelerated, and mass selected using a magnetic momentum analyzer. Reactant ions are then decelerated to well-defined kinetic energies and focused into a rf octopole ion guide, trapping the ions radially.^{20,27,28} The octopole minimizes reactant and product ion loss resulting from scattering. The octopole passes through a static gas cell containing xenon (at pressures between 0.05 to 0.20 mTorr), which is used as the collision gas because it is heavy and polarizable, leading to more efficient kinetic to internal energy transfer.^{29,30} After collision, product ions formed in these collisions and unreacted parent ions drift to the end of the octopole where they are extracted and focused into a quadrupole mass filter for mass analysis. Ions are detected with a high voltage dynode, scintillation ion detector³¹ and the signal is processed using standard pulse counting techniques. Ion intensities, measured as a function of collision energy, are converted to absolute cross sections as described previously.²⁰ The uncertainty in relative cross sections is approximately $\pm 5\%$ and that for the absolute cross sections is approximately $\pm 20\%$. The ion kinetic energy distribution is measured to be Gaussian and has a typical fwhm of 0.2–0.5 eV (lab). Uncertainties in the absolute energy scale are approximately ± 0.05 eV (lab). Ion kinetic energies in the laboratory frame are converted to energies in the center-of-mass (CM) frame using $E_{\text{CM}} = E_{\text{lab}} \cdot m/(m+M)$, where M and m are the masses of the ionic and neutral reactants, respectively.

Threshold regions of the CID reaction cross sections are modeled using procedures developed elsewhere.^{32–35} Details of the analysis procedure, which explicitly accounts for internal and translational energy distributions, the effects of multiple collisions, and the lifetime of the dissociating ions, can be found in the original papers describing the results below. A typical example can be found in ref. 36. The final result is generally the threshold energy at 0 K for dissociation of a ligand from the reactant metal–ligand complex. Because these non-covalent interactions involve heterolytic dissociations (*i.e.*, the ligand retains both electrons involved in the bonding interaction upon bond cleavage) in all cases discussed below,³⁷ such threshold energies correspond directly to the bond dissociation energy (BDE) of the metal–ligand complex and can be adjusted to 298 K values using calculated molecular parameters and standard formulae.

Computational details

Quantum chemical calculations were done using the general procedure that follows, although some details vary from system to system. Likely conformers of the various complexes are explored with a simulated annealing procedure

using the AMBER (version 9) program.³⁸ Each isomer is subsequently optimized in NWChem³⁹ using a low level of theory, HF/3-21G.^{40,41} The Gaussian 09 suite of programs⁴² is then used to optimize all low-lying structures for each system at the B3LYP/6-31G(d) level.^{43,44} Unique structures are further geometry optimized at the B3LYP/6-311+G(d,p) level and vibrational frequencies determined here as well. For heavy metal systems, the def2-TZVPP or def2-TZVPPD basis set is used, where these are size consistent basis sets for all atoms and includes triple zeta+polarization (P) and diffuse (D) functions with an effective core potential (ECP).^{45–47} The def2 basis sets and ECPs were obtained from the EMSL basis set exchange.⁴⁸ Final energies are generally obtained using single point calculations using a 6-311+G(2d,2p) basis set (or one of the def2 basis sets) at B3LYP or MP2(full) levels of theory. These energies all include zero-point vibrational energy (ZPE) corrections and generally include corrections for basis set superposition errors (BSSEs) estimated using the full counterpoise (cp) method.^{49,50}

