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Determination of Intrinsic Binding Modes by Mass Spectrometry: Gas-Phase Behavior of Adamantylated Bisimidazolium Guests Complexed to Cucurbiturils

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The chemistry of cucurbit[*n*]urils (CBs) inclusion complexes with various ligands has been extensively studied in the condensed phase.[1] The joint development of mass spectrometry (MS) techniques has provided insight into the intrinsic binding behavior of these host–guest systems readily available in the gas phase.[2] These MS data have been used to examine self-sorting pseudorotaxane aggregates[3] or distinguish a pseudorotaxane arrangement for the studied complexes. Depending on the initial concentrations, the formation of a 1:1 or 2:1 aggregates of butane-1,4-diamine and CB6 have been observed in the gas phase. Whereas the 1:1 complex adopted a pseudorotaxane arrangement that resulted in loss of guest and simultaneous extensive fragmentation of the CB6 cage under collision-induced dissociation (CID) conditions, the 2:1 portal-bound aggregate solely underwent facile loss of one guest.[4] Correspondingly, the aggregates of CB6 with phenylenediamine isomers have been examined to show that *o*- and *m*-isomers preferentially bound on the exterior, whereas *p*-isomer was buried in the CB6 cavity, in a pseudorotaxane fashion.[5] Additionally, the suppression of fragmentation channels of the ethylenediamine Ni complex after its inclusion into the CB8 cavity has been observed under CID conditions.[6] Furthermore, the CID was used to distinguish rotaxane with phenolic axel and tetralactam macrocyclic wheel, in which the axel centerpiece was cleaved, from nonspecific unthreaded aggregate which decomposed to the wheel and axel.[7]

In some cases of multiply charged aggregates, the CID led to the electrostatic repulsion-driven cleavage of an axel with retention of pseudorotaxane arrangement of host and guest residue as it has been demonstrated for the supramolecular aggregates of molecular tweezers containing dendritic viologen dications[8a,b] or crown-ether/ammonium rotaxanes.[8c] The selective binding of CB6 to lysine residues and the subsequent removal of a lysine fragment-CB6 complex was recently introduced as a probe to determine the structure of small proteins.[9]

Formation of inclusion complexes of various adamantane derivatives with CBs in solution has been well documented. Almost ideally sphere-shaped adamantane cage perfectly fits the hydrophobic interior cavity of CB7 to form highly stable complexes. Typical values of binding constants (e.g., $1.7\cdot10^{14}\,\text{M}^{-1}$ for 1-adamantylammonium with CB7 or $5\cdot10^{15}\,\text{M}^{-1}$ for dication of *N*-(2-aminoethyl)-1-adamantylamine with CB7) allow such adamantane derivatives to be classed as ultrahigh affinity guests for CB7 along with bicyclo[2.2.2]octane and ferrocene derivatives.[10] As the CBs cavity is a magnetic shielding region, the considerable upfield shifts of resonances for the adamantane protons indicate the preferable positioning of the adamantane cage inside the cavity.[1c,11] On the other hand, CB8 with larger cavity binds adamantane derivatives with reduced affinity (a typical binding constant for CB8 with 1-adamantylamonium is $8.2\cdot10^{8}\,\text{M}^{-1}$) and the lower homologue CB6 does not include adamantane cage.[1c] Nevertheless, this specificity allows to design an interesting self-sorting multi-component systems[11] or utilize the adamantane derivatives as competitive controllers of aggregation processes.[12]

Imidazolium-based ionic liquids with various length of alkyl chains demonstrate different stoichiometry (1:1 or 2:1) with CB6 as well as two distinct binding modes differing in the imidazolium unit penetration depth.[13] Bisimidazolium (BIM) salts with short terminal methyl substituents and *p*-xylylene spacer between imidazolium rings form a 1:1 aggregates with CB7 or CB8 in water with binding constants of about $2\text{–}3\cdot10^{6}\,\text{M}^{-1}$. In these complexes, the aromatic spacer occupies the interior of CB cavity and charged imidazolium rings cap both CB portals.[14] It has been described, that complexation of α,α′-bis(3-(1-methylimidazolium))-*p*-xylene dication inside the CB7 cavity significantly decrease the H/

