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ARTICLE TYPE

Evaluating the Cation Binding Strength and Selectivity of Calix[4]pyrroles: A Computational and ESI-MS/MS Study

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Cation binding strength of Calix[4]pyrroles (CPs) in the gas phase has been evaluated by computational studies and further substantiated by ESI mass spectrometry experiments. The DFT optimized geometries of $[CP+X]^+$ complexes are found stable in the 1,3-alternate conformation through cation-π interactions and interestingly CPs are found to be better cation receptor than calix[4]arenes. The binding energy values of $[CP+X]^+$ complexes computed at B2PLYP/TZVP//M05-2X/TZVP follows the binding order, $Li^+ > Na^+ > K^+ > Rb^+ > Cs^+$. The diameter of Li^+ matches very well with the cavity size of CP and thus is optimally disposed to interact simultaneously with all the four pyrrole rings through multiple cation-π interactions. However, other cations due to increase in their size drift away from the cavity center towards the rim of the cavity exhibiting weak cation-π interactions. Energy decomposition analysis (EDA) reveals that the electrostatic and polarization effects act as the major driving force in these interactions.The important outcome of the current study is that the stability of precursor and product ions is found to be crucial in the experimental evaluation of binding affinity of Li^+ and Na^+ complexes of CP. The ESI-MS/MS experiments on the cation complexes of different substituted CPs revealed that the binding strength of CPs towards cations is also depend on the substituents at the *meso*-position.

1. Introduction

The Calix[4]pyrroles (CPs), which first synthesized by Baeyer in 1886[1] and later explored by Sessler *et al.*,[2, 3] belong to a unique model of receptors in supramolecular chemistry. Custelcean *et al.* demonstrated CPs as ion-pair receptors[4] in the solid state of cesium halide/CP complexes. CPs also reported as new transmembrane ion-pair transporters in the solution phase.[5] In biological systems, the role of cations and anions are of profound importance and mutually dependent in different biological events and also in the maintenance of the electric neutrality. Thus, it is essential to understand the binding properties of both anions and cations to CPs. Till date, CPs have been extensively studied as the host molecules for anions and neutral substrates;[6-10] however, their cation binding properties are not explored. Thus understanding the interactions of CPs with cations is of prime importance. In contrast to other cation receptors like crown ethers[11,12] and cryptands,[13] CPs possess deep π-rich cavities. Therefore, CPs are expected to drive the inclusion of positively charged species and the resulting complex stabilizes by multiple cation-π interactions. The ubiquitous role of cation-π interactions in several fields, such as chemistry, materials, biology and allied areas is well-recongnized.[14-16] There have been several experimental and theoretical studies on the complexation of calix[4]arenes with charged species in the literature,[17] but little is known with respect to CPs. In this study, we employed a combination of computational studies and electrospray ionization mass spectrometry (ESI-MS) experiments to evaluate the alkali metal ion binding capabilities of CPs. Such combined experiments have been routinely applied cation/anion binding studies in the gas phase, especially in the absence of solvent molecules and counter ions.

2. Experimental

2.1 Computational Methodology

Geometry optimizations were performed at the M05-2X/TZVP for $[CP+X]^+$complexes where X is Li^+, Na^+, K^+, Rb^+ and Cs^+. The basis set (def2-TZVP) for the Rb and Cs metal ions has been obtained from the EMSL web site.[18,19] To ascertain the nature of the stationary point frequency calculations were done and all of them have been identified as local minima on the potential energy surface (PES). Single point calculations were performed on the M05-2X/TZVP optimized geometries with B2PLYP functional and TZVP basis set.[18] B2PLYP double hybdrid functional has been employed for all $[CP+X]^+$complexes for the calculation of the binding energies (BEs) as it has been demonstrated to describe non-covalent interactions reliably.[20] The BEs of the complexes were obtained from difference of the energy of the complex and the sum of the energies of the CPs and metal ion. The calculated BEs have been checked for the impact of basis set superposition error (BSSE). To analyze the type of interaction between the metal ions and CP and respective fragments, AIM analysis[21] has been carried out on Li^+ and Na^+ complexes. The wavefunction has been created at M05-2X/def2-TZVP level of theory. The calculations were done using Gaussian 09 package.[22] Energy decomposition analysis (EDA) schemes is used to