RESULTS AND DISCUSSION

Hydration of metal cations

Hydration energies of metal cations have been measured using GIBMS for many singly charged metal cations, including Li^+ ,⁵¹ Na^+ , Mg^+ , Al^+ ,⁵² the first-row transition metals, Ti^+ – Cu^+ ,^{30,53} and Ag^+ .⁵⁴ Those for the alkali cations agree well with values obtained from equilibrium measurements using high pressure mass spectrometry (HPMS) by Dzidic and Kebarle,⁵⁵ and those for the transition metals generally agree with previous measurements by Castleman,^{56,57} Michl,^{58,59} and Squires.⁶⁰ For the closed shell alkali cations, the trends observed are simple to understand. The metal–water bond dissociation energies (BDEs) decrease monotonically as the ionic radius of the metal increases and as the number of ligands increases, consistent with an electrostatic bonding mechanism. The ligands cannot approach the larger metals as closely, leading to weaker electrostatic interactions. As the number of ligands increases, the charge becomes delocalized, reducing the electrostatic interactions, and the ligands interact sterically such that ligand–ligand repulsion lowers the BDE. Ultimately, the inner solvent shell is filled and additional ligands cannot bind directly to the metal ion. For the transition metal cations, the open valence d shell introduces new variations such that hybridization of the valence s and d orbitals becomes influential, as first pointed out by Rosi and Bauschlicher.^{61,62}

More recently, the GIBMS studies have been extended

to dications of Ca^{2+} ,^{26,36} Sr^{2+} ,⁶³ Zn^{2+} ,^{64,65} Cd^{2+} ,^{66,67} and Fe^{2+} .⁶⁸ Hydration complexes of the latter three metals have never been studied before, whereas the results for Ca^{2+} and Sr^{2+} agree well with previous studies conducted either by equilibrium measurements using HPMS⁶⁹ or by blackbody infrared radiative dissociation (BIRD).^{70,71} However, because these are both thermal techniques, the smallest complex these methods are capable of studying is 6 and 5 water ligands, respectively. In contrast, because collision-induced dissociation is an energy-based approach, there is intrinsically no limit to how much energy can be introduced, hence the inner shell hydration energies of these dications have been measured for the first time. Generally good agreement is also found between the experimental hydration energies and those obtained from high-level quantum chemical calculations as detailed in the individual reports.

The general trends observed in the BDEs for metal dications follow the same general trends as those for the alkali metal monocations, *i.e.*, they monotonically decline as the size of the metal increases and as the number of water ligands increases. This is shown for the example of Sr^{2+} and Cd^{2+} in Fig. 2. These group 2 and 12 ions are both closed shell and differ in that Cd^{2+} has the valence 4d shell fully occupied. This makes the Cd^{2+} ion slightly smaller (atomic radius= $r=0.99\text{ \AA}$) than Sr^{2+} ($r=1.18\text{ \AA}$) because of the higher nuclear charge. As a consequence, the hydration energies for the third and fourth water ligand are higher for Cd^{2+} than for Sr^{2+} , however, for more ligands, this difference disappears. This suggests that as the inner solvent shell come close to completion, the ligand–ligand repulsion pushes the water molecules to similar distances such that the electrostatic interactions are comparable. The dominance of the electrostatic component on the BDEs is also illustrated by the comparison to the $\text{Na}^+(\text{H}_2\text{O})_x$ complexes, Fig. 2, chosen because this ion has a similar size ($r=0.98\text{ \AA}$) to that of Cd^{2+} . It can be seen that the sodium BDEs are very similar to those of strontium once the effect of the increase in charge is introduced (by multiplying the former by two). One can also note the larger drop between $x=6$ and 7, followed by nearly constant values for $x=7-9$ for both Sr^{2+} and Cd^{2+} . The quantum chemical calculations indicate this is a consequence of filling the first solvent shell at six for both ions and the next

Fig. 2. Comparison of experimental hydration enthalpies (in kJ mol^{-1}) at 298 K for Sr^{2+} (triangles),⁶³ Cd^{2+} (inverted triangles),⁶⁷ and Na^+ (squares, multiplied by 2).^{52,55}

three water ligands each binding to a different pair of inner shell water ligands in similar geometries. For additional water molecules, $x>9$, there are no longer any places where the water can bind to two inner shell ligands; hence the BDEs decrease further.

