Ion Structure Characterization and Energetics in the Gas Phase Using Fourier Transform Ion Cyclotron Resonance Mass Spectrometry and Ion Mobility Spectrometry

Tina Heravi
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Ion Structure Characterization and Energetics in the Gas Phase Using Fourier Transform Ion Cyclotron Resonance Mass Spectrometry and Ion Mobility Spectrometry

Tina Heravi

A dissertation submitted to the faculty of Brigham Young University in partial fulfillment of the requirements for the degree of Doctor of Philosophy

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ABSTRACT

Ion Structure Characterization and Energetics in the Gas Phase Using Fourier Transform Ion Cyclotron Resonance Mass Spectrometry and Ion Mobility Spectrometry

Tina Heravi
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Doctor of Philosophy

In this dissertation, I used Fourier transform ion cyclotron resonance mass spectrometry (FTICR) and ion mobility spectrometry (IMS) to study the structure and energetics of supramolecular complex ions in the gas phase.

Using the CRAFTI (cross sectional areas by Fourier transform ion cyclotron resonance) technique developed by Dearden’s lab we observed that complexes with alkali cations capping the portals of cucurbit[5]uril (CB[5]) bind halide anions size-selectively in the gas phase. Our data suggest that Cl\(^–\) binds inside the CB[5] cavity, Br\(^–\) binds both inside (with Na\(^+\) ions capping the portals of CB[5]) and outside (when K\(^+\) caps CB[5]), and I\(^–\) binds weakly outside. Although geometry optimization at the M06-2X/6-31+G* level of ab initio theory suggests internal anion binding is energetically favored over external binding, we believe the externally-bound complexes observed experimentally must be due to large energetic barriers hindering the passing of large anions through the CB[5] portal, preventing access to the interior. Calculation of the barriers to anion egress using MMFF//M06-2X/6-31+G* theory supports this idea.

Collision cross section (CCS) measurements using the CRAFTI method for CB[5] complexes with various alkali metals and different neutral guests (methanol, ethanol, formic acid, and acetonitrile) along with the results of mass spectra from FTICR show that both the sizes and the resulting charge densities of the alkali metal ions affect the relative tendency of the guests to bind inside CB[5]. The CCS values suggest that methanol, formic acid, and acetonitrile are internally bound CB[5] while ethanol is bound outside the CB[5] host. The relative abundances of the paired peaks in the obtained mass spectra indicate that the inclusion of formic acid and methanol is enhanced when K\(^+\) ions cap the complexes, whereas the inclusion of acetonitrile is enhanced when Cs\(^+\) ions cap the complexes. The relative abundance of ethanol complexes increases when Na\(^+\) ions cap the complexes.

CRAFTI CCS values for singly- and doubly-charged cucurbit[n]uril (n = 5, 6, and 7), decamethylcucurbit[5]uril (mc5), and cyclohexanocucurbit[5]uril (CB*[5]) complexes of alkali metal cations (Li\(^+\)-Cs\(^+\)) show +2 complex ions have CCS values ranging between 94-105% of those of their +1 counterparts (increasing with metal ion size). These results are consistent with CCS values calculated using the projection approximation (PA). Ion mobility measurements of the same complexes find the CCS of +2 complexes to be in all cases 9-12% larger than those of the corresponding +1 complexes, with little metal ion dependence. Trajectory method (TM) calculations of CCS for the same structures consistently yield values 7-10% larger for the +2 complexes than for the corresponding +1 complexes and little metal ion dependence which agrees with experimental values.

Keywords: FTICR, CRAFTI, IMS, supramolecular complexes, molecular interactions
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Chapter 1. Introduction

1.1 Collision Cross Section Measurements

Molecular structure measurements are vital to understanding the properties and reactivity of molecules. Different experimental techniques can be used to characterize molecular structure. Besides X-ray crystallography,\(^1\) NMR spectroscopy,\(^2\) and infrared spectroscopy\(^3\) to determine the locations of atoms in a crystal, define the types of bonds in a structure, and the environment of hydrogen atoms in the molecule, respectively, other techniques can be used to determine collision cross section (CCS)\(^4\) of gaseous ions. CCS, or rotationally averaged cross-sectional area, is the area around a molecule in a buffer gas in which the center of both molecules must be for a collision to happen. CCS measurements are an especially useful way to distinguish the sizes of ions because, unlike in chromatography, there is no need for prior purification or crystallization of the compound of interest; interfering sample solutions do not affect CCS measurements in the gas phase.\(^5\) CCS values may be measured experimentally (Section 1.2) or computed if the 3D structure of the molecule is known or can be calculated. It is necessary to have computational modeling of likely structures and computed CCS values for those structures (under conditions matching those of the experimental measurements) to directly compare them with the experimental measurements (Figure 1.1). Although computational chemistry and modeling were not the focus of my research, to complement my experimental work, I asked an undergraduate research assistant, Spencer Johnson, and my colleague, Dr. Andrew Arslanian, to help me with those measurements. The details of how these measurements were done are in chapters 2-4, where I describe the results of specific studies.
1.2 Experimental determination of collision cross section

The most common method for measuring collision cross sections in the gas phase is ion mobility (IM), especially for characterizing peptide and protein conformations. Interfacing IM with mass spectrometry (IM-MS) was done by Earl W. McDaniel in 1962 for the first time, and has since become an important method that provides structural information.

A more recent method involves measuring the collision cross section using techniques from Fourier transform ion cyclotron resonance mass spectrometry (FTICR-MS). This method is called CRAFTI (an acronym for cross sectional areas by Fourier transform ion cyclotron resonance mass spectrometry) and is complementary to IM measurements for determining collision cross sections.

The following two sections introduce both techniques and the instrumentation used in making the measurements.

1.3 Fourier transform ion cyclotron resonance mass spectrometry (FTICR-MS)

FTICR-MS, like any other mass spectrometric method, is an analytical technique to measure the mass-to-charge ratio (m/z) of one or more molecules introduced into the instrument.
In FTICR-MS, the m/z measurement is based on the ion’s cyclotron frequency in a magnetic field.\textsuperscript{11} I used a Bruker Fourier transform ion cyclotron resonance mass spectrometer model APEX 47e equipped with an Infinity trapping cell\textsuperscript{12} for my research. To generate ions, I used a modified micro electrospray ionization (ESI) source based on an Analytica (Branford, CT, USA) design with a metal capillary drying tube based on the design of Eyler et al.\textsuperscript{13} I also made a dual micro-electrospray (Figure 1-2) with 50 μm inner diameter fused silica capillary tubing emitter tips. The purpose was to spray Li\textsuperscript{+} and cucurbit[5]uril (CB[5]) for one of my projects (see details in chapter 4) to see if I could make them bind together. The dual ESI worked well during the test where I sprayed CB[5]+Cs and Agilent tuning mix simultaneously with a 15 ul/hr flow rate. I observed signal for [CB[5]+2(NH\textsubscript{4})]\textsuperscript{2+} at 433.1569 m/z, [CB[5]+2Cs]\textsuperscript{2+} at 548.0279 m/z and peaks at 622 m/z and 922 m/z from the Agilent tuning mix (Figure 1-3). Unfortunately, I did not successfully get a signal for CB[5]+Li when I sprayed both Li and CB[5] from the new assembly, even after changing different source parameters.

Figure 1-2. Photographs of the new built Dual-ESI spray assembly.
After ions are generated using an ion source, the ions travel through differentially pumped regions and ion optics to a hexapole with a voltage to trap the ions. Ions are periodically pulsed out of the hexapole, and enter the mass analyzer after passing through a set of electronic lenses. As ions are trapped in the trapping cell, they can be excited to larger cyclotron amplitudes using an oscillating electric field perpendicular to the magnetic field. The excitation also causes the ions to move in phase (in a coherent packet) with the excitation field. Coherently orbiting ions can be detected as they pass close to a set of two detection plates in which they induce an image charge, giving a time-domain signal. This signal is digitized, and Fourier transformed to yield a frequency domain spectrum, which is then converted to the m/z domain, giving a mass spectrum. FTICR-MS has the advantages of high mass accuracy and exceptionally high resolving power. The instrument can also be used to measure collision cross sections (CCS),
using a method referred to as CRAFTI, invented by Dr. Dearden’s lab. Thus, both CCS and the mass-to-charge ratio can be measured at the same time using one instrument.\textsuperscript{14}

CRAFTI obtains ion collision cross sections from the pressure-dependent ion linewidths in Fourier transform mass spectra,\textsuperscript{15} which means we allow ions to collide with background gas that we introduced into the cell using a Freiser style pulsed leak valve system\textsuperscript{16} resulting in collision-limited decay of signal intensity. We determine the frequency domain linewidths by fitting the Fourier transformed peaks to Lorentzians. The Lorentzian linewidths increase linearly with pressure; the slope of a plot of linewidth vs. pressure (or, equivalently, neutral number density) is used to compute the collision cross section using the CRAFTI ($\sigma$) equation:\textsuperscript{9-10}

$$\sigma = \frac{f_{\text{whm}} m}{N} \frac{\pi d}{z \beta V_{\text{pp}} T_{\text{exc}}}$$

(1-1)

Here, $f_{\text{whm}}/N$ is the fitted slope, mass (m), ion charge (z), cell diameter (d), cell geometry factor ($\beta$), which is 0.897 for the Bruker Infinity Cell, corresponding peak-to-peak amplitude ($V_{\text{pp}}$), and excitation length ($T_{\text{exc}}$).

While CRAFTI has shown promising results, it still has one significant limitation: accurate pressure measurements are required. To address this drawback, the multiCRAFTI technique can be used.\textsuperscript{17} In multiCRAFTI we measure two (or more) ions at the same time under identical pressure conditions with nearly identical kinetic energies (in the center-of-mass reference frame). In multiCRAFTI experiments, I used a LabVIEW (National Instruments; Austin, TX; 2016 version) program to generate excitation waveforms to excite the ions. Using the LabVIEW program, we can either sequentially perform two single-frequency excites where
the heavier ion (lower frequency) is excited first, and then the lighter ion (higher frequency), referred to as sequential-multiCRAFTI, or sum the two single-frequency excites, so both are applied simultaneously, referred to as simultaneous-multiCRAFTI. The collision cross section ratio of the two ions ($\frac{CCS_2}{CCS_1}$) can be determined from the full width at half maximum linewidths acquired using Lorentzian fits to the mass spectral data for each ion using Equation 1-2:

$$\frac{CCS_1}{CCS_2} = \frac{fwhm_1 m_1 z_2 V_{PP,2} t_{ex,2}}{fwhm_2 m_2 z_1 V_{PP,1} t_{ex,1}}$$

(1-2)

Simultaneous-multiCRAFTI was the primary research method for my CCS measurements for different systems (Chapters 2-4). However, I performed sequential-multiCRAFTI experiments on various pairs of alkylammonium cations relative to tetraoctylammonium ion in a research article describing the multi-CRAFTI technique.17

1.4 Ion mobility mass spectrometry (IM-MS)

Ion mobility (IM) is an analytical technique that rapidly separates gaseous ions as they travel in a buffer gas environment under the influence of an applied electric field (E). Under appropriate conditions, the applied electric field causes ions to travel through the buffer gas with a constant velocity ($V_d$). The velocity of the ions is linked to their specific mobility constant (K) as defined by Equation 1-3:

$$K = \frac{V_d}{E}$$

(1-3)
Smaller ions travel faster in a given electric field than larger, less mobile ions. In other words, ions are separated by their differences in mobility as they interact with the buffer gas. The mobility of ions (which is usually determined by the drift time recorded via an ion mobility instrument with a known drift length and electric field) depends on the gas temperature (T) and the mass of the buffer gas molecules (m), and is related to the ions’ collision cross-sections (CCS or Ω) (Equation 1-4).

\[
K = \left( \frac{3a}{16N} \right) \left( \frac{2\pi}{kT} \right)^{1/2} \left( \frac{m+M}{mM} \right)^{1/2} \left( \frac{1}{\Omega} \right)
\]  

(1-4)

Here \( q \) is the charge on the ion, \( N \) is the number density of the buffer gas, \( k \) is Boltzmann's constant, and \( M \) is the mass of the ion. Drift-time ion mobility spectrometry is the only type of ion mobility that yields CCS directly from the mobility (or drift time).

Ion mobility combined with mass spectrometry (IM-MS) has rapidly grown as a valuable method for determining collision cross section (CCS) values in the past few years. I used the Agilent 6560 Ion Mobility Quadrupole Time-of-Flight mass analyzer (IM-QTOF) for experimental CCS measurements based on ion mobility. A schematic diagram of the instrument is shown in Figure 1-4. After ions are generated using a nanoelectrospray ionization source with 30 \( \mu \)m electrospray tips made by Dr. Ryan Kelly’s group, the ions pass through a single bore capillary to the front ion funnel. The front ion funnel enhances the sensitivity by efficiently moving the ions into the trapping funnel while pumping away excess gas. The trapping funnel stores the ions and then releases discrete packets of ions into the drift tube (~80 cm long and generally operated at 20 V/cm drift field). Ions are separated as they pass through the drift tube based on their size.
and charge. Since the drift cell is operated under low electric field condition, the mobility is more dependent on the size and structure of the molecules and how they interact with the buffer gas at approximately 3.94 torr. After that, the ions enter the rear ion funnel, where they efficiently refocus and are transferred to the hexapole ion guide and then to the mass analyzer. I did all of my ion mobility CCS experiments using the stepped field method,\textsuperscript{20} where the drift voltage is varied for ion mobility dispersion.

![Diagram of a time-of-flight mass spectrometer](image)

**Figure 1-4. General workflow for combining molecular modelling with experiments.\textsuperscript{21}**

### 1.5 Supramolecular Chemistry

Supramolecular chemistry has been a rapidly growing field over the past few decades. It studies the structure and function of the supramolecules that result from the association of smaller molecules held together through intermolecular interactions.\textsuperscript{22} Host-guest chemistry is one of the
main focuses of supramolecular chemistry. In host-guest chemistry, the chemical interaction between the host (a larger molecule with a suitable binding site) and the guest (a smaller molecule) is dominated by noncovalent interactions. Cucurbit[n]urils (CB[n]) are a series of glycoluril-based macrocyclic hosts that have a hydrophobic cavity and two identical carbonyl-fringed portals. The CB[n] family features rigid structures, portals that are suitable for binding with cationic species, and the ability to bind guests with high affinity; they represent an attractive class of host molecules. In my studies, I used CB[5], CB[6], CB[7], decamethylcucurbit[5]uril (mc5), and cyclohexanocucurbit[5]uril (CB*[5]) (Figure 1-5).

I measured CCS values for CB[5] complexes with various alkali cations capping the portals and halide anions bound inside and outside to show that cucurbit[n]uril-metal complexes can be size-selective anion receptors (Chapter 2). I used CB[5] and mc5 and measured their CCS values when complexed with different neutral molecules and alkali metals to determine whether the guests were bound inside or outside the hosts (Chapter 3). The results of that project show size-selectivity for alkali metals in cucurbituril complexes with neutral guests. I also measured CCS values for CB[5], CB[6], CB[7], mc5, and CB*[5] complexed with alkali metal ions using both IM-MS and the multi-CRAFTI technique to compare the CCS results obtained using the two techniques (Chapter 4).
Figure 1-5. Molecular structures of CB[5] (n=5,6,7) and derivatives.
1.6 References


Dr. Jiewen Shen and I contributed equally in this project. I was responsible for all multiCRAFTI measurements and for drafting the article.