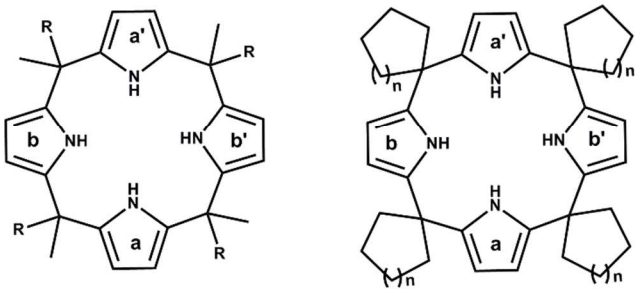
delineate the contribution of various energy components to the BEs. Localized molecular orbital EDA (LMOEDA)[23] scheme as implemented in the program GAMESS[24] at M05-2X/cc-pVDZ level was carried out.

2.2 Chemicals

The CPs (**1**-**5**; Fig. 1) were synthesised by the condensation of pyrrole with suitable ketone in the presence of acid as a catalyst by following known procedures.[25] The compounds were purified by column chromatography. Alkali metal chlorides were purchased from Sigma Aldrich (Steinheim, Germany), and used as received. Methanol (HPLC grade) was obtained from Merck (Mumbai, India). Stock solutions of CPs (10 mM) were made in dichloromethane, and those of metal chlorides (10 mM) were made in water (Millipore). The stock solutions were mixed in appropriate volumes and diluted with methanol to obtain a final concentration of 100 μM each. Solutions of same concentrations were used for mixed cations/CPs experiments.

2.3 Mass Spectrometry

All the experiments were performed using QSTAR XL (Applied Biosystems/MDS Sciex, Foster city, USA) equipped with an ESI source. The optimizing conditions for all the experiments were: capillary voltage 4.0 kV; declustering potential 70 V; mass resolution 10 000 (FWHM). Nitrogen was used as the curtain and collision gas. The data acquisition was under the control of Analyst QS software (Applied Biosystems). All the samples were introduced into the source by direct infusion at the rate of 15 μL/min using builtin syringe pump. For the CID experiments, the precursor ion was selected using the quadrupole analyzer and the product ions were analyzed using the TOF analyzer. The collision energies used were 5 to 55 eV. All the spectra reported were averages of 25 to 30 scans.



R=CH_3 1
R=C_2H_5 2

Fig. 1 Structures of the calix[4]pyrroles studied.

3. Results and discussions

A set of CPs (**1**-**5**, Fig. 1) and alkali metal ions (X^+=Li^+, Na^+, K^+, Rb^+ and Cs^+) were chosen for computational study to evaluate the binding strength of cations with CP, the effect of cation size, structure and geometry of CP. The DFT optimized geometries of the CP-alkali metal ion complexes, [**1**+X]$^+$, are shown in Fig. 2. Several attempts have been made to identify the possibility of alternative low energy conformations. In spite of our efforts to optimize the CP metal complexes in other 1,2 and cone conformations, optimizations always lead to stable 1,3-alternate conformation. It has been noted that the cavity of CP induces cation-π interaction between the cation and the face of electron rich pyrrole ring. The positioning of pyrrole (π) face and the nature of cations are found to be decisive factors in the variation of BE. The computed BEs, given in Fig. 2 at B2PLYP/TZVP//M05-2X/TZVP level showed that it decreases with the increase in the size of the metal cation, as expected in electrostatic sequence. Incorporation of BSSE correction has only a minor contribution to the energetics, and virtually do not alter the trends or quantitative differences. For comparison, plot of calculated BEs with and without BSSE correction is shown in Fig. S1.