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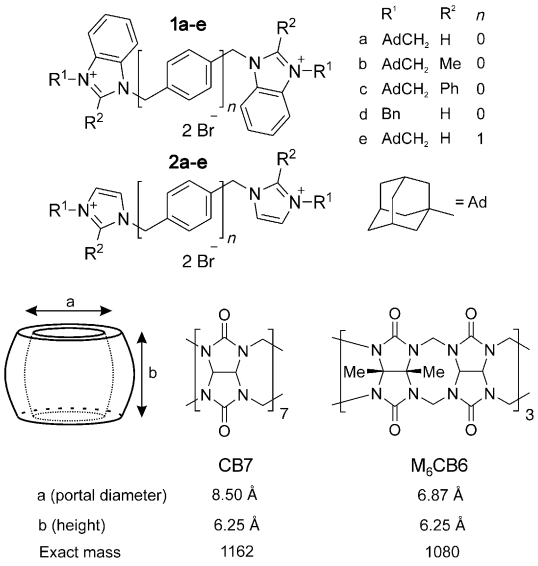

Scheme 1. Structures and dimensions[17] of the bisimidazolium salts and cucurbiturils used in this work.

D exchange rate for the N–CH–N protons due to H-bonding to the CB7 portal carbonyl oxygen atoms.[15] Additionally, the positioning of the CB7 unit on the initially unfavored dicationic binding site of the BIM **2d** (for the structure, see Scheme 1) was observed as a result of a cooperative supramolecular interaction between CB7 and β-cyclodextrin units in the ternary complex.[16a] Upon the ESI-MS data, the similar dicationic binding site was suggested to be complexed to the CB7 due to high initial CB7 concentration.[16b]

Herein, we describe the consecutive fragmentation of CB-complexed BIM guest dications, that is, cleavage of the covalent C–N and C–C bonds, while retaining the supramolecular interactions between the charged guest residue and the CB molecule. In addition to the unprecedented gas-phase reactivity (to the best of our knowledge), we demonstrate that analysis of the ESI-MS spectra of host–guest systems may serve as a tool for estimating the ability of CBs to slip over the molecular axel.

We first analyzed MeOH/H_2O (1:1, v:v) solutions containing only BIM dibromides (Scheme 1). Figure 1a shows that five significant ions were observed in the positive-ion mode ESI-MS spectra for compound **2a** and assigned through a detailed investigation using tandem mass spectrometry and CID experiments. The fragmentation of the ion at *m*/*z* 223 (MS^2) created two product ions at *m*/*z* 297 and 149 (Figure 1b). Further fragmentation of *m*/*z* 297 (MS^3) led to the parallel neutral loss of imidazole, diazine, or diimidazoylmethane to yield the ions at *m*/*z* 229, 217, or 149, respectively (Figure S7c in the Supporting Information). We therefore assigned the ion at *m*/*z* 223 to the doubly charged molecular BIM ion and the ions at *m*/*z* 297 and 149 to its singly charged fragments that form during the ESI process. The loss of the singly charged adamantylmethyl cation (*m*/*z* 149) will hereinafter be referred to as "149" fragmentation. In addition, the supramolecular associate between BIM and Br^-

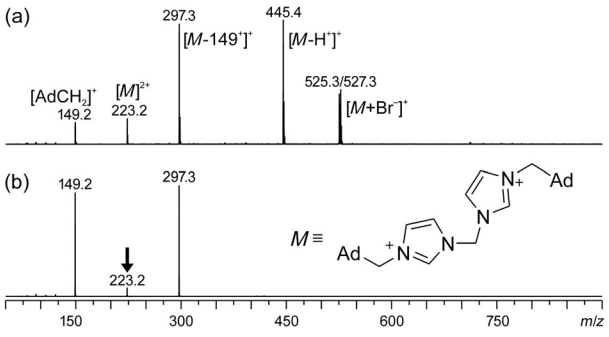

Figure 1. Positive-ion mode ESI mass spectra (full scan) of compound **2a** in a MeOH/H_2O (1:1, v:v) solution. a) First-order mass spectra, b) MS^2 of *m*/*z* 223. The assignments for the observed signals are shown in brackets. The ion being fragmented in the tandem mass spectra is marked with a bold, downward arrow.

was observed based on the ^{79}Br and ^{81}Br isotopologue ion pair at *m*/*z* 525 and 527. This association loses a neutral HBr molecule to produce the sole singly charged N-heterocyclic carbene[18] observed at *m*/*z* 445 (Figure S7d in the Supporting Information).