2.1 Abstract

We report data that suggest complexes with alkali cations capping the portals of cucurbit[5]uril (CB[5]) bind halide anions size-selectively as observed in the gas phase: Cl\(^-\) binds inside the CB[5] cavity, Br\(^-\) is observed both inside and outside, and I\(^-\) binds weakly outside. This is reflected in sustained off-resonance irradiation collision induced dissociation (SORI-CID) experiments: all detected Cl\(^-\) complexes dissociate at higher energies, and Br\(^-\) complexes exhibit unusual bimodal dissociation behavior with part of the ion population dissociating at very low energies with the remainder dissociating at significantly higher energies comparable to those observed for Cl\(^-\). Decoherence cross sections measured in SF\(_6\) using cross sectional areas by Fourier transform ion cyclotron resonance (CRAFTI) techniques for [CB[5]+M\(_2\)X\(^+\)]\(^+\) (M = Na, X = Cl or Br) are comparable to or less than that of [CB[5]+Na\(^+\)] over a wide energy range, suggesting that Cl\(^-\) or Br\(^-\) in these complexes are bound inside the CB[5] cavity. In contrast, [CB[5]+K\(_2\)Br]\(^+\) has a cross section measured about 20% larger than that of
[CB[5]+Na]+, suggesting external binding that may correspond with the weakly-bound component seen in SORI. While I– complexes with alkali cation caps were not observed, alkaline earth iodides with CB[5] yielded complexes with cross sections 5-10% larger than that of [CB[5]+Na]+, suggesting externally-bound iodide. Geometry optimization at the M06-2X/6-31+G* level of ab initio theory suggests internal anion binding is energetically favored by approximately 50-200 kJ mol⁻¹ over external binding; thus, the externally-bound complexes observed experimentally must be due to large energetic barriers hindering the passing of large anions through the CB[5] portal, preventing access to the interior. Calculation of the barriers to anion egress using MMFF//M06-2X/6-31+G* theory supports this idea and suggests that the size-selective binding we observe is due to anion size-dependent differences in the barriers.

2.2 Introduction

Many strategies for selective binding of anions are targeted at polyatomic anions and their hydrogen bonding preferences.¹ Therefore, these strategies tend to be shape-selective for particular anions. While selective binding of cations based on complementarity between the sizes of the guest and host is relatively common, similar size-based selectivity for anions is relatively rare, although it is not unknown.² Binding of the spherical halide anions depends strongly on the extent to which the anion is solvated, so for example complexation of fluoride in protic solvents is very difficult because few hosts can compete effectively against fluoride’s very high solvation energy. The larger halides have progressively lower solvation energies, but their larger sizes also mean electrostatic interactions with potential hosts are weaker. Chloride seems to offer a good compromise between these opposing considerations, with many examples of chloride-binding
and transporting systems known,\textsuperscript{1,3-4} although usually selectivity for one halide over another is not addressed.

Because cucurbit[n]urils (hereafter CB[n] where n indicates the number of repeat units), which are cyclic condensation polymers of glycoluril and formaldehyde (Figure 2-1), are fairly rigid host molecules, both the roughly spherical electropositive interior of the hollow CB[n]-metal ion complex, and to a lesser extent the roughly circular portal that grants access to the interior, have relatively well-defined sizes that might lead to size-selective binding of spherical halide anions. Such size selectivity has frequently been observed for both neutral and cationic guests in CB[n] hosts.\textsuperscript{5-7}

![Figure 2-1. a) Structure of cucurbit[5]uril (CB[5]). b) Electrostatic potential contours on a plane through CB[5] (red=negative, blue=positive). c) Electrostatic potential contours on a plane through [CB[5]+Na2]\textsuperscript{2+}, with the same color coding over the same range of values.](image)

As the potential maps in Figure 2-1b) and c) suggest, CB[5] itself is probably not a good host for anions. However, the two portals of CB[5] (at the top and bottom of the ligand as oriented in the figure) are excellent cation binding sites, and complexes of CB[5] with cations have electrostatic potentials that suggest anion binding in the host cavity should be favorable (Figure 2-1c). More fundamentally, as a simple, rigid, ditopic host with two well-defined cation binding sites, CB[5] offers an opportunity to examine how two proximate cation binding sites interact and how that interaction can be modulated in the presence of an anion.
A few reports\textsuperscript{8-10} have examined CB[n]-based systems as anion receptors, but to our knowledge have not addressed anion size-selectivity. For example, Huang and coworkers synthesized chloride and nitrate anion inclusion complexes of CB[5]-metal species and explored selectivity and metal ion effects using X-ray crystallography and fluorescence spectroscopy.\textsuperscript{8-9} In particular, they synthesized Cl@CB[5] inclusion complexes capped by various metals (K\(^+\), Ba\(^{2+}\), Cd\(^{2+}\), La\(^{3+}\)) and examined binding behaviors. For K\(^+\) and Ba\(^{2+}\) cations, anion complexes of CB[5] bound one metal ion on each portal, while only one metal ion was bound on one of the portals (leaving the other portal open) when Cd\(^{2+}\) or La\(^{3+}\) was the metal. With K\(^+\), a one-dimensional polycationic chain formed, whereas the other three cations resulted in isolated complexes. This condensed-phase work also examined the selectivity of CB[5] toward nitrate and chloride, and found protonated CB[5] favored binding nitrate, whereas coordination of La(III) to CB[5] resulted in a preference for chloride over nitrate in solution and in the solid state.

More recent studies have explored molecules that share structural similarity with cucurbiturils as halide binders, including bambusurils\textsuperscript{11-13} and hemicucurbit[6]urils.\textsuperscript{14} With these hosts, binding involves interactions of H-atoms on the host with the halide. This contrasts with the present work, where we will show that preferential binding occurs inside the CB[5]-metal complex cavity where there are no proximate H atoms; instead, halide binding in CB[5] is largely governed by electrostatic considerations and is strongly dependent on the size relationship between structural features of the host and the halide anion.

Herein, we extend the study of halide binding by CB[5] capped by various metal ions into the gas phase, and in particular demonstrate size selectivity and some degree of metal dependence in these interactions. Our goals included understanding size-based anion-binding selectivity in the absence of solvent effects, combining experimental and computational
approaches to probe the intrinsic binding properties of these host-guest systems without the influence of neighboring molecules, and developing the ability to perform these studies with very small amounts of material, in complex mixtures, without requiring crystals. We employed a combination of gas-phase experimental and computational methods toward these objectives. We measured relative dissociation energies of various complexes involving halide anions, CB[5], and metal cations using the sustained off-resonance irradiation collision-induced dissociation (Sori-CID) technique,\cite{15,16} and measured relative collision cross sections (CCS)—which yield gas phase geometric information otherwise difficult to obtain—using a new variant (unpublished results, which we refer to as “multi-CRAFTI”) of the cross-sectional areas by Fourier transform ion cyclotron resonance (CRAFTI) technique.\cite{17,18,19,20} We complemented the experimental results with computed binding energies using the M06-2X/6-31+G* level of density functional theory, and also calculated barriers to anion egress using structures determined from the Merck Molecular Force Field (MMFF) with energies calculated using M06-2X/6-31+G* theory. Taken together, we believe the results make a strong case for size-selective binding of halide anions by CB[5], based on the relative sizes of the halides and the CB[5] portals.

\section*{2.3 Experimental}

\textit{Materials}

CB[5], as well as fluorides, bromides, and iodides of sodium and potassium, and rubidium chloride (all with ≥ 99% purity) were purchased from Sigma-Aldrich (St. Louis, MO). Sodium chloride was analytical reagent grade from Mallinckrodt Chemical Works (St. Louis, Mo); potassium chloride was reagent grade from Merck & Co. (Kenilworth, NJ). Barium iodide (≥ 95% purity) and strontium iodide (≥ 99% purity) were purchased from Aldrich (Milwaukee, WI).
HPLC-grade water from Avantor Performance Materials (Center Valley, PA) and isopropyl alcohol (≥ 99.5% purity) from Thermo Fisher Scientific (Fair Lawn, NJ) were used for all solutions. Argon (Ar) and sulfur hexafluoride (SF₆) gases (99.9997% and 99.8% purity, respectively) were purchased from Airgas, Inc (Radnor, PA). Solvents, CB[5], and the metal salts were used as supplied without further purification.

Stock solutions of CB[5] and metal salts were prepared at about 4 mM concentration in 50:50 isopropanol:water. Solutions for electrospray were prepared by mixing and diluting the stock solutions with 50:50 isopropanol:water so that the final concentration of CB[5] was 100 μM and the alkali metal halide concentration was about 200 μM.

Instrumentation

All experiments were performed using a Bruker model APEX 47e Fourier transform ion cyclotron resonance mass spectrometer (FTICR-MS) equipped with an Infinity trapping cell²¹ and a 4.7 T superconducting magnet, and controlled by a MIDAS Predator data system (National High Magnetic Field Ion Cyclotron Resonance Facility; Tallahassee, FL).²² Collision gas (Ar for SORI experiments, SF₆ for CRAFTI) was introduced to the FTICR trapping cell using a Freiser-type²³ pulsed leak valve consisting of a 0.004” orifice solenoid pressurization valve backed by a 28 psig supply line and a 0.039” orifice solenoid evacuation valve connected to a mechanical vacuum pump (both valves from General Valve Corp.; Fairfield, NJ). Both solenoid valves were connected to the high-pressure side of a precision variable leak valve (Varian; Palo Alto, CA). Pressure measurements were carried out using a cold cathode gauge (Balzers; Fürstentum, Lichtenstein) mounted outside the high magnetic field about 1 m from the trapping cell. Various steady-state backing pressures for the leak were obtained by varying the length of time the pressurization
solenoid valve was left open, while the evacuation solenoid is left closed, resulting in a corresponding constant pressure in the trapping cell about 0.5 s after the pressurization event. Ions were generated in a micro-electrospray source modified from an Analytica (Branford, MA, USA) design, with a heated metal capillary drying tube based on the design of Eyler. Radio frequency (rf) excitation amplitudes were measured using an oscilloscope at the output of the final excitation amplifier. The ions being compared in multi-CRAFTI experiments were excited using waveforms synthesized via a LabVIEW program. The program produces an excitation waveform with a user-specified duration by adding appropriate single-frequency excitation waveforms with relative amplitudes such that the ions being compared are both excited to the same center-of-mass kinetic energy. Thus, both ions were excited simultaneously at their respective cyclotron frequencies.

*Procedures for SORI-CID and multi-CRAFTI*

In all experiments, ions were generated via electrospray and injected into the FTICR trapping cell. Mono-isotopic peaks were isolated using stored waveform inverse Fourier transform (SWIFT) techniques and then subjected to either SORI-CID or multi-CRAFTI.

In SORI-CID experiments the background Ar collision gas pressure in the trapping cell was raised to \(10^{-5}\) mbar via the pulsed leak valve, waiting 3s after pulsed leak activation to ensure steady-state pressure conditions, followed by a computer-controlled duration, single-frequency, fixed amplitude RF pulse 500 or 1000 Hz below the resonant frequency of the ion of interest. This was followed by evacuation of the pulsed leak for 3s to allow the cell to return to the baseline pressure of around \(10^{-8}\) mbar immediately followed by a broadband chirp excitation and detection. A tool command language (TCL) script was used to modulate the SORI-CID energy deposited into the target ions by varying the duration of the single-frequency SORI-CID excitation event.
The average energy deposited in the ion via the SORI-CID event, $E_{SORI}$, is calculated using:

$$E_{SORI} = N^* \sigma K_v f_E t_{colli} \frac{\beta^3 q^3}{128 \pi^3 d^3 (\Delta f)^3} \left( \frac{M}{M + m} \right) \frac{V_{pp}^3}{m^2}$$

(2-1)

Here, $N^*$ is the neutral gas number density, $\sigma$ is the collision cross section, $K_v$ is a proportionality constant, $f_E$ is an assumed constant fraction of the maximum kinetic energy converted to internal energy in the ion, $t_{colli}$ is the length of the SORI event, $\beta$ is the trapping cell geometry factor (0.897 in the Bruker Infinity Cell used in these experiments), $q$ is the charge on the ion, $d$ is the trapping cell diameter, $\Delta f$ is the frequency offset of the excitation pulse from the ion’s resonant frequency, $M$ is the mass of the neutral, $m$ is the mass of the ion, and $V_{pp}$ is the peak-to-peak amplitude of the SORI excitation pulse.

In multi-CRAFTI experiments, collision gas was admitted into the trapping cell using the pulsed leak valve, followed by a 3s delay to allow collisional damping of possible residual excitation from the isolation. The pressure in the trapping cell was controlled by varying the duration of the pulsed leak pressurization event using a TCL script. The ions were translationally excited via a dual-frequency RF pulse containing components at each of their resonant cyclotron frequencies for (typically) 350 μsec (with excitation times deliberately kept short to minimize collisions during the excitation) followed by detection of the resulting transient signal at the constant, elevated pressure. Signal detection was always of sufficient duration that the signal damped back to background levels. SF₆ was used as the collision gas in these experiments because it enables higher center-of-mass kinetic energy at orbital velocities that allow the ion to remain inside the trapping cell. The resulting time domain image current signal yields a frequency domain
power spectrum after Fourier transformation with one zero fill and no apodization; typically, about 10—20 scans were averaged for each spectrum depending on the intensity of the signal.

Computational modeling

Natural abundance isotope patterns for comparison with experiment were computed using the Scientific Instrument Services web site: https://www.sisweb.com/mstools/isotope.htm.

Molecular structures were obtained using the Spartan '18 package (Wavefunction, Inc.; Irvine, CA, USA) for conformational searching with the Merck Molecular Force Field (MMFF) provided in the package, requesting 10,000 starting conformers (but systematic searches sometimes completed after examining fewer than 10,000 structures). Geometry optimization calculations were performed using density functional theory (M06-2X/6-31+G*; employing the LANL2DZ basis set for atoms not described by the 6-31+G* basis) as implemented in the NWChem28 computational package.

Barriers to anion egress were also calculated using Spartan '18. In these calculations, Spartan’s “Energy Profile” mode was used with MMFF while constraining and systematically increasing the distance between two of the cucurbituril N atoms and the halide anion. Positions of the N atoms were frozen to keep the cucurbituril stationary, but the positions of all other atoms were allowed to fully relax at each step. This forces the anion to egress the CB[5] host without causing significant distortion of the host beyond what is required to allow the anion to leave the host cavity. The geometries obtained from the Energy Profile calculation were then used for single-point energy calculations at the M06-2X/6-31+G* level of theory. Energies relative to the energetic minimum with the anion in the center of the host cavity were then determined and related to the distance of the anion from the center of mass of the host.
Data Analysis

Transient signals were analyzed using the Igor Pro software package (versions 7 and 8 (64-bit); Wavemetrics, Lake Oswego, OR, USA). For SORI experiments, the Igor program was used to extract peak amplitudes for a set of spectra that differ in SORI excitation times, followed by generation of tables of peak intensities as a function of SORI excitation duration. The resulting parent and product ion peak intensities were normalized against their sum, and the relative SORI collision energy was determined from the excitation time scaled to account for differences in mass, pressure, and excitation amplitude (although most experiments were conducted while maintaining a constant excitation amplitude). Energies obtained from these SORI-CID experiments may be compared qualitatively, but are not quantitative due to uncertainties about the absolute kinetic energies of the colliding partners, number of collisions required for dissociation, and conversion efficiency from kinetic to internal energy.

For multi-CRAFTI experiments, at each collision energy a set of power spectra measured at various pressures of the collision gas was collected for each of the two ions being compared. Experimental results were processed using the Igor Pro software package. The collision cross section ratio of the two ions \( \frac{\sigma_1}{\sigma_2} \) was determined from the linewidths of the ions using Equation 2-2.29

\[
\frac{\sigma_1}{\sigma_2} = \frac{fwhm_1 m_1 z_2 V_{PP_2} t_{exc,2}}{fwhm_2 m_2 z_1 V_{PP_1} t_{exc,1}}
\]  

(2-2)

Here \( fwhm_n \) is the full width at half maximum linewidth obtained from Lorentzian fits of the power spectral line for each ion, and \( z_n \) is the ion charge.20 The excitation durations for the two ions, \( t_{exc,n} \), are the same, so that the \( t_{exc,n} \) terms cancel. All other parameters are the same as defined above.
2.4 Results

Electrospray of CB[5] with alkali metal salts

When solutions containing CB[5] and sodium or potassium halide salts were electrosprayed (Figure 2-2 and Figure A1), significant relative abundances were observed for complexes containing either the Cl\(^-\) or Br\(^-\) ion, but no F\(^-\) or I\(^-\) complexes were observed. In the mass spectra, exact masses agree with computed masses within 15 ppm or better, and experimental isotopic patterns are in reasonable agreement with the computed patterns. The observed complexes had general stoichiometry \([\text{CB[5]}+\text{M}_2\text{X}]^+\), where M = Na or K and X is Cl or Br.