Schematic view of [CP+X]$^+$complex and geometrical parameters used for the analysis is given in Fig. 3. Summary of the key structural changes upon cation binding for all the complexes is given in Table 1. A detailed analysis of these geometrical parameters reveals the energetic advantages of multiple cation-π interactions, especially in lithium complex. The Li^+ is disposed at the centre of CP cavity in the plane containing four methylene carbon atoms (0.00 Å) to optimally interact with all the four pyrrole rings simultaneously in [**1**+Li]$^+$ complex. The Na^+ and K^+ ions, with their increased size when compared to Li^+ ion, move upward (0.821, 1.526 Å respectively) to interact with only two pyrrole rings.[26] This can be substantiated from the data given in Table 1, where the distances, C-R_x reduces in ring b, while it increases in ring a. This is accompanied by a tilt of nitrogen .atoms away from CP cavity leading to a significant increase in centroid to nitrogen distances in one ring than the other. Similar effects can be observed on various dihedral angles summarised in the Table S1. We also performed energy decomposition analysis to delineate the contribution of various energy components to the BE. Energy decomposition analysis (EDA) using the LMOEDA scheme has been carried out to for [1+X]$^+$ complexes of Li^+ and Na^+ to analyse the contribution of various energy components to the BE. EDA as summarized in Table S2 reveals that the electrostatic and polarization effects act as the major driving force in these interactions. The strongest attractive interaction for both the complexes is found to be the electrostatic interaction (~40.0 kcal/mol), followed by the polarization, repulsion, dispersion and exchange interactions.

To visualize and incept the nature of multiple cation-π interactions, in the complexes of Li^+, Na^+ and K^+, *atoms-in-molecules* (*AIM*) topological analysis was carried out. AIM analysis demonstrates the existence of four bond critical points (BCP) with four pyrrole rings for all the three complexes and two cage critical points (CCP) in Na^+ complex (Fig. S2, Fig. S3 and Table S3). The variation in electron density values at BCP and CCP is in accordance with the respective BEs and also account for the differences in the nature of binding in the Li^+ complex from the complexes of Na^+ and K^+. The Rb^+ ions due to their larger ionic radii lie at the rim of the cavity and Cs^+ is almost outside the CP cavity. The distance of the cation from the central plane is 1.935 and 2.232 Å for the complex of Rb^+ and Cs^+,

respectively. The analysis reveal that CPs have relatively stronger cation binding strengths than calix[4]arenes[17] by about 12-18 kcal/mol are therefore promising cation receptors.

Mass spectrometry experiments were carried out to validate the computed trends in the binding order of the $[CP+X]^+$ complexes. ESI-MS and/or ESI-tandem mass spectrometry (ESI-MS/MS)

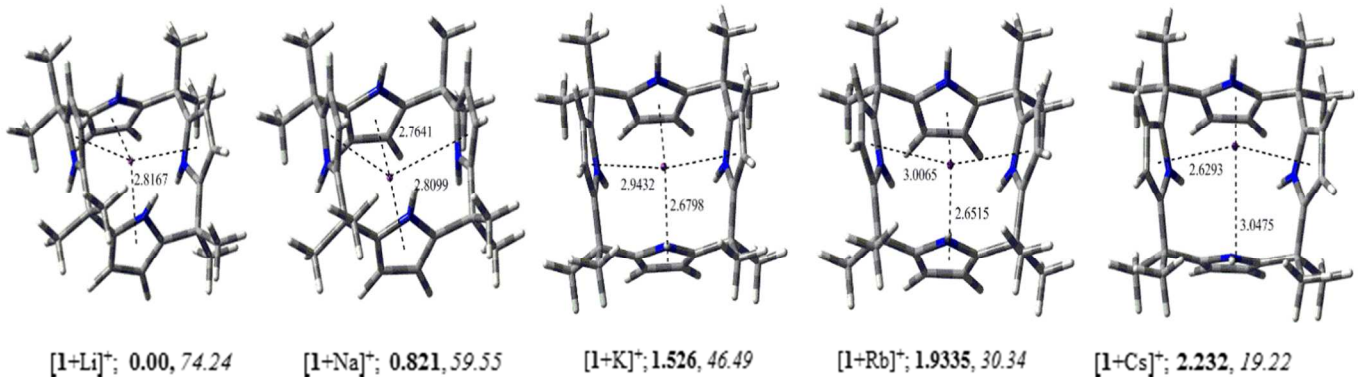


Fig. 2 Optimized geometries of $[\mathbf{1}+X]^+$ Complexes showing distances between metal cation and the centroid of pyrrole ring. Also given the distances between the cation and the plane containing the four methylene bridges (bold) in Å and the BEs (italics) of cation to CP in kcal/mol.

