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COMMUNICATION

Influence of charge repulsion on binding strengths: experimental and computational characterization of mixed alkali metal complexes of decamethylcucurbit[5]uril in the gas phase^{†‡}

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Theory and experiment demonstrate that Coulombic repulsion plays a dominant role in the strength of binding a second cation to a rigid, ditopic host.

Allosterism can be broadly defined as the influence binding a guest in one binding site has on binding in another site. This can involve enhanced binding of the second guest (positive allosterism) or reduced binding (negative allosterism). Herein we examine one of the simplest possible cases of negative allosterism, repulsion of one charged guest by another charged guest in another site.

As simple, ditopic ligands, cucurbiturils provide an opportunity to study some of the simplest cases of allosterism. The cucurbituril family is a series of synthetic, pumpkin shaped molecular cages constructed from glycoluril monomers.^{1–3} Because of their high selectivity in forming inclusion complexes they have been considered for applications in drug delivery, as trapping agents, and for use in catalysis.

As is shown in Fig. 1, decamethylcucurbit[5]uril (hereafter mc5) is well suited for ditopic cation binding. For example, alkali metal ions complex through ion–dipole interactions with the carbonyls along the two portals and can act as lids to close a cage complex. The gas phase provides an ideal environment for studying subtle binding effects without any perturbations from solvation, and should yield experimental data that can be compared directly with high level theory. In this study we have experimentally and computationally examined complexes in which both alkali metal ions are identical, as well as complexes in which one of the lid ions is Cs⁺ and the other is another alkali cation. This allows systematic variation of cation size on the rigid scaffold of mc5.

All experiments were done using a Fourier transform ion-cyclotron resonance mass spectrometer (Bruker model Apex 47e FT-ICR MS) equipped with a MIDAS PREDATOR^{4,5}

data system (National High Magnetic Field Ion Cyclotron Resonance Facility; Tallahassee, FL). Samples of mc5 were provided by IBC Advanced Technologies (American Fork, UT) and used without further purification. Alkali metal salts (LiCl: Fisher Scientific, Fair Lawn, NJ; NaCl and CsCl: Mallinckrodt, Paris, KY; KNO₃: Sigma-Aldrich, Milwaukee, WI; RbCl: Spectrum, Gardena, CA) were also used without further purification. Aqueous solutions containing the desired metals and mc5, each at 100 μM, were electrosprayed with a typical flow rate of 30 μL h^{−1} using a microelectrospray source⁶ modified from an Analytica (Analytica of Branford; Branford, MA) design and a heated metal capillary tube⁷ based on an Eyler design. Peaks of interest were isolated using stored waveform inverse Fourier transform (SWIFT)⁸ techniques. Sustained off-resonance irradiation collision-induced dissociation (SORI-CID)⁹ experiments were conducted on peaks of interest by exciting 1 kHz below the resonant frequency and systematically varying the SORI-CID event length. Argon collision gas was introduced into the cell to a constant pressure of about 10^{−5} mbar using a Fresier-type¹⁰ pulsed leak valve. Five to six runs were performed for each sample.

Data were analyzed using Igor Pro (Lake Oswego, OR) to extract peak amplitudes as a function of SORI duration. The energy collisionally deposited in the ions *via* SORI, E_{SORI} , is proportional to the amplitude and duration of the SORI event as follows:¹¹

$$E_{\text{SORI}} \propto N^* \sigma t_{\text{SORI}} \left(\frac{m_{\text{neut}}}{m_{\text{neut}} + m_{\text{ion}}} \right) \frac{V_{\text{pp}}}{m_{\text{ion}}^2} \quad (1)$$

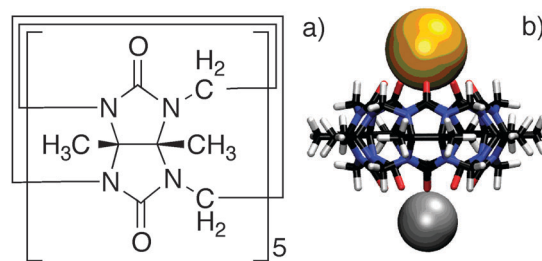


Fig. 1 (a) mc5 is made of five glycoluril monomers, each with two methyl groups along the plane of mc5. (b) A graphical representation of mc5 (tubes) complexed with K⁺ and Cs⁺ (spheres).

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Here N^* is the number density of the neutral collision gas, σ is the collision cross section, t_{SORI} is the duration of the SORI event, m_{neut} is the mass of neutral gas, m_{ion} is the mass of the ion of interest, and V_{pp} is the peak-to-peak amplitude of the SORI event. N^* is constant during the SORI event, and σ is assumed to be the same for all the complexes (a reasonable assumption given that these complexes vary only in the metal ions). Ion survival curves (see supplemental data) were generated by plotting the relative abundance of the parent ion as a function of E_{SORI} . The energy required for 50% dissociation of the parent ion ($E_{\text{SORI},50\%}$) was determined by fitting a Hill equation to the survival curve.