We subsequently analyzed 25 μM mixtures of the BIM ligands and CBs (Scheme 1) in a 50 μM solution of NaCl in water. In the spectra of the BIM/CB7 mixtures, we initially focused on the fragmentation of the doubly charged ions from the 1:1 complexes $[BIM{\cdot}CB]^{2+}$. Figure 2c and d show that, for compound **1c** with CB7, the fragmentation of the 1:1 complex at *m*/*z* 930 forms three ions at *m*/*z* 549, 1163, and 1311. Based on the corresponding MS spectra for the individual BIM and CB7 compounds, we assigned these signals to the singly charged residue of **1c** arising from "149" fragmentation, the singly charged association of $CB7{\cdot}H^+$ and the singly charged $CB7{\cdot}AdCH_2^+$, respectively. The ion at *m*/*z* 1311 loses a neutral AdCH fragment and forms $CB7{\cdot}H^+$ at *m*/*z* 1163 after further fragmentation (MS^3). Therefore, the observed fragmentation for BIM **1c** complexed to CB7 is essentially the identical to that of free BIM (compare Figure S16b in the Supporting Information and Figure 2d).

In contrast, we obtained completely different results for the mixture of **2a** and CB7 (Figure 2a and b). In the MS^2 spectrum for this complex, we observed two ions at *m*/*z* 730 and 656 formed from the parent ion $[BIM{\cdot}CB7]^{2+}$ at *m*/*z* 804. Subsequent fragmentation of the ion at *m*/*z* 730 (MS^3) led to the sole formation of the ion at *m*/*z* 656. This may be rationalized as the sequential loss of neutral 1-adamantylcarbene fragment (or its isomer)[19] from both ends of the BIM scaffold to yield the doubly charged aggregate of the CB7 and BIM residue. This release of neutral AdCH fragments (exact mass of *m*/*z* 148) will be hereinafter referred to as the "148" fragmentation.

All other examined adamantylated BIMs displayed at least one (but usually exactly one) of these fragmentation pathways and no additional significant signals were observed. Little variations in signal intensities can be reasonably attributed to the different axel bulkiness which influen-

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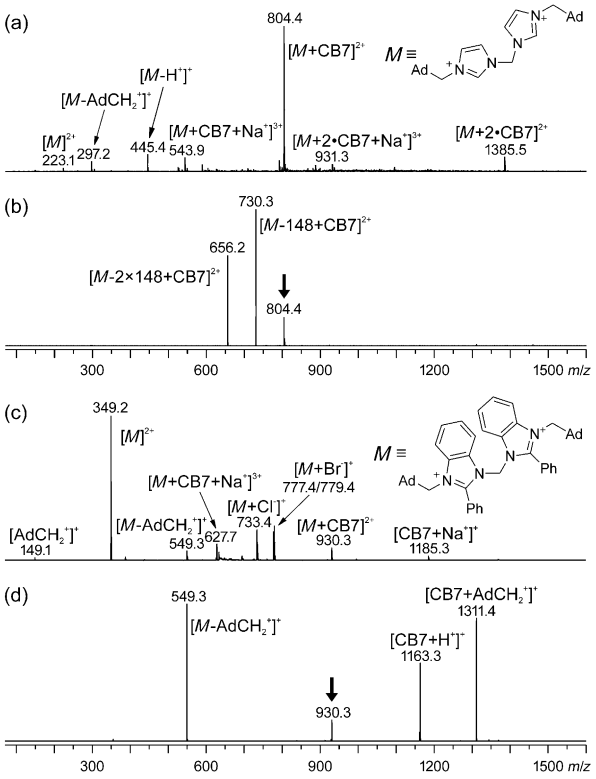

Figure 2. Positive-ion mode ESI mass spectra (full scan) of aqueous solutions of **2a**·CB7 and **1c**·CB7. a) First-order mass spectra of **2a**·CB7, b) MS^2 of *m*/*z* 804, c) first-order mass spectra of **1c**·CB7, d) MS^2 of *m*/*z* 930. The assignments for the observed signals are shown in the brackets. The fragmented ions in the tandem mass spectra are marked with bold, downward arrows.