experiments have been routinely employed to study the cation/anion binding of different host molecules and their binding order with respect to the size of cation or the structure of substrate. At first, we have recorded the positive ion ESI mass spectra for equimolar mixtures (1:1) of the selected CPs and metal ions. The spectra readily exhibited $[CP+X]^+$ ion in addition to $[CP+H]^+$ ions. The higher aggregates, $[2CP+X]^+$ and $[CP+2X]^{2+}$ were absent even at higher concentrations (1:2 to 1:5 of CP:X), which reveals that the CPs form 1:1 stoichiometric complexes with alkali metal ions. When the ESI-MS of CP (**1**) recorded in the presence of mixed cations, the ion yields of $[CP+X]^+$ are found to increase with the size of the metal ion ($Li^+ < Na^+ < K^+ < Rb^+ < Cs^+$), the order of which is in contrast to that obtained from computational studies. Leize *et al.*[27] reported that the ESI-MS response of free alkali metal ions increases from Li^+ to Cs^+ and the ion yields inversely proportional to their solvation energies. Although the experimental solvation energies of CP-cation complexes are not available in the literature, in the present ESI-MS experiments we presume that the ion yields of $[CP+X]^+$ ions are reflecting the differences in solvation energies rather than the actual cation binding order of CP. Comparing the rate of fragmentation of the complex ions by the collision-induced dissociation (CID) experiments in mass spectrometry is another technique to verify the stability of the metal complexes. In such an experiment, a less stable complex ion expected to fragment at lower collision energy than a more stable complex ion. We have performed CID experiments on $[CP+X]^+$ at different collision energies (5 to 55 eV; laboratory-frame). The CID spectra of $[CP+Li]^+$ and $[CP+Na]^+$ yields characteristic product ions (fragment ions) generated by the fragmentation of CP with retention/elimination of the cation, whereas the $[CP+X]^+$ from K^+, Rb^+ and Cs^+ give rise exclusively to the corresponding X^+ as the product ion (the spectra of all $[\mathbf{1}+X]^+$ ions are shown in Fig. S4). The trend remains the same at any collision energies (CEs), except the variations in relative abundances of the precursor and product ion(s). These results imply that the Li^+ and Na^+ ions bind strongly to the CP, therefore are not separated from CP during the fragmentation. However loosely bound cations, K^+, Rb^+ and Cs^+ are easily detached as free cations leaving entire CP as a neutral entity. Unlike ESI-MS results, The MS/MS experimental results seemed to be in line with the binding order obtained in the computational studies. In order to estimate the stability order of $[CP+X]^+$ ions experimentally, we have calculated the relative intensity (%) of $[CP+X]^+$ from relative abundances of the precursor and product ion(s) from the CID spectra at a fixed collision energy (30 eV) using the formula, relative intensity (%)= $[CP+X]^+ / ([CP+X]^+ + \sum$product ions) X 100 (Fig. 4(a)).