The intensities of the halide-containing ions were strongly dependent on conditions in the electrospray ion source, and tended to be stronger under conditions where collision energies in the source were minimized. Although the relative abundances of the halide-containing peaks were often small, that does not imply these peaks are unimportant. In all cases the signal-to-noise was sufficient to allow clear identification. Relative abundances of peaks in electrospray mass spectra do not necessarily reflect relative abundances of the corresponding species in solution, often being strongly affected by ion source conditions, electrospray efficiency, surface activity, solvation energies, etc.\(^{30-33}\) Attempts to electrospray fluoride or iodide salts of alkali metals resulted in intense signal for \([\text{CB[5]}+\text{M}]^+\) without any detected fluoride or iodide complexes. When electrospraying solutions containing CB[5] and alkaline earth halides, signals for
[CB[5]+SrI]^+, [CB[5]+BaI]^+, and [CB[5]+ NaBaI]^2+ were observed. Spectra are shown in Figure 2-3 and Figure A2.

Figure 2-2. Electrospray mass spectrum for CB[5] mixed with NaCl and KCl. Inset: expansion from m/z 900-950. Computed isotopic patterns are overlaid in green.

Figure 2-3. Electrospray mass spectrum for CB[5] mixed with SrI2. Insets: expansions showing isotopic patterns resulting from complexation, with computed isotopic distributions overlaid in green.
Energy-resolved SORI experiments are designed to show how ions fragment as a function of relative kinetic energy, $E_{\text{SORI}}$. We performed SORI for dissociation of chloride and bromide complexes, $[\text{CB}[5]+M_2X]^+$ ($M = \text{Na or K}; X = \text{Cl or Br}$)—see Figure 2-4. Each of the points is an average from at least 3 separate measurements, and the error bars represent standard deviations. Dissociation occurred exclusively by loss of MX. The chloride-containing complexes all exhibit dissociation that is easily fit to a single sigmoid and have similar, relatively high dissociation energies. In contrast, the bromide-containing $[\text{CB}[5]+\text{NaKBr}]^+$ and $[\text{CB}[5]+\text{Na}_2\text{Br}]^+$ complexes exhibit interesting bimodal dissociation behavior, fit using two sigmoids, in which some of the ions fragment at very low relative collision energies but the remainder require much higher relative energies, similar to those required to dissociate $[\text{CB}[5]+\text{M}_2\text{Cl}]^+$. The higher energy dissociation pathway was not observed for $[\text{CB}[5]+\text{K}_2\text{Br}]^+$, which dissociates at much lower energy than the chloride-containing complexes and at similar energies to those observed for the low energy portion of the dissociation of $[\text{CB}[5]+\text{NaKBr}]^+$ and $[\text{CB}[5]+\text{Na}_2\text{Br}]^+$.

We examined dissociation of the mixed-metal complexes more closely as two dissociation channels are possible in these systems. For example, the $[\text{CB}[5]+\text{NaKCl}]^+$ complex dissociates either by loss of NaCl or by loss of KCl. As Figure 2-5 shows, loss of NaCl is more facile, at higher energies about three times more prevalent than loss of KCl. A similar result was found when dissociating chloride complexes with one K$^+$ and one Rb$^+$ (Figure A3). Again, the system has two dissociation products, and dissociation by loss of RbCl is slightly favored over loss of KCl. Similarly, both channels were observed in dissociation of $[\text{CB}[5]+\text{NaKBr}]^+$, with about 75% dissociating via loss of NaBr, 25% via loss of KBr (see Figure 2-6). As was noted above (Figure 2-4), loss of the parent ion appears to be bimodal, as does appearance of both product ions, which
are produced primarily at low total SORI energies with a smaller contribution at significantly higher energies.

Figure 2-4. Parent ion survival curves for [CB[5]+MM’X]+ obtained by SORI-CID techniques. Points are averages of 3 or more runs, error bars are standard deviations, lines are fits of one or two sigmoids to the data.

Figure 2-5. Relative ESORI for dissociation of [CB[5]+NaKCl]+. Points are averages of 3 or more runs, error bars are standard deviations, lines are sigmoidal fits to the data.
Figure 2-6. Relative ESORI for dissociation of [CB[5]+NaKBr]+. Points are averages of 5 runs, error bars are standard deviations, lines are sigmoidal fits to the data (two sigmoids for each set).

**Multi-CRAFTI**

Our attempts to measure collision cross sections using more conventional ion mobility techniques for the halide-containing complexes were unsuccessful, probably due to the relative fragility of these complexes in the gas phase and the fact that mobility measurements require multiple low-energy ion-neutral collisions that potentially result in dissociation of these fragile ions. CRAFTI techniques, where ions are kept under ultrahigh vacuum conditions for most of the experiment, enabled measurement of relative collision cross sections for more fragile species.

CRAFTI cross sections of supramolecules increase with increasing center-of-mass kinetic energy until they reach a limiting value that is generally similar to the hard-sphere cross section computed from the expected molecular structure.\(^\text{18}\) In the current study, “multi-CRAFTI” experiments were performed for the target ions and internal standards for each system simultaneously over a range of kinetic energies obtained by adjusting the amplitudes of the RF
excitation waveforms. We have observed that relative cross sections approach limiting values at lower energies than do absolute cross sections (unpublished results).

The results of multi-CRAFTI experiments for CB[5]-alkali halide complexes are shown in Figure 2-7. Except for the lowest energy point (near 20 eV) in Figure 2-7 (where we might expect multi-collision dephasing to confound the results),\textsuperscript{17-18} the measured \( \frac{\text{CRAFTI} \text{CCS}_{SF6}([\text{CB}[5]+M_2X]^+)}{\text{CRAFTI} \text{CCS}_{SF6}([\text{CB}[5]+Na]^+)} \) ratios remain fairly constant as a function of energy. At higher energies, all the ratios average around 1 or less except in the case of [CB[5]+K\textsubscript{2}Br]\textsuperscript{+}, which has a ratio of about 1.2.

![Figure 2-7. Multi-CRAFTI collision cross sections in SF6 for [CB[5]+M2X]+ (M = Na, K; X = Cl, Br) relative to that of [CB[5]+Na]+. Points are averages of 3 or more runs, error bars are standard errors, lines are simply to guide the eye.](image)

Figure 2-7. Multi-CRAFTI collision cross sections in SF6 for [CB[5]+M2X]+ (M = Na, K; X = Cl, Br) relative to that of [CB[5]+Na]+. Points are averages of 3 or more runs, error bars are standard errors, lines are simply to guide the eye.
Relative collision cross sections were measured for the iodide-containing ions using the same internal standard, [CB[5]+Na]+.

$$\frac{^{\text{CRAFTI}}\text{CCS}_{\text{SF6}}([\text{CB}[5]+\text{Al}]^+)}{^{\text{CRAFTI}}\text{CCS}_{\text{SF6}}([\text{CB}[5]+\text{Na}]^+)}$$ (where A=Sr or Ba) ratios are shown in Figure 2-8. The iodide-containing ions have cross sections about 5% larger than that of CB[5] binding a single Na+, suggesting iodide is attached to the exterior of the complex, outside the cavity. Given the large size of I− (ionic radius 206 pm34) relative to the CB[5] portal (radius 120 pm) and cavity (radius 220 pm),35 this is not surprising. The [CB[5]+SrI]⁺ and [CB[5]+BaI]⁺ ions have cross sections that are approximately the same within experimental error. For [CB[5]+NaBal]²⁺, we were unable to simultaneously observe [CB[5]+Na]⁺ and [CB[5]+NaBal]²⁺, so we used a different internal standard, the easily observed [CB[5]+Ba]²⁺ ion. The result is shown in Figure A4. All the measured ratios are significantly greater than 1, which suggests that [CB[5]+NaBal]²⁺ is significantly larger than [CB[5]+Ba]²⁺.

Relative collision cross sections were measured for the iodide-containing ions using the same internal standard, [CB[5]+Na]+.

$$\frac{^{\text{CRAFTI}}\text{CCS}_{\text{SF6}}([\text{CB}[5]+\text{Al}]^+)}{^{\text{CRAFTI}}\text{CCS}_{\text{SF6}}([\text{CB}[5]+\text{Na}]^+)}$$ (where A=Sr or Ba) ratios are shown in Figure 2-8. The iodide-containing ions have cross sections about 5% larger than that of CB[5] binding a single Na+, suggesting iodide is attached to the exterior of the complex, outside the cavity. Given the large size of I− (ionic radius 206 pm34) relative to the CB[5] portal (radius 120 pm) and cavity (radius 220 pm),35 this is not surprising. The [CB[5]+SrI]⁺ and [CB[5]+BaI]⁺ ions have cross sections that are approximately the same within experimental error. For [CB[5]+NaBal]²⁺, we were unable to simultaneously observe [CB[5]+Na]⁺ and [CB[5]+NaBal]²⁺, so we used a different internal standard, the easily observed [CB[5]+Ba]²⁺ ion. The result is shown in
Figure A4. All the measured ratios are significantly greater than 1, which suggests that [CB[5]+NaBal]^{2+} is significantly larger than [CB[5]+Ba]^{2+}.

Figure 2-8. Multi-CRAFTI collision cross section in SF6 for [CB[5]+SrI]+ and [CB[5]+BaI]+ relative to that of [CB[5]+Na]+. Points are averages of 3 or more runs, error bars are standard errors, lines are simply to guide the eye.

**Computational results**

Modeling suggests at least eight distinct binding motifs for the [CB[5]+NaKBr]^{+} complex, illustrated in Figure 2-9, which are qualitatively similar to the binding motifs found for the other halide anions. Of these, Figure 2-9a), with Br⁻ bound internally, is by far the lowest in energy according to M06-2X/6-31+G* modeling. The remaining seven structures all have bromide externally bound. The lowest-energy external structure, Figure 2-9b), places the Br⁻ on the CB[5] equator, centered over an 8-membered ring comprised of 4 C and 4 N atoms, but is calculated to be 181 kJ mol⁻¹ higher in energy than the structure with Br⁻ bound internally.
Placement of Br⁻ over a 5-membered ring of CB[5] results in higher energies, up 15 or 16 kJ mol⁻¹ higher than the equatorial structure depending on whether the 5-membered ring is closer to the Na⁺- or K⁺-bound portal of CB[5], respectively. Placement of Br⁻ externally but closer to the CB[5] axis results in higher energies; Figure 2-9e), with a 118° K-Na-Br angle, is 44 kJ mol⁻¹ higher than the equatorial placement, and Figure 2-9f), with a 171° K-Na-Br angle, is 81 kJ mol⁻¹ higher than the equatorial structure. Placement of both metal ions and the bromide ion all on the same CB[5] portal, Figure 2-9g) and h), was only slightly higher than the 171° structure.

Figure 2-9. M06-2X/6-31+G* computed structures and relative energies for [CB[5]+NaBr]⁺. H atoms are white, C are black, N are blue, O are red, Na are yellow, K are purple, and Br are dark red. Angles in parantheses are K-Na-Br angles.

X = F the internally-bound complexes are still favored, but by a smaller amount. Comparing the halides, the computed order of binding for the internal complexes is Br\(^–\) > I\(^–\) > Cl\(^–\) > F\(^–\) with sodium, while with potassium the order is I\(^–\) > Br\(^–\) > Cl\(^–\) > F\(^–\). For externally-bound complexes the binding energies of each of the halides is similar, spanning a range of 19 kJ mol\(^–1\) for the Na-containing complexes and a range of 28 kJ mol\(^–1\) for those containing K.

Table 2-1. Energies for \([\text{CB}[5]+\text{M}]^+ + \text{MX} \rightarrow [\text{CB}[5]+\text{M2X}]^+\) Computed at the M06-2X/6-31+G* Level of Theory.

<table>
<thead>
<tr>
<th>Anion, X</th>
<th>Ionic Radius(^36) (pm)</th>
<th>Energy for ([\text{CB}[5]+\text{M}]^+ + \text{MX} \rightarrow [\text{CB}[5]+\text{M2X}]^+ ) (kJ mol(^–1))</th>
<th>M = Na</th>
<th>M = K</th>
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</tr>
<tr>
<td>I</td>
<td>206</td>
<td>Internal-External</td>
<td>-417</td>
<td>-202</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Internal-External</td>
<td>-215</td>
<td>-436</td>
</tr>
<tr>
<td></td>
<td></td>
<td>External</td>
<td>-245</td>
<td>-190</td>
</tr>
</tbody>
</table>

The thermodynamic binding energies of the experimentally-observed mixed-metal halide complexes at 0 K were also calculated and compared. The results are shown in Table 2-2. For mixed NaK caps, loss of NaCl requires about 44 kJ mol\(^–1\) less net energy than loss of KCl. Loss of the corresponding bromides is 30-40 kJ mol\(^–1\) higher in energy than chloride losses, and loss of
NaBr requires 51 kJ mol\(^{-1}\) less energy than loss of KBr. For mixed KRb caps, loss of RbCl requires 22 kJ mol\(^{-1}\) less energy than loss of KCl. Loss of external bromides, from [Br•CB\([5]\)+NaK]\(^+\), is easier than loss of internally-bound bromides, but again loss of NaBr requires less energy (about 52 kJ mol\(^{-1}\) less) than loss of KBr. The thermodynamic calculations therefore predict that K\(^+\) will be preferentially retained on the CB\([5]\) host when any of these complexes dissociate, as observed experimentally (Figure 2-5, Figure A3, and Figure 2-6).

Table 2-2. Energies for [CB\([5]\)+M\(^+\)]\(^+\) + MX → [CB\([5]\)+MM\(\cdot\)X\(^+\)]\(^+\) Computed at the M06-2X/6-31+G* Level of Theory.

<table>
<thead>
<tr>
<th>MX</th>
<th>[Cl@CB([5])+NaK(^+)](^+)</th>
<th>[Cl@CB([5])+KRb(^+)](^+)</th>
<th>[Br@CB([5])+NaK(^+)](^+)</th>
<th>[Br•CB([5])+NaK(^+)](^+)</th>
</tr>
</thead>
<tbody>
<tr>
<td>NaCl</td>
<td>-374</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>KCl</td>
<td>-418</td>
<td>-384</td>
<td></td>
<td></td>
</tr>
<tr>
<td>RbCl</td>
<td></td>
<td>-362</td>
<td></td>
<td></td>
</tr>
<tr>
<td>NaBr</td>
<td></td>
<td>-404</td>
<td>-206</td>
<td></td>
</tr>
<tr>
<td>KBr</td>
<td></td>
<td>-455</td>
<td>-258</td>
<td></td>
</tr>
</tbody>
</table>

Table 2-3. Barriers for MX Loss from [X@CB\([5]\)MM\(^+\)]\(^+\) Computed at MMFF//M06-2X/6-31+G* Level of Theory, kJ/mol.