Alkali metal cation binding to amino acids

Relative measurements of the interactions of lithium^{72–74} and sodium^{73,75} cations with most amino acids have been performed using the kinetic method,^{76,77} with absolute thermochemistry obtained using GIBMS for all the alkali metal cations with several amino acids: glycine (Gly),^{78–82} proline (Pro),^{81–83} serine (Ser),^{81,82,84} threonine (Thr),^{81,82,84} cysteine (Cys),^{82,85} methionine (Met),⁸⁶ aspartic acid (Asp), asparagine (Asn), glutamic acid (Glu), glutamine (Gln),^{25,87} phenylalanine (Phe), tyrosine (Tyr), and tryptophan (Trp).⁸⁸ In all cases, the TCID experiments yield quantitative BDEs that are generally consistent with quantum chemical values. As for any other ligands,⁵ the BDEs increase as the size of the metal cation decreases.^{81,82} This is shown in Fig. 3 for Na^+ and K^+ , the alkali metals for which the most data are available, largely because these are the most relevant biologically. In addition, it can be seen that there is an overall trend such that the BDEs generally increase with the polarizability of the amino acid ligand, as first noted by Rodgers and Armentrout for the systems indicated by solid symbols.¹⁶ Notably, the amino acids involved in this correlation generally have side-chains without heteroatoms, except for the sulfur in Met. Figure 3 also shows that most amino acids having heteroatomic side-chains have enhanced BDEs compared to those suggested from the polarizability trend. This indicates that the local dipole moments of these side chains also contribute to the strength of the electrostatic interactions. Indeed, it can be seen that amino acids with hydroxyl side-chains (Ser and Thr) and those with carboxamide side-chains (Asn and Gln) form complexes with BDEs that parallel the polarizability trend previously established, whereas those for carboxylic acid side-chains (Asp and Glu) are intermediate. The decrease in the latter BDEs can be attributed to inductive effects in which the hydroxyl group

Fig. 3. Bond dissociation energies for amino acids (AA) to Na^+ (circles) and K^+ (triangles) at 0 K (in kJ mol^{-1}) versus estimated polarizability (in $\text{\AA}^3$). Long lines are linear regression fits to the solid symbols for each alkali metal cation. Data are taken from the references given in the text.

removes electron density from the metal-coordinating carbonyl group. This inductive effect can also be seen by noting that the carboxamides (Asn and Gln) bind more tightly than the corresponding acids (Asp and Glu) by $\sim 15 \text{ kJ mol}^{-1}$ for Na^+ and $\sim 9 \text{ kJ mol}^{-1}$ for K^+ . In addition, the longer side-chain amino acids (Glu and Gln) bind more tightly than the corresponding shorter side-chains (Asp and Asn) by $\sim 5 \text{ kJ/mol}$ for both Na^+ and K^+ , in agreement with the increase in polarizability that the additional CH_2 group provides.

Alkali metal cation binding to crown ethers

Crown ethers are a prototypical molecular recognition system, acting as a “host” that can accommodate many different “guest” species, including the alkali metal cations. Crown ethers, *e.g.*, 12-crown-4 (12C4=1,4,7,10-tetraoxacyclododecane), 15-crown-5 (15C5=1,4,7,10,13-pentaoxacyclopentadecane), and 18-crown-6 (18C6=1,4,7,10,13,16-hexaoxacyclooctadecane), were first characterized by Pedersen.^{89,90} Early qualitative studies of the intrinsic affinities of the crowns for the five alkali metal cations were conducted by Brodbelt^{91,92} and Dearden,^{93–95} with much more systematic studies by More, Ray, and Armentrout,^{96–101} in parallel with quantum chemical calculations of Feller and coworkers.^{96,97,102} As with the other ligands discussed above, the metal cation–crown BDEs decrease as the size of the metal ion increases and increase with increasing number of oxygens available in the crown. Furthermore, comparison to comparable but independent ligands, dimethyl ether (DME) and dimethoxyethane (DXE), showed that steric constraints on the cyclic crown ethers reduce the BDEs compared to the same number of oxygens on independent ligands. In contrast to the behavior observed in solution, no obvious selectivity for particular-sized cations by the crown ethers was evident in the thermodynamic information; however, by combining these quantitative data with the hydration energies of the alkali metal cations, it can be shown that the solution-phase selectivity (for instance, for K^+ by 18C6) arises from the competition between hydration and complexation by the crown ether.¹⁰³