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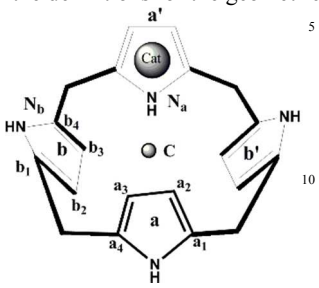
Table 1. Distance from centre of mass of **1** to various atoms present in the pyrrole ring (**C-X**) and to the centre of mass of the pyrrole ring (**C-R**). All distances are in Å

	C-X										C-R			
Complexes	C-$N_{a/a'}$	C-$N_{b/b'}$	C-C_{a1}	C-C_{a2}	C-C_{a3}	C-C_{a4}	C-C_{b1}	C-C_{b2}	C-C_{b3}	C-C_{b4}	C-R_a	C-$R_{a'}$	C-R_b	C-$R_{b'}$
1	2.406	2.406	2.928	3.619	3.618	2.928	2.928	3.619	3.618	2.928	2.906	2.906	2.906	2.906
1-Li^+	2.366	2.366	2.859	3.474	3.504	2.916	2.859	3.474	3.504	2.916	2.817	2.817	2.817	2.817
1-Na^+	2.563	2.526	2.877	3.330	3.331	2.880	2.920	3.370	3.375	2.929	2.810	2.810	2.764	2.764
1-K^+	2.457	2.643	2.972	3.463	3.463	2.972	2.859	3.124	3.124	2.859	2.943	2.943	2.680	2.680
1-Rb^+	2.411	2.637	3.001	3.761	3.761	3.001	2.840	3.083	3.083	2.840	3.006	3.006	2.651	2.651
1-Cs^+	2.373	2.650	3.019	3.841	3.841	3.019	2.827	3.040	3.040	2.827	3.048	3.048	2.630	2.630

[a]All the definitions for the geometrical parameters are given in Fig. 3.



[C] represents the centre of mass of the pyrrole rings in the CP.
[N] represents the nitrogen atoms in pyrrole rings in the CP.
[a,a'] represents the pair of pyrrole rings which are near to the centroid of the CP.
[b,b'] represents the pair of pyrrole rings which are far from the centroid of the CP
C_{an} represents the distance of the carbon atoms in the pyrrole ring from the centre of mass of CP

Fig. 3 Schematic view of the CP and geometrical parameters used for analysis

Higher the relative intensity value better is the stability of the selectead precursor. Dissociation (breakdown) curves help to correlate the stability of complexes (precursor ions), and the same is drawn using the relative intensity value as a function of CEs. The dissociation curves obtained for $[\mathbf{1}+X]^+$ ions demonstrate that the $[CP+Na]^+$ dissociate at higher CE value than $[CP+Li]^+$, and other complex ions (K^+, Rb^+ and Cs^+) follow next in the order. Based on the obtained relative intensity values from dissociation curves, the stability order of the complex ion $[CP+X]^+$ may be given as $Na^+ > Li^+ > K^+ > Rb^+ > Cs^+$. This order is almost similar to the binding order obtained from theoretical studies, except Li^+ and Na^+. The ESI-MS/MS experiments reveals that the $[CP+Na]^+$ ion is fragmenting at higher CE values than $[CP+Li]^+$ ions, which indirectly suggests that $[CP+Na]^+$ is more stable than $[CP+Li]^+$ ion. The question, then arises: how the $[CP+Na]^+$ attain more stability than $[CP+Li]^+$ in spite of its lower BE (obtained from theoretical studies)?

In the CID experiments, the abundances of the ions in the spectra may depend on the stability of the selected precursor ion as well as the product ions (fragment ions) formed. The anomalous ESI-MS/MS behaviour of $[CP+Na]^+$ ion when compared to the $[CP+Li]^+$ ion may be because of variations in the product ion stabilities. Thus, we have performed theoretical calculation studies on all the product ions formed from $[CP+X]^+$ ions. The geometries of all possible product ions of $[\mathbf{1}+X]^+$ were optimized and the BEs were computed for each product ion with the metal ion (Li^+ and Na^+ ions). The optimized geometries of the product ions are given in Fig. S5 and Fig. S6 and corresponding plot of BEs is given in Fig. 4 (b). As evident from the Fig. 4(b), the first two product ions at *m/z* 368 and 328 of $[\mathbf{1}+Li]^+$ complex are more stable than the parent ion (*m/z* 435) by about 0.5-1 kcal/mol. Whereas, the BEs of all the fragments of $[\mathbf{1}+Na]^+$ complex decreases exponentially. A closer scrutiny of geometries of these fragments indicate that in *m/z* 368 and 328, the Li^+ move towards centroid of pyrrole ring thereby enhancing its binding with interacting distance of 2.124 and 2.152 Å, respectively (shorter than 2.817 Å of parent, Fig. 4(c)). However such kind of energy differences are not found for the product ions of $[\mathbf{1}+Na]^+$. The electron density values at BCP and CCP for the product ions of Li^+ and Na^+ complexes from AIM analysis and respective BEs (Tables S3-S4) further corroborate the enhanced stability to *m/z* 368 and 328 of Li^+ complex. This explains the higher relative intensity (%) for $[CP+Na]^+$ ions than $[CP+Li]^+$ from CID experiments; during CID the $[CP+Na]^+$ complex remains in the complex form, w shereas $[CP+Li]^+$ complex prefers to undergo fragmentation to result in product ions that are more stable than the parent complex.