<table>
<thead>
<tr>
<th>X</th>
<th>NaX from XNa(_2)</th>
<th>NaX from XNaK</th>
<th>KX from XNa(_2)</th>
<th>KX from XNaK</th>
<th>KX from XK(_2)</th>
<th>KX from XK(_2)</th>
<th>KX from XKRb</th>
<th>RbX from XKRb</th>
</tr>
</thead>
<tbody>
<tr>
<td>F</td>
<td>265</td>
<td>250</td>
<td>308</td>
<td>321*</td>
<td>-a</td>
<td>-a</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cl</td>
<td>373</td>
<td>355</td>
<td>397</td>
<td>381</td>
<td>363</td>
<td>385</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Br</td>
<td>394</td>
<td>375</td>
<td>422</td>
<td>404</td>
<td>-a</td>
<td>-a</td>
<td></td>
<td></td>
</tr>
<tr>
<td>I</td>
<td>457</td>
<td>457</td>
<td>478</td>
<td>477</td>
<td>-a</td>
<td>-a</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*This dissociation involved pulling K\(^+\) through the CB\([5]\) cavity along with the departing F\(^-\), which is mechanistically different from all the others.

*aNot computed.
SORI experiments should reflect differences in energetic barriers to dissociation of the complexes, and in the case of internally-bound anions they should reflect barriers to egress of the various anions from the central cavity of the CB[5] host molecule. We therefore carried out calculations to compare the barriers for MX (M = Na or K; X = F, Cl, Br, or I) loss from various [X@CB[5]MM']⁺ complexes. The results of these calculations are plotted in Figure A5, and the computed barriers are compiled in Table 2-3. The computed barrier heights are strongly halogen-dependent, increasing in the order F < Cl < Br < I, and less strongly dependent on which metal ions cap the complex. Barriers to NaX loss are consistently less than barriers to KX loss. From the mixed-metal complexes, NaX loss always occurs at lower energy than KX loss from the same complex, although the difference between these two dissociation channels decreases with increasing halide size. We also modeled the barriers to loss of KCl and RbCl from [Cl@CB[5]+KRb]⁺ for comparison with the experimentally observed dissociation of this ion. These calculations yielded a barrier of 363 kJ mol⁻¹ for KCl loss and of 385 kJ mol⁻¹ for RbCl loss. Whereas the thermodynamic calculations are consistent with the experimental observations (more facile loss of RbCl, Figure S3), these barrier calculations for the Rb-containing complexes are not.

2.5 Discussion

Structure and size-based anion selectivity in CB[5]-metal halide complexes

Modeling suggests anions may be bound on CB[5]-metal ion complexes either inside the CB[5] cavity between the two metal cations or outside the cavity, with the potential energy surface for the various external binding sites being relatively flat (the energies of the external structures shown in Figure 2-9b), c), and d) are all within 16 kJ mol⁻¹ of each other, and
geometric convergence of each of these structures was slow due to small changes in energy 
gradients with halide position). Computational results (Table 2-1) show the internally-bound 
anion isomers are much lower in energy than the externally-bound isomers, even for large anions 
such as iodide. Therefore, according to the calculations the internal isomers are strongly favored 
thermodynamically, and any observed external isomers would have to be kinetically trapped, 
presumably because the barrier to entering the cavity is large. The barrier calculations 
summarized in Table 2-3 are consistent with this explanation, as they suggest Cl$^-$ can pass 
through the CB[5] portal at energies 20-25 kJ mol$^{-1}$ less than are required for Br$^-$, with I$^-$ 
requiring at least 40 kJ mol$^{-1}$ more than Br$^-$. 

X-ray data indicate that the portal of CB[5] has a radius of about 120 pm, whereas the 
internal cavity is larger, with a radius of about 220 pm.$^{35}$ Comparison with the sizes of the halide 
anions (Table 2-1) indicates that F$^-$, Cl$^-$, Br$^-$, and I$^-$ are all small enough to fit within the binding 
cavity, but that all but F$^-$ are larger than the equilibrium size of the portal. Thus, simply based on 
size considerations we might expect internal binding of the halides to be favorable 
thermodynamically, but that there could be significant kinetic barriers to passing through the 
portal and entering the internal cavity, with barriers increasing with anion size, as Table 2-3 
indicates is the case. Therefore, we believe the size-selective halide binding observed in CB[5] 
complexes originates from differing abilities to pass through the CB[5] portal. We will now 
examine each of the halides.

*Fluoride complexes*

We attempted to spray CB[5] in the presence of fluoride salts, but no complexes 
containing F$^-$ were observed, despite the fact that F$^-$ should be small enough to enter the CB[5]
cavity and to bind strongly there. Perhaps the high solvation energy of F\textsuperscript{−} and its ability to act as a good hydrogen bond acceptor prevented formation or observation of any complexes under the conditions of our experiments, which involved electrospray from 50:50 isopropanol:water solvent, in which we expect fluoride has a very high solvation energy.

**Chloride complexes.** As noted earlier, inclusion of Cl\textsuperscript{−} within the central cavity of CB[5]-metal complexes has previously been demonstrated via single-crystal X-ray diffraction.\textsuperscript{8-9} In the gas phase,\textsuperscript{37} we expect the internally-bound-anion structures to be similar to those characterized in the solid state, with the metal cations binding to the portal carbonyl oxygen atoms of the cucurbituril and with halide anions such as Cl\textsuperscript{−} bound inside the CB[5] cavity.

**Chloride complexes**

As noted earlier, inclusion of Cl\textsuperscript{−} within the central cavity of CB[5]-metal complexes has previously been demonstrated via single-crystal X-ray diffraction.\textsuperscript{8-9} In the gas phase,\textsuperscript{37} we expect the internally-bound-anion structures to be similar to those characterized in the solid state, with the metal cations binding to the portal carbonyl oxygen atoms of the cucurbituril and with halide anions such as Cl\textsuperscript{−} bound inside the CB[5] cavity.

Our results for chloride complexes are consistent with these expectations. Chloride-containing complexes were easily observed. All dissociate at relatively high energies (Figure 2-4) and have CRAFTI cross sections similar to, or smaller than, those of [CB[5]+Na]\textsuperscript{+} (Figure 2-7). We might expect an internally-bound Cl\textsuperscript{−} to cause overall contraction of the complex as the negative charge attracts the positive alkali metal cations and pulls them inward. Internal binding is consistent with the computational results (Table 2-1), which indicate internal binding of chloride is thermodynamically very favorable and that the energetic differences between sodium- and
potassium-capped complexes are small. The results for dissociation of [CB[5]+NaKCl]^+ (Figure 2-5) are also consistent with internal binding of Cl\(^-\). An internally-bound structure could easily dissociate via either KCl or NaCl loss, and the thermodynamic energy differences obtained from the computational studies (Table 2-2) could qualitatively account for the observed 25:75 branching ratio between these two dissociation channels. The computed egress barriers for MCl losses from [CB[5]+NaKCl]^+ (Table 2-3) differ by about the same amount as the binding energies and also favor loss of NaCl, as observed. We believe this is good evidence that chloride binds strongly within the CB[5] cavity in the gas phase, with only minor differences as the alkali metal cations are varied. Therefore, the CB[5] portal, nominally about 120 pm in radius, must be flexible enough at thermal energies to easily allow passage of 167 pm Cl\(^-\).

**Bromide complexes**

The results are different for larger halide guests such as Br\(^-\). Bromide is about 15 pm larger in radius than chloride, and the behavior of the bromide-containing complexes exhibits interesting complexity. The SORI results (Figure 2-4) suggest at least two isomers for the Br\(^-\) complexes containing Na\(^+\): one that is weakly-bound, presumably with Br\(^-\) on the exterior of CB[5], and a more strongly-bound isomer, presumably with Br\(^-\) inside the CB[5] cavity. The fact that the multi-CRAFTI experiments (Figure 2-7) indicate the cross sections of the observed [CB[5]+Na\(_2\)Br]^+ complexes are smaller than that of [CB[5]+Na]^+–bromide bound inside the CB[5] cavity draws the two capping cations inward–suggests that only the more strongly-bound, internal isomers contribute to the multi-CRAFTI measurements. It is likely that the 60% portion of the population in which bromide is bound outside did not contribute to the cross section measurements because it is so weakly bound (about 212 kJ mol\(^{-1}\) according to the calculations, Table 2-1) that the external
complexes dissociated (perhaps due to residual energy deposited in the process of desolvating and isolating the ions)\textsuperscript{38} prior to the cross section determination. Similarly, \([\text{CB}[5]+\text{NaKBr}]^+\) also gave cross sections comparable to or smaller than that of \([\text{CB}[5]+\text{Na}]^+\) at all collision energies, again consistent with an internally-bound complex and dissociative loss of the externally-bound isomers prior to the cross section measurement.

SORI measurements of the \([\text{CB}[5]+\text{K}_2\text{Br}]^+\) complex (Figure 2-4) detected only ions that dissociate at low energies, and the multi-CRAFTI results for this complex (Figure 2-7) are consistent with \(\text{Br}^-\) bound on the exterior of \text{CB}[5], as they indicate \([\text{CB}[5]+\text{K}_2\text{Br}]^+\) has a significantly greater collision cross section than \([\text{CB}[5]+\text{Na}]^+\) at all examined energies. These complexes have somewhat higher binding energies than those containing \(\text{Na}^+\) capping cations (Tables 2-1 and 2-2), that apparently survive long enough for the cross section measurement.

Overall, the data indicate that the \text{CB}[5] portal only allows \(\text{Br}^-\) entry when stretched significantly beyond its equilibrium size at thermal energies. Perhaps heating the complexes would allow more \(\text{Br}^-\) ingress.

As for the structures of the externally-bound bromide complexes, the SORI experiments on \([\text{CB}[5]+\text{NaKBr}]^+\) (Figure 2-6) also shed some light. The complexes dissociating at very low energies yield both loss of NaBr and loss of KBr, with the NaBr loss products more abundant by a factor of about 4. This suggests that either there is one isomer with the \(\text{Br}^-\) in approximately equal proximity to the two metal ions or there are two (or more) isomers with very similar energies that produce these two products. The computed lowest-energy external structure, Figure 2-9b), is consistent with this expectation as the bromide ion lies on the equator of \text{CB}[5], approximately equidistant between the two capping cations such that this isomer might be expected to produce both NaBr and KBr products. The structures of Figure 2-9c) and Figure 2-9d) are close to each
other in energy and might also account for the observed products. The two structures in which Br– is bound to only one metal ion, Figure 2-9f) and the corresponding structure with Br– proximate to K+ (not shown), are calculated to be 81 and 97 kJ mol–1 higher in energy, respectively, than the equatorially-bound structure, Figure 2-9b). The two structures with both cations and the anion on the same CB[5] portal are at comparably higher energies. Thus, we favor the equatorial structure Figure 2-9b) as most consistent with the SORI experiment and the calculations.

**Iodide complexes**

At 206 pm radius, iodide is evidently too large to pass through the CB[5] portal as no iodide-containing complexes of CB[5] with singly-charged alkali cation caps were observed. The failure to observe externally-bound iodide is interesting in that calculated stabilities of externally-bound iodide complexes are only slightly less than those of the externally-bound bromides (Table 2-1), which were observed. This may reflect a weakness in using the M06-2X functional with modest basis sets to compute energies for complexes that include highly-polarizable anions such as I–; more dispersion correction may be needed than this approach provides. In any event, the CB[5] portal appears to be exquisitely sensitive to the size of potential anionic guests.

The observation of externally-bound bromide complexes with specific metal caps encouraged us to try more highly-charged metals (+2 alkaline earth cations) to see if the higher charge might stabilize externally-bound I– complexes. [CB[5]+SrI]+, [CB[5]+NaSrI]2+, [CB[5]+BaI]+, and [CB[5]+NaBaI]2+ were all observed, whereas no triply-charged complexes comprised of two alkaline earth metals and a halide were detected (Figure 2-3 and Figure A2). Based on the multi-CRAFTI results (Figure 2-8 and Figure A4), all of these complexes bind the iodide externally, as expected given the large size of this anion and the corresponding high barrier

**Influence of capping cations on internal vs. external binding**

The data suggest the capping metal ions influence the preference for internal vs. external binding. The SORI results (Figure 2-4) indicate that under the conditions of our experiments the observed [CB[5]+Na2Br]^+ was 60% weakly-bound (external) and 40% strongly bound (internal), that [CB[5]+NaKBr]^+ was 90% external and 10% internal, and that [CB[5]+K2Br]^+ was essentially 100% external. This is reasonably consistent with the computational results for binding strengths (Table 2-1) and egress barriers (Table 2-3); external binding is 36 kJ mol\(^{-1}\) stronger for K\(^+\) than for Na\(^+\) (Table 2-1), and the barrier for MBr loss (and for Br ingress) is 10 kJ mol\(^{-1}\) greater for two K\(^+\) capping cations than for two Na\(^+\) capping cations (Table 2-3). It is possible this increase in barrier results from placing the larger K\(^+\) in one portal, forcing the other portal to tighten up somewhat. Similarly, dissociation of [CB[5]+NaKBr]^+, which, as noted above, is probably mostly an externally-bound bromide structure, resulted in 75% loss of NaBr and 25% loss of KBr (Figure 2-6), because KBr loss requires greater energy. Overall, substitution of Na\(^+\) by K\(^+\) in these complexes leads to increased preference for external binding of Br\(^-\). This dependence of anion binding site selectivity on metal ion probably deserves further investigation.
2.6 Conclusion

This work demonstrates that cucurbit[n]uril-metal complexes can be size-selective anion receptors, and that this can be observed using mass spectrometric methods. In fact, cucurbit[5]uril is probably better described in the present context as an ion-pair receptor, as cations bind on the portal of the host and anions, in close contact with the cations, bind selectively in the cucurbituril interior and non-selectively outside the host. We found that Cl\textsuperscript{−} binds inside CB[5] complexed with various alkali metals; Br\textsuperscript{−} binds both inside (with Na\textsuperscript{+}-capped CB[5] portals), and outside the CB[5] cavity (when K\textsuperscript{+} is the capping cation). I\textsuperscript{−} complexes were not observed with alkali metal cations serving as caps, but I\textsuperscript{−} does bind strongly enough to the exterior in the presence of alkaline earth cation caps to be observed in electrospray mass spectrometry. Finally, the results obtained from multi-CRAFTI are consistent with the dissociation behavior observed from SORI-CID experiments and with computational calculations. This increases our confidence in the multi-CRAFTI method.
2.7 References


Chapter 3. Size-Selectivity for Alkali Cations in Supramolecular Complexes with Neutral Guests Characterized Using MultiCRAFTI Collision Cross Sections

3.1 Abstract

Based on the results from Fourier transform ion cyclotron resonance mass spectra along with collision cross section (CCS) data from computed structures and measured using the CRAFTI method, we observed that both the sizes and the resulting charge densities of the capping alkali metal ions affect the relative propensity for binding with different guests (methanol, ethanol, formic acid, and acetonitrile) inside alkali-cationized cucurbit[5]uril (CB[5]) complexes. We measured relative CCS values in Ar for pairs of full and empty CB[5] complexes over a range of collision energies. CCS values calculated using the projection approximation for computationally-modeled structures are consistent with the CCS values from the CRAFTI method. The CCS values suggest that in the gas phase methanol, formic acid, and acetonitrile are internally bound while ethanol is bound outside the CB[5] host. The relative abundances of the paired peaks in the mass spectra show that the inclusion of formic acid or methanol is enhanced when K$^+$ ions cap the complexes, whereas the inclusion of acetonitrile is enhanced when Cs$^+$ ions cap the complexes. The relative abundance of ethanol complexes increases when Na$^+$ ions cap the complexes.