We carried out molecular mechanics conformational searches for each of the complexes followed by full geometry optimizations at the B3LYP/6-31+G* level of theory for the lowest energy conformers. Molecular mechanics calculations employed the Maestro/Macromodel modelling package (Macromodel version 7.1; Schrödinger Inc; Portland, OR) using the MMFF94s force field and 2000 starting structures. Full geometry optimizations were performed using NWChem (Version 5.1.1; Pacific Northwest National Laboratory; Richland, WA).¹² We used the 6-31+G* basis set for all atoms except K, Rb, and Cs, which were described with the LANL2DZ basis set. Calculations were set up and monitored using ECCE (Version 6.0; Pacific Northwest National Laboratory; Richland, WA).¹³ Reported interaction energies, $D(\text{M}'\text{-mc5M})$, are at 0 K and are not zero-point corrected.

Perusal of the computational results in Table 1 reveals several trends arising from repulsion of the charges on the two metal cations. In the complexes with only one metal ion, the metal binding strengths due to the collective interaction of the rim carbonyl oxygens with the charge on the metal are quite strong, comparable to the strengths expected for the covalent bonds within the cucurbituril ligand. Thus, it is not surprising that loss of the metal ion from the $[\text{mc5} + \text{M}]^+$ complexes is difficult to observe experimentally. Binding strengths decrease monotonically as the size of the alkali cation increases, reflecting the decreasing ability of the cations to polarize the neutral cucurbituril as the cation size increases. Further, $D(\text{M}'\text{-mc5})$ is always much greater than $D(\text{M}'\text{-mc5M})$,

as expected; a large decrease in binding strengths should occur when a second cation is present to repel the first.

For complexes where the two metal ions are identical, the computed binding energy is strongly dependent on the identity of the metal, ranging from 290 kJ mol⁻¹ for $\text{D}(\text{Li-mc5Li})$ down to only 125 kJ mol⁻¹ for the complex with two Cs⁺ ions. The experimental threshold results (Fig. 2) are consistent: we were unable to observe dissociation of the $[\text{mc5} + 2\text{Li}]^{2+}$ complex, and thresholds decrease for the $[\text{mc5} + 2\text{M}]^{2+}$ complexes as we move down the periodic table. The polarizing capabilities of the cations decrease down the table, and so do their binding energies.

The $[\text{mc5-MCs}]^{2+}$ complexes are particularly interesting in that they show the influence of M^+ on the binding of Cs⁺ by mc5. All of these complexes dissociate exclusively by loss of Cs⁺ upon collisional activation. According to the B3LYP calculations, as the size of M^+ increases the M-Cs distances increase, even though the distance between Cs and the mc5 equatorial plane remains approximately constant. This suggests that for most of these complexes the second metal does little to perturb the Cs⁺ binding site. However, the increasing distances mean that the repulsion between the two charges decreases, and the Cs⁺ binding energy correspondingly increases. The effect is relatively small, spanning a range of less than 25 kJ mol⁻¹ as M is varied from Li to Cs, but is still measurable in the experimentally observed variation in SORI dissociation thresholds (Fig. 3).

If the effects are purely due to electrostatic repulsion between the charges, one would expect the binding to vary linearly with the Coulombic potential energy, which is proportional to $1/r$, where r is the distance between the two charges (which are assumed to be localized primarily on the metal ions). A simple way to examine this effect is to consider the differences between the computed binding strengths in the mc5-M^+ complexes, $D(\text{M}'\text{-mc5})$, and those computed for complexes with the second ion present, $D(\text{M}'\text{-mc5M})$. Assuming no distortion of the ligand structure due to the presence of a second metal cation, this difference should correspond to the Coulomb repulsion. A plot of these differences vs. $1/r$ is given in Fig. 4. The plot suggests a good linear correlation

Table 1 B3LYP/6-31+G* computed geometries and energetics for alkali cation complexes of decamethylcucurbit[5]uril, $[\text{mc5} + \text{MM}']^{2+}$

M, M'	$r_{\text{M-M}'}/\text{\AA}$	$r_{\text{M-plane}}/\text{\AA}^a$	$r_{\text{M'-plane}}/\text{\AA}^a$	$D(\text{M}'\text{-mc5M})^b/\text{kJ mol}^{-1}$	$\Delta^c/\text{kJ mol}^{-1}$
Li	—	3.27	—	-505	—
Na	—	3.28	—	-437	—
K	—	3.84	—	-367	—
Rb	—	4.20	—	-334	—
Cs	—	4.57	—	-300	—
Li, Li	6.28	2.95	3.23	-290	215
Na, Na	6.79	3.39	3.39	-236	201
K, K	7.90	3.95	3.95	-175	192
Rb, Rb	8.58	4.29	4.29	-150	184
Cs, Cs	9.37	4.68	4.68	-125	175
Li, Cs	8.01	3.22	4.68	-103	197
Na, Cs	8.03	3.35	4.68	-112	188
K, Cs	8.61	3.94	4.67	-117	183
Rb, Cs	8.95	4.29	4.67	-121	179

^a Distance from the metal to the mc5 equatorial plane containing the ten methyl carbon atoms. ^b Computed interaction energy at 0 K for the $\text{M}'\text{-mc5M}$ interaction. ^c $D(\text{M-mc5}) - D(\text{M}'\text{-mc5M})$.