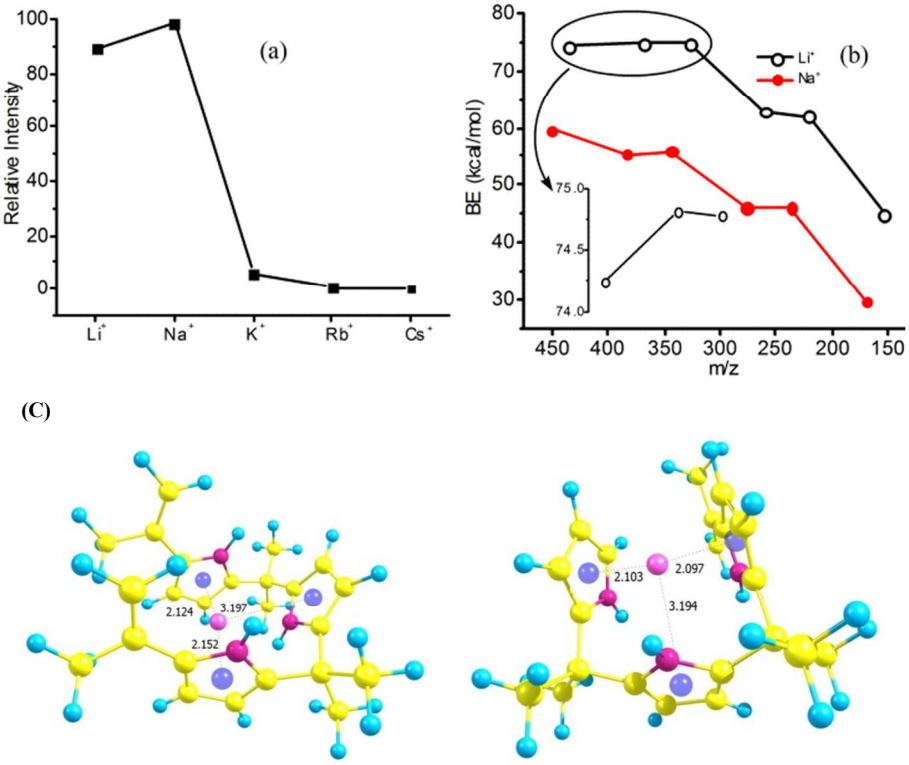


Fig. 4 (a)The relative intensity values obtained from the CID spectra of [**1**+X]$^+$ ions, where X=Li$^+$, Na$^+$, K$^+$, Rb$^+$, Cs$^+$. (b) Plot showing the variation in the BE for parent and various fragment complex ions for Li$^+$ and Na$^+$. (c) Optimized geometries showing cation to centroid of pyrrole distances of fragments complexed with Li$^+$ ion Calculated at M05-2X/TZVP level of theory.

The computational study explain the non-existence of the fragmented complexes of K$^+$, Rb$^+$ and Cs$^+$ metal ions as this may be traced to their small interaction energy. Thus, stabilities of both parent and product ions have to be carefully evaluated from theoretical calculations to interpret the stability of the complex from MS/MS experimental data.