3.2 Introduction

Cucurbit[n]urils (CBn) are rigid macrocyclic hosts with pumpkin-like shapes. These hosts have a non-polar and hydrophobic cavity that allows for the inclusion of neutral guests through two carbonyl-lined rims that are suitable to form ion-dipole interactions with cations.\textsuperscript{1,2}
Cucurbit[n]uril molecules and their derivatives have become important macrocyclic hosts for various application in material, medicine, pharmaceutical, and biomedical science.\textsuperscript{2-6}

CB[n]s with different sizes have different properties. CB[5] (Figure 3-1) and CB[7] possess the highest solubilities in water among the CB[n] family. CB[5], with a 9.1 Å depth, portal width of 2.4 Å, and 4.4 Å width in the cavity has attracted attention from scientists.\textsuperscript{7-8} For instance, our group has demonstrated anion size-selectivity in complexes with alkali metal ions capping the portals of CB[5]\textsuperscript{9} and also observed nonrotaxane structures in various CB[5] complexes of alkylmonoammonium ions.\textsuperscript{10} In this study, we will show size-selectivity for neutral guests in CB[5] molecules complexed with alkali cations using mass spectra obtained from Fourier transform ion cyclotron resonance mass spectrometry (FTICR-MS) combined with CRAFTI measurements\textsuperscript{11-12} to characterize the size and shape of each complex. CRAFTI allows us to indicate whether the guests are bound inside the CB[5] cavity or outside.

CRAFTI (an acronym for cross sectional areas by Fourier transform ion cyclotron resonance mass spectrometry)\textsuperscript{12-13} measures ion-neutral collision cross sections (CCS) from the pressure-dependent ion linewidths in Fourier transform mass spectra.\textsuperscript{14} The CRAFTI technique has the advantage that most of the experiment is conducted under high vacuum conditions, so ion-molecule collisions are minimized until the ion motion is excited for ion detection. The pressure is increased during the detection event such that the ions dephase out of a coherently orbiting packet via single ion-neutral collisions with background gas at sufficiently high pressure. This means that fragile molecules that might dissociate or rearrange under multiple-collision conditions can be studied using the CRAFTI method.

Factors affecting the size of metal ion-capped CB[5] complexes with neutral guests were studied by analyzing the intensity of the peaks without and with the neutral guests, by molecular
mechanics simulations, and by using the multiCRAFT\textsuperscript{15} technique (multiCRAFTI performs CRAFTI on two or more ions at the same time, under identical pressure conditions at nearly identical center-of-mass kinetic energies). The binding in these non-covalent complexes is governed by the size- and shape-selectivity of the host cavities, as well as by the charge density effects of the cation caps. It has been shown that the binding of guests with cucurbiturils depends on the size of the guest.\textsuperscript{16} Here, we show that the size of the alkali metal ion can also affect the binding of different guests in these complexes.

Figure 3-1. (a) Skeletal formula of a cucurbit[5]uril molecule. (b) side and (c) top views.

3.3 Experimental

Sample preparation

CB[5] and all alkali metal salts are commercially available at Sigma-Aldrich (St. Louis, MO). A sample of mc5 was acquired from IBC Advanced Technologies (American Fork, Utah). ACS-grade formic acid was purchased from Mallinckrodt (St. Louis, MO); HPLC-grade methanol and acetonitrile from Fisher Scientific (Hampton, NH) were used. Ar, used as a collision gas in the FTICR (99.9997% purity) was purchased from Airgas, Inc. (Radnor, Pennsylvania). All the solvents, cucurbituril complexes, and metal salts were used as supplied without further purification.
All solutions were prepared with cucurbit[5]uril host concentrations of 100 μM and an alkali salt concentration equal to twice that of the cucurbituril. Methanol and acetonitrile were trapped in CB[5] complexes by preparing the complexes in 1:1 methanol: water solutions and neat acetonitrile, respectively. All other complexes were prepared in 1:1 isopropanol: water solutions. Formic acid and ethanol guest complexes were prepared by adding the guest to the solution at a concentration in excess of that of CB[5]. These solutions were then electrosprayed into the FTICR instrument. The solutions were electrosprayed with a flow rate of 20 μL h⁻¹.

**FTICR Instrumentation**

All experiments were performed using a Bruker Fourier transform ion cyclotron resonance mass spectrometer model APEX 47e thru an Infinity trapping cell.¹⁷-¹⁸ Ions were generated via a modified micro-electrospray source from an Analytica (Branford, MA, USA) design with a metal capillary drying tube based on the design of Eyler et al.¹⁹ We isolated the ions of interest using stored waveform inverse Fourier transform (SWIFT) techniques.²⁰ Ar collision gas was introduced into the FTICR cell using a Freiser-type pulsed leak valve²¹ for multiCRAFTI and SORI-CID experiments, and the pressure inside the cell was controlled by varying the duration of the leak valve pressurization event. The pressures in the cell were determined by using a cold cathode pressure transducer. Collision energies were varied by varying the peak-to-peak amplitude of the excitation event, either at the resonant frequencies of the ions of interest in multiCRAFTI experiments or 1.000 kHz above or below the resonant frequency for SORI experiments. The ions being compared in multiCRAFTI experiments were excited to nearly identical collision energies in the center-of-mass reference frame using waveforms synthesized via a LabVIEW program. Data were analyzed using the Igor Pro software package (version 7, Wavemetrics Inc.; Lake Oswego,
OR) to extract mass spectral peak amplitudes as a function of the peak-to-peak excitation voltage. Knowing the peak-to-peak excitation voltage (Vpp), we calculated the average energy deposited in the ions (ESORI) for SORI-CID experiments. ESORI is proportional to the cube of the peak-to-peak excitation voltage, as shown in equation 3-1.

\[ ESORI \propto N^* \sigma t_{SORI} \left( \frac{M}{M+m} \right) \frac{V_{pp}^3}{m^2} \]  

(3-1)

Here N* is the number density of the neutral collision gas, σ is the collision cross section of the ion, and t_{SORI} is the duration of the SORI excitation event. M is the mass of the neutral collision gas, and m is the mass of the ion.

SORI-CID was performed on [MeOH@CB[5]+2Cs]^{2+} and [MeOH@mc[5]+2Cs]^{2+}. Relative ESORI values corresponding to 50% dissociation (ESORI,50%) of the CB[5] and mc5 complexes were determined using sigmoidal fits to the data as a function of SORI energy (shown in the result section). The uncertainties reported in the figure are standard deviations calculated from three replicate measurements.

The collision cross section ratio of the two ions (\( \frac{CCS_2}{CCS_1} \)) (where CCS_1 = host-guest doubly charged ion, and CCS_2 = empty doubly-charged host ion) was determined from the fwhm linewidths of the ions using Equation 3-2.\(^{15}\)

\[ \frac{CCS_2}{CCS_1} = \frac{fwhm_2 m_2 \bar{z}_1 V_{pp,1} t_{exc,1}}{fwhm_1 m_1 \bar{z}_2 V_{pp,2} t_{exc,2}} \]  

(3-2)
Here $fwhm_n$ is the full width at half maximum linewidth acquired using Lorentzian fits to the mass spectral data, $z_n$ is the ion charge which cancels out here and the excitation durations for the two ions, $t_{exc,n}$, are the same, so that the $t_{exc,n}$ terms cancel as well. $V_{pp}$ is the peak-to-peak amplitude of the excitation pulse at the frequency of interest, and $m_n$ is the mass of the ion.

**Computational Modeling**

Low level molecular mechanics calculations using Spartan ‘18, which are fast but relatively less accurate, were used for conformational searching and obtaining starting structures for high-level calculation. Then the results were examined using M06-2X/6-31+G* calculations for more accurate binding energies of internal complexes vs. the externally-bound complexes using different metal caps. This study’s computational modeling and experimental results were in excellent agreement. We also used MMFF modeling of the complexes for each alkali metal to compare the metal-metal distance of $[\text{HCOOH}@\text{CB}[5]+2\text{M}]^{2+}$ ($\text{M} = \text{alkali metal}$) and the metal-metal distance of $[\text{CB}[5]+2\text{M}]^{2+}$ empty hosts to observe the behavior of the ions having different caps. Collision cross sections in Å² were calculated with Ar collision gas using the IMoS (version 1.10c) projected area approximation.

**3.4 Results**

Multi-CRAFTI experiments give ratios of CCS values for ions of interest. The relative CCS values in the form $\text{CCS}[\text{X}@\text{CB}[5]+2\text{M}]^{2+}/\text{CCS}[\text{CB}[5]+2\text{M}]^{2+}$ (X=neutral guest and M=alkali metal) were calculated for both experiment and for computed model structures. Although absolute CCS values could be easily obtained by comparing the CCS of the analyte with standards of known CCS, relative CCS was sufficient for the goal of this study.
Computational Results

Computed collision cross section ratios for most of the host-guest complexes (Table 3-1) are close to 1, suggesting that the guests are bound internally except in the case of ethanol, for which the “full” complexes are 10% larger than the corresponding empty complexes. This implies that ethanol is bound externally to mc[5]. Figure 3-2 plots the distance between the two capping metal cations as a function of the average metal ionic radius for formic acid inclusion complexes with CB[5] capped by various combinations of alkali metal cations. The metal-metal distance increases smoothly as average metal ionic radius increases, except when two K⁺ ions or when K⁺ and Rb⁺ cap the complex. The distance in these cases is smaller than the trend observed for the other capping cations, suggesting some kind of exceptional fit for K⁺ and perhaps Rb⁺.

Figure 3-2. MMFF modeling of the metal-metal distance of [X@CB[5]+2M]²⁺ (X = formic acid and M = alkali metal) and the metal-metal distance of [CB[5]+2M]²⁺ empty hosts.
**Multi-CRAFTI Experimental Results**

We did multi-CRAFTI experiments for CB[5]-alkali cation with and without guest molecules in Ar on the pair peaks with the highest intensity to determine whether the guests are bound inside the cavity of the cucurbituril host or outside. These measurements were carried out over a range of kinetic energies. The relative collision cross sections of $(\sigma_{\text{HCOOH@CB[5]+2M}^{2+}}/\sigma_{\text{CB[5]+2M}^{2+}}$, $M =$ alkali metal are shown in Table 3-1. The CCS of the formic acid complexes relative to the cross sections of empty complexes remain relatively constant as a function of energy and are close to 1.

The results of multiCRAFTI experiments that have been done on the complexes containing methanol and acetonitrile with various alkali metals are also shown in Table 3-1. The experimental data indicate methanol, formic acid, and acetonitrile complexes of CB[5] are internal (all these ratios are close to 1), and the guest does not significantly affect the CCS of the CB[5] complexes containing various caps. The results are in very good agreement with the computational results also shown in Table 3-1.

We observed no signal for the sample solution of CB[5] and ethanol. We therefore used decamethylcucurbit[5]uril (mc5) which is a CB[5] derivative. CB[5] and mc5 differ only in substituents on their exterior; they have alike interior volume. The multiCRAFTI CCS ratios of ethanol•mc5 with various caps (Table 3-1) suggest ethanol bound outside the mc5 host. The result is consistent with computational lowest-energy structures.

Since we had data for methanol and CB[5] with 2 Cs$^+$ ions and also because we wanted to compare CB[5] and mc5 behavior, methanol was complexed with the mc5 host with 2 Cs$^+$ caps. The ratios for $\sigma_{\text{MeOH@Host+2Cs}^{2+}}/\sigma_{\text{Host+2Cs}^{2+}}$ show inclusion of methanol perhaps makes the overall complex slightly smaller, but the change in size is negligible (Table 3-1). Also,
SORI-CID experiments were done for methanol complexes inside CB[5] and mc5 with identical Ar pressures and SORI excitation lengths (Figure 3-3), resulting exclusively in the loss of methanol from the complexes. The data show that the CB[5] complex dissociates at significantly lower energy than the mc5 complex.

Table 3-1. Collision cross section ratios from multiCRAFTI experiments and theory for alkali cation complexes of cucurbit[5]uril and mc5 with neutral guests in Ar.

<table>
<thead>
<tr>
<th>Guest.host, metal (M)</th>
<th>multi-CRAFTI(Ar)a</th>
<th>PA Internal (Ar)b</th>
<th>PA (Ar)b External</th>
</tr>
</thead>
<tbody>
<tr>
<td>HCOOH,CB[5],NaK</td>
<td>0.95±0.05</td>
<td>1.00</td>
<td>1.05</td>
</tr>
<tr>
<td>HCOOH,CB[5], KK</td>
<td>0.99±0.03</td>
<td>1.00</td>
<td>1.07</td>
</tr>
<tr>
<td>HCOOH,CB[5], KCs</td>
<td>1.00±0.02</td>
<td>1.00</td>
<td>1.06</td>
</tr>
<tr>
<td>MeOH,CB[5], KCs</td>
<td>1.00±0.01</td>
<td>1.00</td>
<td>1.07</td>
</tr>
<tr>
<td>MeOH,CB[5], CsCs</td>
<td>0.97±0.01</td>
<td>1.00</td>
<td>1.06</td>
</tr>
<tr>
<td>ACN,CB[5], KCs</td>
<td>1.04±0.003</td>
<td>1.01</td>
<td>1.11</td>
</tr>
<tr>
<td>ACN,CB[5], CsCs</td>
<td>1.02±0.02</td>
<td>1.01</td>
<td>1.09</td>
</tr>
<tr>
<td>EtOH,mc5, NaK</td>
<td>1.15±0.04</td>
<td>1.01</td>
<td>1.07</td>
</tr>
<tr>
<td>EtOH,mc5, KK</td>
<td>1.15±0.01</td>
<td>1.02</td>
<td>1.07</td>
</tr>
<tr>
<td>EtOH, KCs</td>
<td>1.13±0.04</td>
<td>1.00</td>
<td>1.06</td>
</tr>
<tr>
<td>MeOH,mc5, CsCs</td>
<td>0.99±0.01</td>
<td>1.00</td>
<td>1.05</td>
</tr>
</tbody>
</table>

aAverage ± standard deviation for ratios measured at the 3 highest center-of-mass kinetic energies in Ar collision gas.
bBoltzmann-weighted averages from MMFF94 conformational searches to generate structures and energies and IMoS projected area approximation calculation for collision cross sections with Ar.
Mass Spectral Results

Mass spectra were typically obtained simultaneously for many different capping metal ions and a given host-guest combination, where the guest was typically present in large molar excess relative to the host. For example, Figure 3-4 shows the mass spectra of CB[5] in the presence of formic acid and various alkali metal ions, and is typical of the mass spectra observed for other guests (see Appendix B, Figures B1-B3). We compare the amplitudes of the mass spectrometric peaks for the guest-containing complexes with those for the “empty” complexes in Table 3-2. Certain patterns are evident in the ratios. The relative amplitudes of the peaks with formic acid or methanol are greater when K⁺ is a capping cation, and greatest with two K⁺ caps. The relative amplitude of the peaks with acetonitrile are greater when Cs⁺ ion caps the complex. Na⁺ caps enhances the binding of ethanol to mc[5] host.
Figure 3-4. Full spectra of CB[5] complexed with various alkali metal cations and formic acid.

Table 3-2. Intensity analysis of CB[5] complexed with various alkali metal cations and neutral guests.

<table>
<thead>
<tr>
<th>Metal Caps</th>
<th>Neutral guests</th>
<th>Intensity Ratio (full/empty)</th>
<th>ACN</th>
<th>MeOH</th>
<th>HCOOH</th>
<th>EtOH</th>
</tr>
</thead>
<tbody>
<tr>
<td>NaNa</td>
<td></td>
<td>0.00%</td>
<td>11.09%</td>
<td>0.77%</td>
<td>83.61%</td>
<td></td>
</tr>
<tr>
<td>NaK</td>
<td></td>
<td>0.00%</td>
<td>123.73%</td>
<td>15.49%</td>
<td>100.07%</td>
<td></td>
</tr>
<tr>
<td>NaCs</td>
<td></td>
<td>19.74%</td>
<td>61.79%</td>
<td>5.28%</td>
<td>78.97%</td>
<td></td>
</tr>
<tr>
<td>KK</td>
<td></td>
<td>0.00%</td>
<td>111.88%</td>
<td>76.94%</td>
<td>54.96%</td>
<td></td>
</tr>
<tr>
<td>KCs</td>
<td></td>
<td>27.63%</td>
<td>125.48%</td>
<td>11.38%</td>
<td>42.15%</td>
<td></td>
</tr>
<tr>
<td>CsCs</td>
<td></td>
<td>44.80%</td>
<td>50.15%</td>
<td>3.16%</td>
<td>21.13%</td>
<td></td>
</tr>
</tbody>
</table>
3.5 Discussion

Methanol Complexes and their Dissociation Behavior

The collision cross section data show methanol is inside CB[5]. If methanol were outside, the cross sections would be greater (computed ratio of 1.06 and 1.05 for externally bound methanol to CB[5] and mc5, respectively) for the methanol complexes than for the empty complexes. Comparing CCS value of CB[5] and mc5 with Cs⁺ caps containing methanol with their corresponding empty complexes shows that the relative CCS ratio of the full complex over the empty one (which is very close to 1) agrees with computed cross sections for internal complexes (Table 3-1). This is also consistent with condensed phase results where studies of the structures of cucurbituril complexes in the solid state using X-ray crystallography show alkali metal ion complexes are capable of encapsulating and releasing guest molecules. Methanol inclusion may lead to slight contraction of the complexes as the methanol pulls the metals inward.