ces the activation barriers to the slipping of CB7 between particular binding sites. Thus, the intensity of the second "148" fragmentation product signals was rather lowered in the case of BIM **2b**, **1e**, or **2e** and completely disappeared in the case of BIM **1a** or **1b**. Additionally, the CID (MS^2) of doubly charged aggregates of the BIM **1a** or **1b** with CB7 resulted in products of "149" fragmentation accompanied by products of one "148" fragmentation. Comparing the intensities of the corresponding signals (Figure S40 and S41 in the Supporting Information), we may see that the **1a**·CB7 complex was predominantly cleaved via the "148" fragmentation in contrast to the **1b**·CB7. The complexes of CB7 and BIM **1e** or **2e** (Figure S43 and S47 in the Supporting Information) displayed fragmentation pattern similar to those observed for the corresponding methylene-bridged BIMs and the additional hypothetical binding site on the aromatic bridge did not affect fragmentation pattern.

The ^{1}H NMR spectra recorded for the mixtures of BIMs with CB7 in D_2O indicated formation of inclusion complexes with pseudorotaxane geometry (Figure S60 in the Supporting Information). The considerable upfield shift of all adamantane signals hand in hand with diminishing of signals of free BIM when the CB7 molar fraction reached of 0.7 evidenced that both terminal adamantane cages were successively complexed to the CB7 interior cavity to form the 1:1 or 1:2 aggregates depending on the CB7 concentration. In contrast, the downfield shift of signals of methylene or *p*-xylylene bridges suggested the location of the central part of BIM close to the CB7 portal. Considering previously discussed binding constants for similar structure motifs with CBs, we assume that binding of CB7 at adamantane site is strongly favored and observation of any other potential arrangements is disabled using NMR. However, this finding does not contradict the formation of pseudorotaxane complexes with different geometry under treatment in the gas phase.

We propose that the aggregates evidenced in solution are transferred to the gas phase using ESI to observe corresponding signals in the first-order mass spectra. We believe that the CB host cannot reach the opposite end of the guest skeleton by walking "outside" of the guest molecule without decomposing the supramolecular complex. Therefore, the presence of substituents with varying bulk results in three distinct situations (Figure 3), as indicated via further fragmentation analyses: 1) The CB is bound to the end of the BIM molecule and cannot slip over the imidazolium unit. Only the products of "149" fragmentation are observed. Typical examples of such BIM salts are **1c** or **2c** (Figure 2d and Figure S45 in the Supporting Information). 2) The CB may slip over the imidazolium unit once bound to the BIM but cannot easily reach the opposite end of the BIM. In such cases we observed products from both "149" and "148" fragmentations. However, the "148" fragmentation occurred only once. In other words, only one adamantylmethyl substituent can be released in this manner. Typical examples of such BIM salts are **1a** or **1b** (Figures S40 and S41 in the Supporting Information). 3) The CB can freely slip over the BIM skeleton, and the products of "148" fragmentation were predominantly observed. Typical examples of such BIM salts are **2a**, **1e**, **2b**, or **2e** (Figure 2b and Figures S43, S44, and S47 in the Supporting Information).

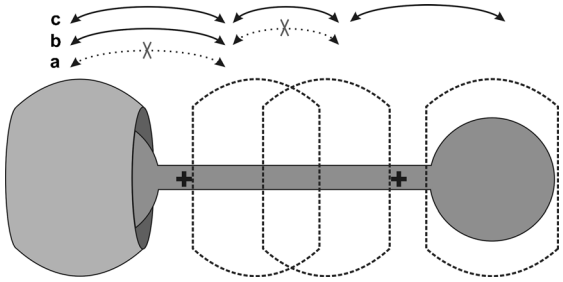

Figure 3. Schematic drawing of the slipping modes of the CB unit over the BIM dication.