In our earlier study,[28] the isomeric CPs (a set of C_7H_{13}-cycloalkyl CPs; normal vs N-confused CPs) demonstrated the selectivity in the extent of sodium adducts that reflected the structural effects of CP. It is also well known that the substituents at *meso*-position of CP affect the anion binding strength of CP.[29, 30] Similarly, to evaluate the substituent effects of CP on its cation binding, the CID spectra of [CP+X]$^+$ ions, where CP = **1**-**5**, X = Li$^+$ to Cs$^+$, were recorded at different collision energies (5 to 55 eV). The relative intensity (%) values of [CP+X]$^+$ were calculated at each CE value and dissociation curves were drawn.[31] The typical curves obtained for the studied metal ions were shown in Fig. S7. The plots also include $E_{com}^{50\%}$values (eV), which represent the centre-of-mass activation energy required for dissociation of the complex to its relative half-intensity. The stability order of [CP+X]$^+$ ion from these curves is found to be, **4 > 5 > 3 > 2 > 1**.This order reveal better cation binding ability of cycloalkyl substituted CPs than the dialkyl substituted CPs. Among the dialkyl substituted CPs, the binding efficiency increases with the size of alkyl chains. Computational results on the geometries of Li$^+$, Na$^+$ and K$^+$ ion complexes of ethyl (**2**) cyclopentanone (**3**), cyclohexanone (**4**) and cycloheptanone (**5**) also predicted a similar result, an increase in the ring size at *meso*-position found to stabilize the binding of CP to cation.

4. Conclusions

The gas phase binding affinity of CPs towards various alkali metal cations was investigated with computational calculations and substantiated by ESI-MS/MS experiments. The binding order of the CP with different metal cations (Li$^+$ > Na$^+$ > K$^+$ >Rb$^+$ > Cs$^+$) is evidenced by the theoretical BEs and experimental stability of [CP+X]$^+$ ions. The formation the [CP+X]$^+$ complexes were rationalized by multiple cation-π interactions involving the π electrons of pyrrole rings in 1,3-alternate conformation of CP. The size and structure of alkyl group(s) at *meso*-position of CP also influence the stabilization of [CP+X]$^+$ complex. The CPs are found to be better cation receptors than calix[4]arenes. The stability of precursor and product ions are crucial in evaluation of binding affinity of metal complexes by ESI-MS/MS.

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† Electronic Supplementary Information (ESI) available: [Experimental and computational details. Tables S1-S5 and Figures S1-S7. Cartesian coordinates of the complexes considered in the study at M05-2X/TZVP level of theory are given in Table S5.] See DOI: 10.1039/b000000x/