Further, we note that mc5 complexes have higher dissociation threshold energy (as measured via SORI-CID) than the corresponding CB[5] complexes. This is because of RRKM effects, which make the dissociation thresholds greater for the larger host.

Inclusion of Neutral Guests Does Not Adversely Affect MultiCRAFTI Measurements

Figure 3-5 shows the relative CCS of full complexes to their corresponding empty ones. Although the acetonitrile complexes have significantly larger CCS ratios than the methanol or formic acid complexes for each combination of capping metal ions we studied, the ratio is not much larger than 1. We believe this reflects the large size and linear shape of acetonitrile, which pushes the metal ions outward and increases the resulting CCS of the complex. Methanol and formic acid are smaller and similar to each other, so they didn’t cause any expansion. The effects appear larger for smaller metal ions. We also saw that accurate relative cross sections of
cucurbit[5]uril complexes with neutral guests can be obtained through the multiCRAFTI method. The experiment results match the calculation values and confirm the same phenomena.

![Figure 3-5. computational collision cross section of complexes with different guests inside CB[5] relative to the corresponding empty ones.](image)

**Effects of Alkali Metals on Controlling Guest Inclusion in Cucurbituril-based Complexes**

Studies show CB[5] and mc5 bind more tightly with smaller alkali ion caps. Na⁺ pulls the electronegative oxygen atoms in the portals of CB[5] and mc5 together, resulting in a smaller cavity than when Cs⁺ ion caps the host.²⁵ Capping K⁺ makes the cavity volume of CB[5] host “just right” for binding with methanol or formic acid. A bigger cavity is needed for acetonitrile and the Cs⁺ ion provides that as it caps the host. Figure 3-6 shows how different capping metals affect the peak amplitude ratio of $\text{CCS[guest@CB[5]+2M]}^{2+} / \text{CCS[CB[5]+2M]}^{2+}$ (M=metal ions). We observed that ethanol complexes are external having the strongest binding with Na⁺ ions. Na⁺ is the smallest metal ions we studied and therefore it is a better polarizer than the other metals. Ethanol bound best to Na⁺ because of a stronger electrostatic attraction between ethanol and the small metal ion.
Figure 3-6. Peak amplitude ratio of \([\text{guest@CB}[5]+2\text{M}]^{2+}/\text{CCS}[\text{CB}[5]+2\text{M}]^{2+}\) in the presence of various alkali metal ions (M).

3.6 Conclusion

Alkali metal ions size-specifically control guest inclusion in cucurbituril-based complexes. The extrusion of methanol from mc5 requires more energy than from CB[5]. Overall the multiCRAFTI method gives accurate relative cross-sections for two ions simultaneously that agree with calculations.
3.7 References


3. Hendrikse, S. I. S., The journey of supramolecular polymers to biomaterials: from fundamental studies to applications. **2018**.


Chapter 4. Ion Mobility and Fourier Transform Ion Cyclotron Resonance Collision Cross Section (CRAFTI) Techniques Yield Long-range and Hard-sphere Results, Respectively

This section is adapted from a manuscript submitted to the *Journal of the American Society for Mass Spectrometry* in April 2022 and is currently under review.

Title: "Ion Mobility and Fourier Transform Ion Cyclotron Resonance Collision Cross Section (CRAFTI) Techniques Yield Long-range and Hard-sphere Results, Respectively."

Authors: Heravi, Tina; Arslanian, Andrew; Johnson, Spencer; Dearden, David.

4.1 Abstract

We determined collision cross section (CCS) values for singly- and doubly-charged cucurbit[n]uril (n = 5, 6, and 7), decamethylcucurbit[5]uril, and cyclohexanocucurbit[5]uril complexes of alkali metal cations (Li+-Cs+). These hosts are relatively rigid. CCS values calculated using the projection approximation (PA) for computationally-modeled structures of a given host are nearly identical for +1 and +2 complexes, with weak metal ion dependence, whereas trajectory method (TM) calculations of CCS for the same structures consistently yield values 7-10% larger for the +2 complexes than for the corresponding +1 complexes and little metal ion dependence. Experimentally, we measured relative CCS values in SF6 for pairs of +1 and +2 complexes of the cucurbituril hosts using the cross sectional areas by Fourier transform ion cyclotron resonance (“CRAFTI”) method. At center-of-mass collision energies < ~30 eV, CRAFTI CCS values are sensitive to the relative binding energies in the +1 and +2 complexes, but at collision energies > ~40 eV (sufficient that ion decoherence occurs on essentially every collision) that dependence is not evident. Consistent with the PA calculations, these experiments found that the +2 complex ions have CCS values ranging between 94-105% of those of their +1...
counterparts (increasing with metal ion size). In contrast, but consistent with the TM CCS calculations, ion mobility measurements of the same complexes at close to thermal energies in much less polarizable N₂ find the CCS +2 complexes to be in all cases 9-12% larger than those of the corresponding +1 complexes, with little metal ion dependence.

4.2 Introduction

Collision cross section (CCS) measurements have recently seen a dramatic increase in popularity and importance because cross section measurements give information about molecular conformation while requiring only small amounts of material. For example, cross section measurements can often distinguish between isomers that would otherwise appear identical in a mass spectrum. For supramolecular complexes, cross section data are useful for structure elucidation; externally- and internally-bound guests in host-guest complexes often yield distinguishably different CCS values.

The most common method for measuring CCS in the gas phase is ion mobility coupled with mass spectrometry (IM-MS), especially for characterizing peptide and protein conformations. In a conventional drift tube ion mobility instrument, ions travel through a uniform electric field in the presence of a buffer gas. IM-MS experiments inherently involve multiple low-energy collisions with the neutral buffer gas. The proportionality constant between the drift velocity of the ions and the electric field is the ion mobility, and is dependent on the collision integral between the ion and the buffer gas. Larger ions undergo more collisions with the buffer gas compared to smaller ions and thus have lower mobilities, other things being equal. It should be noted that IM-MS directly measures mobilities, which can be related to collision integrals (and less directly) to CCS via the Mason-Schamp equation. Long-range
interactions between the ion and the buffer gas can affect the conformations of the ions\textsuperscript{8-9} and influence CCS values at low collision energies.\textsuperscript{10}

A more recent method involves measuring CCS using techniques from Fourier transform ion cyclotron resonance mass spectrometry (FTICR-MS). We refer to this method as CRAFTI (an acronym for cross sectional areas by Fourier transform ion cyclotron resonance mass spectrometry).\textsuperscript{11-13} CRAFTI obtains ion-neutral collision cross sections from the pressure-limited rate of signal decay, reflected in the ion linewidths in Fourier transform mass spectra. Thus, both CCS and the mass-to-charge ratio can be measured at the same time using one instrument. The CRAFTI technique importantly differs from drift IM-MS in that most of the CRAFTI experiment is conducted under high vacuum conditions. As a result, ion-molecule collisions are minimized prior to the CCS measurement. The pressure of a neutral collision gas is temporarily increased for the detection event of the experiment to ensure that the ions decohere from a coherently orbiting packet primarily via single ion-neutral collisions at relatively high kinetic energy. This can enable measurement of collision cross sections for collisionally-labile complexes that are difficult to measure in the collision-rich environment of drift IM-MS.\textsuperscript{14}

Earlier work has shown that collision-induced dissociation (CID) is a primary means of decoherence in CRAFTI.\textsuperscript{11} This leads to a concern that complexes that dissociate easily might therefore yield larger cross sections than complexes of the same physical size that are more strongly bound. As long as single collisions always decohere the ions (and dissociation always results in decoherence, because it changes the cyclotron frequency of the resulting fragment ion) this would not be a problem. However, CRAFTI measurements of higher \textit{m/z} ions can be problematic if the center-of-mass collision energies required for single-collision CID cannot be reached prior to ejecting the ions from the trapping cell. One way of addressing this problem is to
apply the technique to ions that can dissociate at lower energies. Because they are relatively weakly bound, multiply-charged complexes of cucurbit[n]uril host molecules with alkali metal cations (Figure 4-1) provide an opportunity for studying this approach.

Figure 4-1. (a) Skeletal formula of cucurbit[n]uril (CB[n]). R = H for CB[5], CB[6], and CB[7], and R = CH3 for decamethylcucurbit[5]uril (mc5). Cyclohexanocucurbit[5]uril (CB*[5]) has the two R groups connected to each other, forming a 6-membered ring. (b) Complex of CB[5] with two Na+ ions.

Cucurbit[n]urils and their derivatives are macrocyclic molecular receptors built from the association of n glycoluril repeat units. They have a hydrophobic inner cavity and two identical carbonyl-lined portals that allow them to readily form host-guest complexes. The two electronegative portals represent two binding sites for cations; thus, these hosts often function as ditopic ligands. The structure of such a complex is illustrated in Figure 4-1. These hollow, pumpkin-shaped molecules have attracted interest in the field of supramolecular chemistry due to their potential applications in areas such as drug delivery or sensitive analytical assays. Further, these relatively small, simple molecular containers can serve as prototypes for much larger, more complicated structures, such as the binding pockets of enzymes. We are interested in measuring collision cross sections.

Cucurbit[n]uril (CB[n], n=5, 6, and 7), decamethylcucurbit[5]uril (mc5), and cyclohexanocucurbit[5]uril (CB*[5]) (Figure 4-1) complexes of alkali metal cations are ideal
targets for probing the effects of binding energy on CRAFTI CCS measurements. Whereas the cations are strongly bound in the +1 complexes, Coulombic repulsion in the +2 complexes decreases the binding strength of the second alkali metal cation\textsuperscript{22} to levels that make dissociation relatively easy despite the fact that the ion is relatively massive compared to the neutral collision gas. Further, because the ligands are relatively rigid, we would expect the +1 and +2 complexes to have similar physical sizes.

In this study, we measure collision cross sections of CB[5], mc5, CB*[5], CB[6], and CB[7] complexed with alkali metal ions using both IM-MS and the “multi-CRAFTI”\textsuperscript{23} technique (multi-CRAFTI is a method that performs CRAFTI on two or more ions at the same time, under identical pressure conditions at nearly identical center-of-mass kinetic energies). We compare the results obtained using the two techniques, and also compare the experimental results with computational methods using density functional theory for geometry optimization coupled with cross section calculations.\textsuperscript{24}

In particular we are interested in any differences that might arise due to differences in dissociation energies rather than due to real differences in physical size. Although we usually observed mixed-metal complexes as well, here we focus on homo-metal complexes to simplify the discussion. We will show that relative CCS values from IM-MS and multi-CRAFTI reflect the differences in intermolecular interactions that dominate under low- (in the case of drift IM-MS) vs. high-energy (in the case of CRAFTI) collision conditions.
4.3 Experimental

Sample preparation

CB[5], CB[6], CB[7], and all alkali metal salts are commercially available at Sigma-Aldrich (St. Louis, MO). A sample of mc5 was acquired from IBC Advanced Technologies (American Fork, Utah). CB∗[5]25 was provided by Professor Kimoon Kim. ESI low concentration tune mix was obtained from Agilent Technologies (Santa Clara, CA). Ar and SF6, which were used as collision gases in FTICR, and N2, used as buffer gas in IM-MS (99.9997%, 99.8%, 99.999% purity, respectively) were purchased from Airgas, Inc (Radnor, Pennsylvania). All solutions were prepared with cucurbit[n]uril host concentrations of 100 μM and an alkali salt concentration equal to twice that of the cucurbituril, in 1:1 isopropanol:water. These solutions were electrospayed directly for multi-CRAFTI and diluted to a final concentration of about 20 μM in host to be used in IM-MS. Tune mix (specifically, Agilent standard m/z 922 with CCS of 243.64 ± 0.30 Å2)26 was added to all the IM-MS samples for calibration of the CCS. HPLC-grade solvents were used for all solutions. All the solvents, cucurbituril complexes, and the alkali metal salts were used as supplied without further purification.

FTICR Instrumentation

A Bruker model APEX 47e Fourier transform ion cyclotron resonance mass spectrometer with an Infinity trapping cell,27-28 a micro-electrospray source modified from an Analytica (Branford, CT, USA) design, and a metal capillary drying tube based on the design of Eyler et al.,29 was used in our experiments. Data were acquired using a MIDAS Predator data station.30 The excitation clock rate was 5 MHz. Ions of interest were isolated using stored waveform inverse Fourier transform (SWIFT) techniques.31 Ar or SF6 collision gases were introduced into
the FTICR cell using a Freiser-type pulsed leak valve. Some multi-CRAFTI experiments were performed using both gases for comparison, but all systems were examined in SF₆ because it enables higher center-of-mass kinetic energy without ejecting the ions from the trapping cell. The pressure inside the cell was controlled by varying the duration of the leak valve pressurization event. Relative pressures in the cell were determined using a cold cathode pressure transducer. Collision energies were varied by changing the peak-to-peak amplitude of the excitation event at the resonant frequencies of the ions of interest in multi-CRAFTI experiments. The ions being compared in multi-CRAFTI experiments were excited to nearly identical collision energies in the center-of-mass reference frame. We used summed single-frequency waveforms of identical duration (typically 0.5 ms, with relative amplitudes adjusted so as to produce the same center-of-mass collision energies $E_{CM}$ with the neutral molecules according to equation 4-133), yielding a simultaneous dual-frequency excitation. These waveforms were synthesized via a LabVIEW program.

$$E_{CM} = \frac{\beta^2 q^2 V_{pp}^2 t_{exc}^2}{8d^2 m} \frac{M}{M+m} \quad (4-1)$$

In this equation, $\beta$ is an instrument-dependent scaling factor (0.897 for the Infinity cell used here), $q$ is the ion charge, $V_{pp}$ is the peak-to-peak excitation amplitude, $t_{exc}$ is the duration of the excitation, $d$ is the trapping cell diameter, and $m$ and $M$ are the masses of the ion and neutral, respectively. Data were analyzed using the Igor Pro software package (version 7, Wavemetrics Inc.; Lake Oswego, OR) to collect a set of power spectra measured at various collision gas pressures at each collision energy for each of the ion pairs. The collision cross section ratio of the
two ions \( \frac{CCS_2}{CCS_1} \) (where CCS\(_1\) = singly-charged ion, and CCS\(_2\)= doubly-charged ion) was
determined from the fwhm linewidths of the ions using Equation 4-2:\(^{23}\)

\[
\frac{CCS_2}{CCS_1} = \frac{fwhm_2 m_2 z_1 V_{pp,1} t_{exc,1}}{fwhm_1 m_1 z_2 V_{pp,2} t_{exc,2}}
\]

(4-2)

Here \( fwhm_n \) is the full width at half maximum linewidth acquired using Lorentzian fits to the
mass spectral data,\(^{35}\) \( z_n \) is the ion charge, and the excitation durations for the two ions, \( t_{exc,n} \), are
the same, so that the \( t_{exc,n} \) terms cancel. \( V_{pp} \) is the peak-to-peak amplitude of the excitation
waveform at the frequency of interest, and \( m_n \) is the mass of the ion.