We next focused on the fragmentation analysis of 2:1 aggregates of CB with BIM. With the exception of compounds **1a** and **2a**, the signals obtained for the 2:1 aggregates were not observed for the equimolar aqueous solutions of CB and BIM in the presence of NaCl. The transfer of the 2:1 aggre-

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gates from solution to the gas phase was supported by excluding NaCl from the tested mixture and enhancing the mole fraction of CB in the solution. The 2:1 aggregates were typically observed as either doubly charged ions or their triply charged Na^+ associations. A further CID experiment led to the loss of the CB unit to form the doubly charged 1:1 complex with nearly identical fragmentation patterns to those previously described (Figures S48–S57 in the Supporting Information). However, for BIMs **2a** and **2b**, the fragmentation of the doubly charged 2·CB7·BIM at *m*/*z* 1385 and *m*/*z* 1399 yielded an unexpected pair of ions at *m*/*z* 1311 and 1237 and *m*/*z* 1325 and 1251, respectively (Figures S53 and S54 in the Supporting Information). We assigned these ions to the doubly charged products of the sequential "148" fragmentation complexed to two CB7 units. The 2:1 aggregates of two CB7 and doubly protonated diimidazoylmethane with signals at *m*/*z* 1237 and 1251 further fragmented (MS^4) to yield signals at *m*/*z* 1311 and 1339, respectively. In both cases, these ions were accompanied with a signal at *m*/*z* 1163. We interpreted this as an electrostatic repulsion-driven cleavage of the 2:1 complex to form a $[CB7{\cdot}H]^+$ ion at *m*/*z* 1163 and the singly charged aggregates of the CB7 and corresponding singly protonated diimidazoylmethane at *m*/*z* 1311 and 1339, respectively.

To examine the scope of the described phenomenon, we analyzed mixtures of the benzylated BIMs **1d** and **2d** with CB7 and Me_6CB6. Typically, in the MS spectrum of **2d** we observed ions at *m*/*z* 409/411, 329, 239, and 91, which we assigned to $[BIM+Br^-]^+$, $[BIM\text{-}H^+]^+$, $[BIM\text{-}Bn^+]^+$ and Bn^+ (Figure S25 in the Supporting Information), respectively. Under the same experimental conditions, we observed two additional signals at *m*/*z* 746 and 505 when analyzing the equimolar mixture of **2d** and CB7. Upon further fragmentation analysis, we assigned these signals to the $[CB7{\cdot}BIM]^{2+}$ and $[CB7{\cdot}BIM{\cdot}Na]^{3+}$ aggregates, respectively. The former ion decomposed into the fragments observed at *m*/*z* 253, 707, 1161, and 1401 (Figure S46b in the Supporting Information). The assignment of the ion at *m*/*z* 1161 is discussed below and the rest were assigned to $[BIM\text{-}77^+]^+$, $[CB7+BIM\text{-}78]^{2+}$, and $[CB7+BIM\text{-}Bn^+]^+$, respectively. As can be clearly observed, the presence of CB7 promoted alternative fragmentation pathways involving the loss of a neutral fragment. We can conclude that CB7 clearly changed the fragmentation mechanism and supported the charge retention on the axel residue during the fragmentation process. With a view to extension of our work to other CB homologue, we analyzed mixtures of BIM salts **1d** and **2d** with Me_6CB6, a water-soluble analogue of CB6. Signals for $[BIM+Me_6CB6]^{2+}$ were clearly observed and fragmented (Figures S58 and S59 in the Supporting Information) to yield ions assigned to $[BIM\text{-}Bn^+]^+$, $[Me_6CB6+BIM\text{-}Bn^+]^+$, $[Me_6CB6+Bn^+]^+$ at *m*/*z* 1171 and the ion at *m*/*z* 1079 (see below). These results indicate that Me_6CB6 can form supramolecular complexes with benzylated BIM but cannot slip over the BIM skeleton to provide the alternative fragmentations contrary to CB7, which has a larger internal cavity diameter.