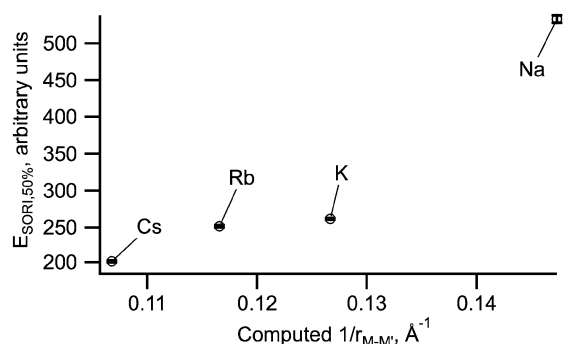


Fig. 2 Dissociation thresholds for $[\text{mc}5+2\text{M}]^{2+}$ complexes. The identity of M is indicated for each point.

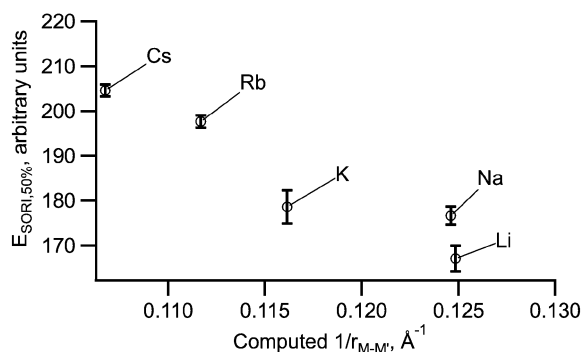


Fig. 3 Dissociation thresholds for $[\text{mc}5+\text{MCs}]^+$ complexes. The identity of M is indicated for each point. Energies decrease as M becomes smaller and closer to Cs^+ .

($R^2 = 0.94$) between the difference in binding strengths in the singly- and doubly-charged complexes and $1/r$. In fact, the correlation improves significantly (to $R^2 = 0.98$) if the point for the $[\text{mc}5-\text{LiCs}]^{2+}$ complex is not considered. There is some justification for this: the computed structure for the $[\text{mc}5-\text{LiCs}]^{2+}$ complex indicates that the small Li^+ cation, which is too small to simultaneously interact with all the rim carbonyl oxygens, causes significant distortion of the mc5 framework and likely disrupts the bonding of the Cs^+ accordingly.

Corresponding trends are evident in the experimental results (Fig. 3), although the lack of data for simple dissociation *via* loss of the metal ion for the singly-charged $[\text{mc}5+\text{M}]^+$

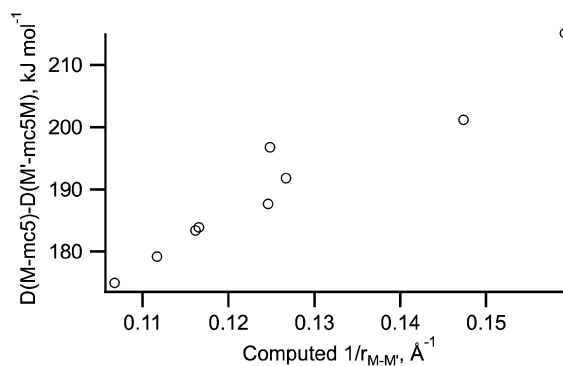


Fig. 4 Coulomb dependence of computed mc5-metal binding strengths.

complexes means we are restricted to examining only the change in $E_{\text{SORI},50\%}$ as M is varied. The greatest energy is required to dissociate Cs^+ from $[\text{mc}5+2\text{Cs}]^{2+}$, and the 50% threshold decreases monotonically as the other cation becomes smaller, and thus closer, to the Cs^+ binding site. As with the computed binding energies, the variation is linear with $1/r_{M-M'}$, suggesting that the effects are primarily electrostatic.

We are excited about these initial results both as a demonstration of fundamental negative allostereism resulting from electrostatic repulsion that agrees well with first-principles predictions, and as a demonstration of the ability of this type of SORI-CID threshold technique to measure small changes. We intend to continue these experiments by placing dielectric materials within the cucurbituril cage to see how they affect the mutual repulsion of the ions.

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