**IM-MS Instrumentation**

An Agilent 6560 Ion Mobility Quadrupole Time-of-Flight (IM-QTOF) device operated
under uniform low field conditions was used to measure mobilities and corresponding CCS
values of the ions. An Agilent nano-electrospray ionization source (G1992A) was used to
generate the ions. The IM-QTOF consists of a front funnel that runs at high pressure (4–4.50
torr), a trap funnel and trapping gate that store and then release discrete packets of ions, a drift
tube (~80 cm long) that separates ions based on their mobility, and a rear funnel that refocuses
the ions before they enter a hexapole and are transmitted to the Q-TOF mass analyzer.\(^{36}\) The
front funnel and trap funnel were operated at 200 V peak-to-peak, and the rear ion funnel was
operated at 100 V peak-to-peak (except for the case of CB[7], which was set to 200 V) . A fill
time of 30,000 µs and release time of 300 µs were applied to the trap funnel.
The instrument provides drift time ($t_d$) information for ions. The Agilent IM-MS Browser software then calibrates and corrects the $t_d$ information from the stepped-field measurements, and converts this to collision cross section using the Mason-Schamp equation.

**Computational Modeling.** Modeling provides structural and energetic data to be compared with experimental data. We began with a Monte Carlo conformation search using the Merck molecular force field (MMFF94) within the Spartan’18 software package (Wavefunction Inc., Irvine, CA). Since MMFF94 does not include parameters for rubidium and cesium, user-selected parameters for those ions were inserted into the force field. For cucurbit[n]uril and derivatives, the number of structures that need to be considered is relatively small because the host molecules are rigid. We used Spartan’s Monte Carlo search algorithm to generate starting structures. Once low energy conformers were identified, geometry optimizations on the lowest energy conformers for each host•cation system were performed at the B3LYP/6-311+G** level of theory to obtain final structures and energies, enabling host•cation binding energies to be determined. We report energies at 0 K, without counterpoise or vibrational corrections. Since the 6-311+G** basis set does not include parameters for rubidium and cesium, Spartan ’18 defaults to a split basis set with def2-TZPPD (with pseudopotential) applied to rubidium and cesium. IMoS version 1.10c was used to compute collision cross sections from the theoretical structures. Either the very simple projection approximation (PA) or the somewhat more sophisticated exact hard-sphere scattering (EHSS) method could be used to compute CCS values from calculated molecular structures for comparison with CRAFTI. The differences between PA and EHSS results for a given structure are small and comparable to the inherent error in the experimental measurements. Because the PA method is computationally inexpensive compared to EHSS and models the single-collision dephasing conditions expected in
CRAFTI, we opted to use the simple PA approach, but would expect very similar results with EHSS. We therefore used PA with Ar and SF₆ collision gases to model CRAFTI, and used the trajectory method (TM)⁹ with N₂ as the buffer gas for comparison and for modeling IM-MS. For the TM calculations, nitrogen’s quadrupole moment was included, along with host•guest partial charges assigned using electrostatic potential (ESP) charges from the ab initio calculations. ⁴³-⁴⁴

**4.4 Results**

Multi-CRAFTI experiments directly yield ratios of CCS values for the ions being compared. Because relative CCS values are the focus here, we report all results in terms of ratios in the form \(\text{CCS}[\text{host}+2\text{M}]^{2+}/\text{CCS}[\text{host}+\text{M}]^+\). Absolute CCS values can be obtained by comparison with standards of known CCS²³ (and are reported in the Supporting Information), but are not required for the comparisons that follow.

*Computational Results.*

In the projection approximation (PA) calculations, all of the complexes of a given host have similar CCS values and CCS values increase with increasing host size. Examining ratios (Table 4-1), doubly-charged complexes have cross sections about 1-5% larger than their singly-charged counterparts, except in the case of Li⁺ and Na⁺, for which the doubly-charged complexes are 1-2% smaller than the corresponding singly-charged complexes. In contrast, TM calculations for doubly-charged complexes consistently yield collision cross sections 7-10% larger than their singly-charged counterparts. For a given metal, as the host is varied the CCS +2/+1 ratio decreases as the size of the host increases, as expected given that the cross sections increasingly depend on the size of the host rather than on the metal.
Computational results for binding energies are shown in Table 4-2, without counterpoise or vibrational corrections, which would be small compared with the observed large differences between binding of the first and second cation to the complexes. Binding of an alkali cation to the neutral host is always significantly stronger (usually by a factor of 2 or more) than binding of a second cation to the singly-charged (host+M)$^+$ complex, as expected due to significant Coulomb repulsion in the latter case.

Table 4-1. Collision cross section ratios from calculations and experiments for alkali cation complexes of cucurbit[n]uril (CB[n], n=5,6,7), mc5 and CB*[5], with neutral collision gases as indicated in parentheses.

<table>
<thead>
<tr>
<th>host, metal (M)</th>
<th>Masses (+1, +2), Da</th>
<th>PA (SF$_6$)$^a$</th>
<th>multi-CRAFTI (SF$_6$)$^b$</th>
<th>TM (N$_2$)</th>
<th>IM-MS (N$_2$)</th>
</tr>
</thead>
<tbody>
<tr>
<td>CB[5], Li</td>
<td>837.3, 844.3</td>
<td>0.98</td>
<td>c</td>
<td>1.10</td>
<td>1.11±0.003</td>
</tr>
<tr>
<td>CB[5], Na</td>
<td>853.2, 876.2</td>
<td>0.99</td>
<td>0.95±0.02</td>
<td>1.10</td>
<td>1.12±0.007</td>
</tr>
<tr>
<td>CB[5], K</td>
<td>869.2, 908.2</td>
<td>1.01</td>
<td>1.04±0.02</td>
<td>1.10</td>
<td>1.12±0.002</td>
</tr>
<tr>
<td>CB[5], Rb</td>
<td>915.2, 1000.1</td>
<td>1.03</td>
<td>1.04±0.02</td>
<td>1.10</td>
<td>1.11±0.001</td>
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<tr>
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<td>1.10</td>
<td>1.12±0.001</td>
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<td>1.10±0.002</td>
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<td>1.09±0.003</td>
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<td>1.09±0.004</td>
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<td>1.10±0.007</td>
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<td>CB[7], Cs</td>
<td>1295.2, 1428.2</td>
<td>1.02</td>
<td>c</td>
<td>1.07</td>
<td>1.09±0.005</td>
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</table>

$^a$ Boltzmann-weighted averages from MMFF94 conformational searches to generate structures and energies and IMoS projected area approximation calculation for collision cross sections with SF$_6$.

$^b$ Average ± standard deviation for ratios measured at the 3 highest center-of-mass kinetic energies in SF$_6$ collision gas.

$^c$ Complex not detected experimentally.
Table 4-2. Computed binding energies (B3LYP/6-311+G**) of cucurbituril complexes

<table>
<thead>
<tr>
<th>host, metal (M)</th>
<th>D(CB[n]-M⁺) (kJ/mol)</th>
<th>D(CB[n]M⁺ - M⁺) (kJ/mol)</th>
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<tbody>
<tr>
<td>CB[5], Na</td>
<td>-404</td>
<td>-201</td>
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<td>CB[5], K</td>
<td>-339</td>
<td>-144</td>
</tr>
<tr>
<td>CB[5], Rb</td>
<td>-309</td>
<td>-121</td>
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<tr>
<td>CB[5], Cs</td>
<td>-277</td>
<td>-99</td>
</tr>
<tr>
<td>mc5, Na</td>
<td>-437</td>
<td>-235</td>
</tr>
<tr>
<td>mc5, K</td>
<td>-367</td>
<td>-175</td>
</tr>
<tr>
<td>mc5, Rb</td>
<td>-361</td>
<td>-150</td>
</tr>
<tr>
<td>mc5, Cs</td>
<td>-300</td>
<td>-125</td>
</tr>
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<td>CB*[5], Na</td>
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<td>-243</td>
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<td>CB*[5], Cs</td>
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<tr>
<td>CB[6], Na</td>
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<td>CB[6], Cs</td>
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<td>-101</td>
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<tr>
<td>CB[7], Na</td>
<td>-405</td>
<td>-188</td>
</tr>
<tr>
<td>CB[7], Cs</td>
<td>-332</td>
<td>-34</td>
</tr>
</tbody>
</table>

**Multi-CRAFTI Experimental Results**

All the doubly- and singly-charged cucurbituril complex ions are easily observed in the electrospay mass spectra except for complexes of Li⁺ ion and doubly-charged complex of CB[7] with two Cs⁺ ions. We performed multi-CRAFTI experiments in different collision gases (Ar and SF₆) for some of the complexes and obtained answers in decent agreement (Table C1). We report relative CCS in SF₆ collision gas in all the multi-CRAFTI experiments because SF₆ yields higher center-of-mass kinetic energy at any given ion orbit radius and thus is more likely to satisfy the energetic hard-sphere collision requirement intrinsic to CRAFTI.

Relative collision cross sections (CCS[host+2M]²⁺/CCS[host+M]⁺, M = alkali metal) from multi-CRAFTI experiments are shown in Table 4-1 (absolute values are shown in Table B2). The multi-CRAFTI ratios involving the CB[5] host are shown in Figure 4-2 as a function of center-of-mass collision energy; the results for other hosts are similar (Appendix C, Figures C1 – C4).
each case, the ratio decreases with collision energy until reaching a constant value at higher energies.

At the lowest energies (below 30-40 eV in the center-of-mass frame), the results are not reliable because the assumption of single-collision decoherence for both ions being compared, which is essential to CRAFTI, is not valid. Because dissociation energies are lower for the +2 ions than for the corresponding +1 ions, collisions at these lower energies are more likely to dissociate the +2 ions and be “counted” as collisions than are similar interactions with +1 ions. Hence, the resulting ratios at low collision energies overemphasize CCS values for +2 ions and are larger than would be predicted from hard-sphere modeling.

At collision energies greater than about 35-40 eV for these complexes the multi-CRAFTI ratios become approximately constant as essentially all collisions result in dissociation for both +1 and +2 ions. Therefore, we concentrate on ratios at the high energy limit as accurate reflections of CCS ratios. The high-energy limiting value of $CCS[\text{host}+2\text{M}]^2+/CCS[\text{host}+\text{M}]^+$ is slightly less than 1 when $\text{M} = \text{Na}$, and is slightly greater than 1 for the larger alkali metal ions. These limiting values increase with the size of M in the order $\text{Na}^+ < \text{K}^+ \approx \text{Rb}^+ < \text{Cs}^+$, as expected based on the relative sizes of the alkali cations. We see the same trends for all other cucurbituril host complexes as well.
Collision cross section data for the various complex ions were measured by directly infusing them into the Agilent IM-MS instrument at seven different drift fields in N₂ buffer gas. The $t_0$ values for each complex were obtained from drift time vs. 1/voltage graphs and then the corrected drift times ($t_d$) were used for CCS calculations. As shown in the last column of Table 4-1 (absolute values are shown in Table C2), the CCS[host+2M]$^{2+}$/CCS[host+M]$^+$ ratios from IM-MS for all examined hosts with different alkali metal ions are consistently greater than 1. Doubly-charged complexes range between 9-12% larger than their singly-charged counterpart complex ions, and are in excellent agreement with values computed using TM.
4.5 Discussion

Effects of Binding Strength on CRAFTI Measurements

One of the original motivations for this study was to examine the influence of binding strength on CRAFTI measurements. We therefore compared CRAFTI cross sections for singly-charged, relatively strongly-bound complexes of the hosts and alkali metal ions with doubly-charged, relatively weakly-bound complexes.

Although $m/z$ varies by nearly a factor of 2, the corresponding singly- and doubly-charged complexes of the same host should have similar physical sizes due to the rigidity of the host molecules. These expectations were generally borne out by our PA modeling results (Table 4-1), which indicate similar CCS values for +1 and +2 complexes. Interestingly, the model calculations predict that the +2 complexes of Li and Na should be a few percent smaller than the +1 complexes. We will address this further below.

In accordance with expectation, the modeling also shows that the singly-charged complexes have much greater interaction energies than the corresponding doubly-charged complexes (Table 4-2). Hence, if weaker binding yields larger apparent CRAFTI cross sections, we should observe the ratio $\text{CCS(host+M}_2^+) / \text{CCS(host+M)}^+$ to be significantly greater than 1, especially where the difference in interaction energies is large. This is what we do observe at the lowest collision energies (below about 30 eV in Figure 4-2, for example). At higher collision energies, as both +1 and +2 ions dissociate on essentially every collision, the observed CCS ratio approaches a constant, high energy limit value, which we argue reflects the relative physical sizes of the molecules being compared. Thus, if binding interactions do not influence the high energy limit measurements significantly, for the complexes examined here we should observe $\text{CCS(host+M}_2^+) / \text{CCS(host+M)}^+$ ratios near 1 that are consistent with the values from modeling.
Examination of the high energy limit values reported in Table 4-1 shows experimental multi-CRAFTI ratios consistent with the computationally modeled PA results for all hosts.

When M = Na, the experimental ratio is significantly smaller than 1. While this is qualitatively consistent with the computational result, the experimental ratios are smaller than those computationally predicted, not larger as might be expected if interaction energy differences cause errors. Thus, we conclude that if interaction energy differences on the order of ~175—300 kJ mol⁻¹ cause error in high energy limit CRAFTI cross section measurements, those errors are smaller than we can measure using current techniques.

Effects of Shifts in the Center-of-Mass

We note that both multi-CRAFTI and drift IM-MS CCS measurements involve rotational averaging, and that a shift in the center-of-mass of the complex away from its geometric center could therefore affect the measured CCS ratios. The symmetric +2 complexes have mass uniformly distributed about the geometric center of the complex, whereas the +1 complexes have a guest ion on only one side, shifting the center-of-mass away from the geometric center and therefore possibly increasing the radius of rotation for the +1 ions. This should decrease the CCS(host+M₂)²⁺/CCS(host+M)⁺ ratio slightly (we estimate by 1-2%). Neither the PA nor the TM calculations take possible center-of-mass shifts into account, so comparison of the experimental results with the calculations might reveal possible center-of-mass effects. Comparison of multi-CRAFTI results with the PA calculations reveals that in almost all cases the experimentally-measured CCS(host+M₂)²⁺/CCS(host+M)⁺ ratio is slightly smaller than that from the PA calculations, as would be expected if center-of-mass effects were skewing the results. However, the effect does not seem to become larger as the cation mass increases, as would be expected if
center-of-mass shifts were the correct explanation. In contrast, the ratios from the IM-MS measurements are in every case slightly larger than those from the corresponding PA or TM calculations and are independent of alkali cation, so if center-of-mass effects are significant they do not show up at all in the IM-MS measurements. We conclude that neither the CRAFTI results nor the IM-MS results show obvious effects from shifts in the center-of-mass of the complexes.

Metal Size-dependent “Pinching” Effects in Cucurbituril Complexes Observed via multi-CRAFTI

Our initial expectation was that perhaps the +2 complexes would have cross sections slightly larger than the +1 complexes because the +2 complexes have an additional surface atom, and Coulombic repulsion between the two metal ions might also stretch the complex somewhat. A perusal of the PA results in Table 4-1 shows that for M = Li or Na, CCS(host+M)\textsuperscript{2+}/CCS(host+M)\textsuperscript{+} is less than 1 for all hosts, indicating the +2 complexes are computed to have collision cross sections a few percent smaller than those of the +1 complexes. The same is the case for the multi-CRAFTI measured cross sections involving M = Na, for all the hosts. In fact, for all hosts, the PA value of CCS(host+M)\textsuperscript{2+}/CCS(host+M)\textsuperscript{+} increases monotonically with increasing metal size, and the experimental multi-CRAFTI values of the ratio are consistent with this trend.