Finally, we would like to note the unusual forms observed of the CBs. In some cases, the complex between the CB7 and the charged BIM fragments decompose to neutral BIM residues and a CB ion at *m*/*z* 1161. Similarly, the fragment at *m*/*z* 1079 was observed when mixtures containing Me_6CB6 and a suitable ligand were analyzed. Figure 4 shows the obtained tandem mass spectrum for the mixture of CB7 with **1a**. The ion at *m*/*z* 1559 was obtained through sequential MS^2 experiments beginning with the ion at *m*/*z* 855 (doubly charged CB7·BIM), which produced the minor ion at *m*/*z* 1559 under CID conditions (Figure S40b in the Supporting Information). We assigned this ion to $[CB7+BIM\text{-}AdCH_2^+]^+$ and a further fragmentation (Figure S40c in the Supporting Information) led to the loss of a neutral dibenzimidazoylmethane unit to yield $[CB7+AdCH_2^+]^+$ at *m*/*z* 1311. The parallel fragmentation of *m*/*z* 1559 led to the loss of neutral adamantylmethylbenzimidazole and the ion at *m*/*z* 1293. Subsequent fragmentation yielded the ion at *m*/*z* 1161 (Figure S40d in the Supporting Information). The suggested pathway was supported by the further isolation and fragmentation analyses of the ions at *m*/*z* 1311 and 1293. Using these data, we were able to assign the ions at *m*/*z* 1293 and 1161 to the singly charged complex of CB7 and benzimidazolylmethyl and the singly charged CB7 without a single hydrogen atom, respectively. We can speculate that latter ion is possibly formed by a hydride transfer from the neutral CB7 molecule to the benzimidazolylmethyl cation. To support this idea, the structure and formation of the $[CB7\text{-}H^-]^+$ cation was further studied using a computational chemistry framework (for details and analysis, see the Supporting information). Density functional calculations indicated that the reaction depicted in Figure 4 is favorable towards the products by $-160\ kJ\,mol^{-1}$. It can be expected that the transfer probably occurs within the CB7·benzimidazolylmethyl cation complex. Indeed, its predicted structure shows reasonable mutual orientation of both donor and acceptor atoms of hydride ion with atom-to-atom distance of 3.5 Å.

In conclusion, we have demonstrated that CBs may dramatically change the fragmentation pathways of axel mole-

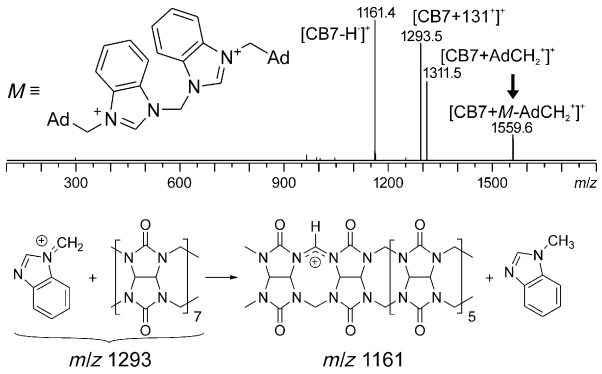

Figure 4. Tandem mass spectra (MS^3) of *m*/*z* 1559 (top) and a schematic representation of the final step in the proposed pathway toward *m*/*z* 1161 product ion (bottom).

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cules in the gas phase. Whereas sole bisimidazolium dications decompose to two singly charged fragments in accordance with electrostatic repulsion, some complexed dications release neutral fragments to form doubly charged complex of CB and axel residue. Furthermore, latter fragmentation occurred only when the slippage of the CB unit over the axel was sterically allowed. This phenomenon has general importance for the description of binding modes using mass spectrometry. We are currently preparing a set of BIM ligands with a spacer of various lengths bearing a steric hindrance between the imidazolium rings to clarify the mechanism of unusual "148" fragmentation. In addition, we have demonstrated the ability of CBs to act as a hydride donor in the gas phase. This property of CBs, as soon as proved in solution, may open a new way towards functionalized CBs.

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Gas-Phase Reactions

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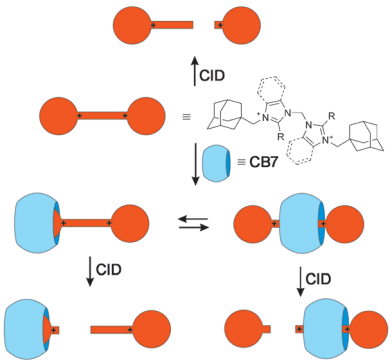
Determination of Intrinsic Binding Modes by Mass Spectrometry: Gas-Phase Behavior of Adamantylated Bisimidazolium Guests Complexed to Cucurbiturils



Adamantylated bisimidazolium cations exhibit a distinct fragmentation pathway in contrast to their cucurbit[7]uril (CB7) complexes (see scheme). The observed alternative fragmentation of the guest molecule in a complex clearly correlates to the supposed sterically hindered or allowed slippage of the macrocycle over the axel molecule.

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