Notes and references

1 A. Baeyer, *Ber. Dtsch. Chem. Ges.*, 1886, **19**, 2184.
2 P. A. Gale, J. L. Sessler, V. Karl, V. Lynch, *J. Am. Chem. Soc.,* 1996, **118**, 5140.
3 P. A. Gale, J. L. Sessler, V. Karl, *Chem. Commun.,* 1998, 1.
4 R. Custelcean, L. H. Delmau, B. A. Moyer, J. L. Sessler, W. Cho, D. Gross, G. W. Bates, S. J. Brooks, M. E. Light, P. A. Gale, *Angew. Chem. Int. Ed.*, 2005, **44**, 2537.
5 C. C. Tong, R. Quesada, J. L. Sessler, P. A. Gale, *Chem. Commun.,* 2008, 6321.
6 J. L. Sessler, P. A. Gale, J. W. Genge, *Chem. Eur. J.,* 1998, **4**, 1905.
7 V. Karl, P. Anzenbacher Jr., K. Jursikova, V. Lynch, J. L. Sessler, V. Karl, P. Anzenbacher Jr., *Chem. Commun.,* 1998, 9.
8 Y. Furusho, T. Aida, *Chem. Commun.,* 1997, 2205.
9 W. E. Allen, P. A. Gale, C. T. Brown, V. M. Lynch, J. L. Sessler, *J. Am. Chem. Soc.,* 1996, **118**, 12471.
10 N. G. Giri, S. M. S. Chauhan, *Spectrochimica Acta Part A*., 2009, **74**, 297.
11 C. J. Pedersen, *J. Am. Chem. Soc.,* 1967, **89**, 2495.
12 C. J. Pedersen, *J. Am. Chem. Soc.,* 1967, **89**, 7017.
13 B. Dietrich, J. M. Lehn, J. P. Sauvage, *Tetrahedron Lett.,* 1969, **10**, 2889.
14 A. S. Mahadevi, G. N. Sastry, *Chem. Rev.,* 2013, **113**, 2100.
15 (a) D. Vijay, G. N. Sastry, *Phys. Chem. Chem. Phys.*, 2008, **10**, 582; (b) A. S. Reddy, G. M. Sastry, G. N. Sastry, *Proteins: Struct. Funct. Bioinform.,* 2007, **67**, 1179; (c) M. Chourasia, G. M. Sastry, G. N. Sastry, *Int. J. Biol. Macromol.*, 2011, **48**, 540; (d) D. Vijay, G. N. Sastry, *J. Phys. Chem., A* 2006, **110**, 10148.
16 (a) J. C. Ma, D. A. Doughetry, *Chem. Rev.,* 1997, **97**, 1303; (b) D. A. Dougherty, *Science*., 1996, **271**, 163; (c) J. Sunner, K. Nishiwaza, P. Kebarle, *J. Phy. Chem*., 1981, **85**, 1814.
17 A. T. Macias, J. E. Norton, J. D. Evanseck, *J. Am. Chem. Soc.,* 2003, **125**, 2351.
18 D. Feller, *J. Comp. Chem.,* 1996**, 17,** 157.
19 K. L. Schuhardt, B. T. Didier, T. Elesthagen, L. Sun, V. Gurumoorthi, J. Li, T. L. Windus, *J. Chem. Inf. Model.,* 2007, **47**, 1045.
20 a) S. Grimme., J. Chem. Phys., 2006, **124**, 034108. b) Y. Zhao, G. D. Truhlar, J. Chem. Theory Comput., 2006, **2**, 1009.
21 R. F. W. Bader, *Atoms in molecules, A quantum Theory,* Oxford University Press, Oxford, 1990.
22 Gaussan 09, Revision B.0.1, Gaussian, Inc, Wallingford CT 2010.
23 P. Su, H. J. Li, *J. Chem. Phys.,* 2009, **131**, 1.
24 M. W. Schmidt, K. K. Baldridge, J. A. Boatz, S. T. Elbert, M. S. Gordan, J. H. Jensen, S. Koseki, N. Matsunaga, K. A. Nguyen, S. J. Su, T. L. Windus, M. Dupuis, J. A. Montgomery, *J. Comput. Chem.,* 1993, **14**, 1347.
25 S. Dey, K. Pal, S. Sarkar, *Tetrahedron Lett.,* 2006, **47**, 5851.
26 C. Ruan, Z. Yang, M. T. Rodgers, *Int. J. Mass. Spectrom.,* 2007, **267**, 233.
27 E. Leize, A. Jaffrezic, A. V. Dorsselaer, *J. Mass. Spectrom.,* 1996, **31**, 537.
28 G. Bhaskar, S. Prabhakar, G. S. Ramanjaneyulu, M. Vairamani, V. N. V. Srinivas, K. Srininvas, *J. Mass. Spectrom.,* 2007, **42**, 1194.
29 Jr. P. Anzenbacher, K. Jursikova, J. L. Sessler, *J. Am. Chem. Soc.,* 2000, **122**, 9350.
30 J. L. Sessler, A. Andrievsky, P. A. Gale, V. Lynch, *Angew. Chem. Int. Ed. Engl.,* 1996, **35**, 2782.
31 M. Torvinen, E. Kalenius, F. Sansone, A. Casnati, J. Janis, *J. Mass. Spectrom.,* 2011, **46**, 787.