What accounts for the Li\textsuperscript{+} and Na\textsuperscript{+} cases, which have +2 complexes that are smaller than the corresponding +1 complexes? As was noted above, one possibility is that shifts in the center-of-mass might account for this, but if so, center-of-mass effects should become more pronounced as the metal ions become heavier, and this is not observed. However, the results are consistent with a “pinching” effect when small metal ions bind in the portal of a cucurbituril host and attract the O atoms inward. To explore this idea, in Figure 4-3 we plot the change in the sum of O—O center-
to-center distances around each portal of CB[5] as various alkali metal ions are added (as measured in structures from DFT theory) from the same sum in the free ligand. Not surprisingly, binding a metal ion in the portal of CB[5] causes the O—O circumferential distance to decrease as the positive metal ion pulls the electronegative oxygen atoms together, with Na⁺ resulting in the most pinching of the portal and Cs⁺ the least (Li⁺ is too small to effectively interact with all 5 portal O atoms and distorts the portal shape, so while Li⁺ does cause contraction, it has a smaller net effect than Na⁺).

We initially expected that pinching one side of the ligand closer together might result in opening of the other portal, possibly accounting for the observed change in size of the +1 vs. +2 complexes. The circles in Figure 4-3 report the change in portal size for the portal in the +1 complexes that does not contain a metal ion. The modeling results do not support the idea of the “opposite” side being pinched open. Rather, the O—O distances also decrease (relative to the free ligand) on the portal opposite that where the metal binds, although the changes are small and not strongly sensitive to the size of the metal ion. Pinching in the doubly-charged complexes as measured via O—O distances (green triangles in Figure 4-3) is about the same on both portals as in the ion-bearing side of the singly-charged complexes (blue squares in Figure 4-3) and again is greatest for the smallest metal ions. Pinching both portals in the +2 complexes causes a decrease in collision cross section, which is offset by the increases due to more surface atoms and Coulombic repulsion noted above. For the smallest alkali metal cations, the pinching on both sides of the +2 complexes is sufficient to make the +2 complexes have smaller CRAFTI cross sections than the corresponding +1 complexes, which are pinched on only one side. These changes are subtle but reproducible, consistent with modeling, and observed for every cucurbituril host we examined. This suggests that multi-CRAFTI cross section measurements can reveal structural
changes that are relatively subtle. Multi-CRAFTI Results Reflect Hard-sphere Collisions, IM-MS Results Reflect Long-range Interactions. We recognize that the neutral gas used in the CCS measurements plays a crucial role, and the best comparisons between CRAFTI and IM-MS could be made using the same neutral gas for both types of experiment. Unfortunately, such a direct comparison was not practical. One of the key conditions for CRAFTI experiments is that collisions occur in the energetic hard sphere limit, where ions are lost in single collisions from the coherently-orbiting packet prepared via resonant excitation. The preferred way to ensure single-collision decoherence is to conduct the experiments at collision energies high enough that the ions dissociate on virtually every collision. For the ions studied here, center-of-mass collision energies greater than about 30 eV are required to meet this condition. To achieve these collision energies for ions such as the cucurbituril complexes, relatively heavy neutral gases must be used (see equation (2)). We have previously examined the effects of collision gases on CRAFTI results and found that Ar and SF$_6$ can both yield satisfactory data for CB[n] complexes, although especially for the singly-charged complexes the higher energies accessible using SF$_6$ are beneficial. Thus, SF$_6$ was the best collision gas for CRAFTI experiments. We did not use SF$_6$ in the IM-MS experiments because the continuous flow and long equilibration requirements of IM-MS mean that large amounts must be used. This was impractical with an expensive gas such as SF$_6$.

Hence, CRAFTI experiments on the FTICR were done in SF$_6$ (and to a limited extent in Ar), but IM-MS experiments were done in N$_2$. To mitigate the differences between the collision gases, we used internal standards in all experiments and report the ratios of cross sections measured against these internal standards. In addition, we note that the polarizabilities of N$_2$ (1.710 Å$^3$) and Ar (1.664 Å$^3$) are similar, whereas that of SF$_6$ (4.490 Å$^3$) is much greater. The effects of
long-range interactions should therefore be significantly greater in SF₆ than in N₂ (or Ar), whereas despite this we will show that CRAFTI experiments in highly polarizable SF₆ are more consistent with hard-sphere interactions than are IM-MS results in less polarizable N₂.

Figure 4-3. Change in portal circumference upon metal cation binding (as determined by summed O—O center-to-center distances around the portal) from B3LYP/6-31+G* calculations.

Relative CCS ratios obtained from multi-CRAFTI and IM-MS for singly- vs. doubly-charged complexes are clearly different (Table 4-1). Multi-CRAFTI results appear to correlate best with CCS values obtained using PA calculations from the model structures, whereas IM-MS measurements correlate better with CCS values from TM calculations on the same model structures. Figure 4-4 plots experimental measurements using multi-CRAFTI and IM-MS vs. computed CCS values using PA and TM calculations for the same computed structures to show these correlations. We note that perfect agreement between theory and experiment in such a plot would yield a slope of 1, intercept of 0, and \( R^2 = 1 \). The plot of multi-CRAFTI vs. PA has a slope of \( 1.1 \pm 0.2 \) and intercept of \(-0.1 \pm 0.2\), with \( R^2 = 0.70 \), whereas plotting multi-CRAFTI vs. TM
yields slope 1.3 ± 0.3, intercept -0.4 ± 0.4, and $R^2 = 0.24$ (a much worse correlation). Similarly, plotting IM-MS CCS vs. those calculated using TM gives slope $= 1.1 ± 0.1$, intercept $-0.1 ± 0.1$, and $R^2 = 0.83$, while plotting IM-MS vs. PA gives slope $0.28 ± 0.02$, intercept $0.83 ± 0.02$, and $R^2 = 0.34$ (a much poorer correlation). In summary, the multi-CRAFTI measurements are more consistent with the PA calculations and show trends of increasing ratios as the sizes of the metal cations increase—they are sensitive to changes in CCS arising from changes in metal ion. The relative IM-MS experimental CCS measurements are in excellent agreement with values computed using TM and show little variation with metal ion, perhaps because long-range interactions smooth out those differences.

An increase of 9-12% in CCS for +2 over +1 complexes is consistent with a much larger role for long-range interactions in IM-MS measurements as compared with multi-CRAFTI. Long-range interactions depend strongly on the charge of the ion and the polarizability of the neutral, and are much more important at low collision velocities than at high collision velocities. IM-MS measurements are deliberately carried out with low drift fields and low (close to thermal) ion-neutral collision energies and corresponding low velocities, where long-range interactions are expected to be important. In contrast, to satisfy the requirement that ion decoherence occurs in single collisions, multi-CRAFTI is performed at much higher energies (typically tens to hundreds of eV in the center-of-mass reference frame) and correspondingly high relative velocities where long-range interactions are much less important, and collision cross sections are expected to be more accurately modeled via hard-sphere interactions. Therefore, even though the IM-MS measurements were done in N$_2$, which is much less polarizable than the SF$_6$ used in the multi-
CRAFTI measurements, long-range interactions are much more important in our IM-MS measurements than in our multi-CRAFTI measurements.

![Diagram showing relative collision cross section comparison of IM-MS, CRAFTI, TM and PA methods. Error bars represent standard errors from IM-MS measurements and standard deviations from 3 or more replicate CRAFTI measurements.](image)

4.6 Conclusion

We explored the differences between the collision cross sections of the singly- and doubly-charged metal-cationized complexes of rigid host cucurbituril molecules that have similar physical sizes but quite different binding energies using both multi-CRAFTI and IM-MS techniques. The experimental data suggest that binding energy does not affect the CRAFTI cross section measurements noticeably, as long as the single-collision decoherence requirement is met.

The results of the current study also demonstrate theoretically-expected differences between multi-CRAFTI and IM-MS measurements. Collision cross sections from multi-CRAFTI experiments tend to reflect hard-sphere interactions, which may allow probing of subtle differences...
in the physical sizes of the molecules that are more difficult to study using IM-MS experiments where long-range potentials play a larger role.

An example is found in the results presented here. The multi-CRAFTI measurements suggest small alkali cations pinch the portals of the hosts closed, causing smaller cross sections for the doubly-charged ions than are observed for complexes of one small alkali cation on CB[5] or mc5. Larger cations do not pull the CB[n] portal as tightly closed and protrude more, resulting in larger physical sizes for the doubly-charged ions. The multi-CRAFTI measurements are sufficiently sensitive to observe subtle structural effects such as these, whereas our IM-MS measurements show very little variation as the metal ions vary, perhaps because these small effects are masked by long-range interactions. Interestingly, we note recent trapped ion mobility-time of flight (TIMS-TOF) measurements that did successfully measure differences due to the different sizes of lanthanide ions, so at least in some cases mobility measurements at sufficiently high mobility resolution are able to detect these types of subtle structural effects.
4.7 References


Chapter 5. Summary and Perspective

Most of the work described here focused on the multiCRAFTI method for determining cucurbit[n]uril conformations. Ion mobility techniques and cross sections determined from electronic structure calculations were successfully used to complement multiCRAFTI measurements.

In Chapter 2, multiCRAFTI was applied to CB[5] complexes with alkali metals capping the host and halide anion guests and to explain the observed SORI-CID data. The results acquired from multiCRAFTI are consistent with the dissociation behavior seen in SORI-CID experiments. We found that Cl\(^-\) binds inside CB[5] complexed with various alkali metals; Br\(^-\) binds both inside (with Na\(^+\)-capped CB[5] portals), and outside the CB[5] cavity (when K\(^+\) is the capping cation). I\(^-\) complexes were not observed with alkali metal cations serving as caps, but I\(^-\) does bind strongly enough to the exterior to be observed in the presence of alkaline earth cation caps. This study shows CB[5]-metal complexes can be size-selective anion receptors.

In Chapter 3, neutral guests were trapped inside the CB[5] cavity. MultiCRAFTI experiments, along with analysis of mass spectra and modeling suggest that the alkali metal ions affect the binding selectivity for different guests inside the CB[5] complexes. We observed the inclusion of formic acid and methanol enhanced when K\(^+\) ions cap the complexes, whereas the inclusion of acetonitrile was enhanced when Cs\(^+\) ions cap the complexes and attachment of ethanol was enhanced when Na\(^+\) ions cap the complexes.

In Chapter 4, IM and multiCRAFTI were done on various cucurbituril complexes. Comparing the results from both techniques shows that the CRAFTI technique, which reflects hard-sphere interactions, can measure subtle differences in the physical sizes of cucurbituril complexes. The results from multi-CRAFTI measurements suggest that small alkali cations pinch
the portals of the hosts closed, causing smaller CCS for the doubly-charged ions compared to doubly-charged ions for CB[5] or mc5. Larger cations did not pull the CB[n] portals as tightly closed, resulting in larger CCS for the doubly-charged ions. These subtleties were not observed in our IMS measurements, which suggested that the CCS values for all the doubly-charged ions were larger than their singly-charged counterparts. In IMS, long-range potentials play an essential role in determining the CCS values and may mask such subtle differences.

Although the work described here demonstrates that multiCRAFTI works (sometimes even better than the ion mobility technique), some areas need further attention. For example, Dr. Andrew Arslanian and I started a project to compare the sequential and simultaneous multi-CRAFTI strategies. The results from that project could answer questions about whether the sequential or simultaneous excitation method is the best. The multiCRAFTI experiments could be done with larger buffer gas molecules such as Xe to improve the CCS accuracy for heavier ions such as cucurbituril complexes. Also where we used both IM and multiCRAFTI to compare the results of the two techniques, more definitive comparisons could be made using the same buffer gas with both methods. More neutral guests need to be trapped in CB[5] to study the metal selectivity trends.
Figure A 1. Electrospray mass spectrum for CB[5] mixed with NaBr and KBr. Inset: expansion from m/z 950-1000. Computed isotopic patterns are overlaid in green.
Figure A 2. Electrospray mass spectrum for CB[5] mixed with BaI₂. Insets: expansions showing isotopic patterns resulting from complexation, with computed isotopic distributions overlaid in green.

Figure A 3. Relative ESORI for dissociation of [CB[5]+KRbCl]⁺. Points are averages of 3 or more runs, error bars are standard deviations, lines are sigmoidal fits to the data.
Figure A 4. Multi-CRAFTI collision cross section in SF₆ for [CB[5]+NaBal]²⁺ relative to that of [CB[5]+Ba]²⁺. Points are averages of 3 or more runs, error bars are standard errors, lines are simply to guide the eye.
Figure A 5. Approximate potential energy profiles for loss of MX from [X@CB[5]MM’]⁺ (M = Na, K; X = F, Cl, Br, I) computed at the MMFF//M06-2X/6-31+G* level of theory.
Figure B 1. Full spectra of CB[5] complexed with various alkali metal cations and methanol.
Figure B 2. Full spectra of CB[5] complexed with various alkali metal cations and Acetonitrile.
Figure B 3. Full spectra of CB[5] complexed with various alkali metal cations and Acetonitrile.
APPENDIX C. Supporting information for Chapter 4

Table C 1. Multi-CRAFTI collision cross section ratios in Ar and SF$_6$

<table>
<thead>
<tr>
<th>host &amp; metal (M)</th>
<th>Ar collision gas</th>
<th>SF$_6$ collision gas</th>
</tr>
</thead>
<tbody>
<tr>
<td>CB[5]-Na</td>
<td>0.93±0.03</td>
<td>0.95±0.02</td>
</tr>
<tr>
<td>CB[5]-Cs</td>
<td>1.06±0.01</td>
<td>1.05±0.01</td>
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<tr>
<td>mc5-Cs</td>
<td>1.04±0.02</td>
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Table C 2. Collision cross sections in SF$_6$ of all cucurbit[n]uril CB[n] (n=5,6,7) and derivative complex ions obtained from multiCRAFTI measurements and projection approximation calculations.

<table>
<thead>
<tr>
<th>host &amp; metal (M)</th>
<th>Multi-CRAFTI</th>
<th>Projection Approximation</th>
</tr>
</thead>
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<td></td>
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<td>CCS of (host•M$^+$)</td>
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<tr>
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<td>--$^b$</td>
</tr>
<tr>
<td>CB[5]-Na</td>
<td>35.16</td>
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<td>CB[5]-Rb</td>
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<td>mc5-Cs</td>
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<td>CB*[5]-Na</td>
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<td>32.70</td>
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<td>CB[6]-Cs</td>
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<tr>
<td>CB[7]-Na</td>
<td>47.83</td>
<td>48.42</td>
</tr>
<tr>
<td>CB[7]-Cs</td>
<td>--$^b$</td>
<td>--$^b$</td>
</tr>
</tbody>
</table>

$^a$ The multi-CRAFTI results here are not calibrated as calibrated values were not needed for ratio comparisons.

$^b$ Complex not detected experimentally
Figure C 1. MultiCRAFTI relative collision cross section ratio in SF6 for doubly-charged mc5 complexes/singly-charged complexes capped by various alkali metal cations. Error bars represent standard deviations for 3 or more replicate measurements.

Figure C 2. MultiCRAFTI relative collision cross section ratio in SF6 for doubly-charged CB*[5] complexes/singly-charged complexes capped by Na⁺ and Cs⁺ cations. Error bars represent standard deviations for 3 or more replicate measurements, and lines are exponential fits to the experimental points.
Figure C 3. MultiCRAFTI relative collision cross section ratio in SF₆ for doubly-charged CB[6] complexes/singly-charged complexes capped by Na⁺ and Cs⁺ cations. Error bars represent standard deviations for 3 or more replicate measurements, and lines are exponential fits to the experimental points.

Figure C 4. MultiCRAFTI relative collision cross section ratio in SF₆ for doubly-charged CB[7] complexes/singly-charged complexes capped by Na⁺ cation. Error bars represent standard deviations for 3 or more replicate measurements, and lines are exponential fits to the experimental points.