Although most of the experimental BDEs determined

in these studies agreed well with the theoretical calculations,^{96–99} those for 12C4 ligands with Rb^+ and Cs^+ were lower by $50\text{--}60 \text{ kJ mol}^{-1}$.^{100,102} This is shown in Fig. 4 by the solid symbols. The explanation offered at the time¹⁰⁰ was that excited conformers of these complexes were generated experimentally in the dc discharge/flow tube (DC/FT) source utilized, such that the measured BDEs do not correspond to the ground state complex. In this source, the complexes are formed by condensation of the metal cation and the ligand followed by stabilization and thermalization by collisions with the He and Ar bath gases present. This method of ion generation may allow complexes in excited conformations to be formed and stabilized before rearrangement to the ground state. Because the energy needed to dissociate these excited conformers is much less than that for the ground state, their behavior can dominate the observed CID behavior.

Recently, this hypothesis has been tested by examining the CID of the $\text{Rb}^+(12\text{C4})$ and $\text{Cs}^+(12\text{C4})$ complexes formed by electrospray ionization.¹⁰⁴ In electrospray ionization, the complexes are preformed in solution and can therefore be expected to correspond to the most stable conformer. Indeed, comparison of the new CID data to the original data shows a distinct shift in the thresholds for both systems to higher energies, and a resultant decrease in the cross section magnitude. In addition, the older data for $\text{Na}^+(12\text{C4})$ and $\text{K}^+(12\text{C4})$ were reanalyzed so that the interpretation of the resulting thermochemistry was consistent for all four systems. Interestingly, this analysis showed that there was a small tail in the $\text{K}^+(12\text{C4})$ data that can be attributed to a small population of an excited conformer, again with an excitation energy of about 50 kJ mol^{-1} . In contrast, the $\text{Na}^+(12\text{C4})$ data showed no indications of such an excited conformer. The new BDEs for all four metal cations are also shown in Fig. 4, where it can be seen that the interpretation of the data for the two lighter metals is robust. In contrast, the BDEs for the heavier metals have now shifted up into agreement with theoretical values, calculated at the B3LYP/def2-TZVPPD and MP2(full)/def2-TZVPPD levels. A comprehensive exploration of the potential energy surfaces for

Fig. 4. Comparison of the experimental threshold collision-induced dissociation (TCID) bond energies for $\text{M}^+-12\text{C4}$ for $\text{M}^+=\text{Na}^+$, K^+ , Rb^+ , and Cs^+ with those calculated at the B3LYP (circles and diamonds) or MP2(full) (triangles and inverted triangle) levels of theory using the def2-TZVPPD basis set including counterpoise corrections.¹⁰⁴ The full line shows perfect agreement between experiment and theory. New experimental values¹⁰⁴ are shown by open symbols, whereas closed symbols show previous values.^{98–100}

interaction of the metal cations with 12C4 shows that the $\sim 50 \text{ kJ mol}^{-1}$ excitation energy found for K^+ , Rb^+ , and Cs^+ most closely corresponds to a conformer in which the ions interact with only two of the oxygens in the crown ether. Surprisingly, there is not a large barrier separating this conformer from lower energy conformers in which three and four (for the ground state) oxygens bind to the metal cation. Nor is there an appreciable difference in the potential energy surface landscape for the four metal cations except for the differences in the $\text{M}^+ + 12\text{C}_4$ asymptotic energies. We conclude that the likelihood of forming the excited conformation in the DC/FT ion source is a consequence of the kinetics of formation. Namely, condensation of M^+ and 12C4 initially yields the C2 complexes with internal energies that vary considerably as M^+ changes, such that fewer stabilizing collisions are needed to form the excited conformer for the more weakly bound Rb^+ and Cs^+ complexes. In addition, the weaker binding of these metals results in lower metal–ligand frequencies, increasing the density of states, thereby decreasing the rate of dissociation, such that the longer lifetime allows more efficient three-body collisional stabilization of the excited conformation.

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