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Enhanced Cation Recognition by a Macrocycle Ionophore at the air-solution interface probed by mass spectrometry

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Interfacial environments have the potential to drive unexpected events of supramolecular recognition, leading to advances in the development of novel functional materials and molecular sensing techniques. We present experimental evidence for a noticeable enhancement of the cation binding specificity of a prototype calixarene macrocycle (Cesium Ionophore II) at the air-solution interface, in comparison to bulk solution and to isolated solvent-less conditions. A rationalization of this intriguing finding is outlined, with the support of quantum calculations, in terms of the 'half-solvation' conditions provided by the interface and of conformational effects posed by the backbone structure and the side chains of the macrocycle ionophore. The investigation involves the introduction of a mass spectrometry method to determine the relative abundances of interfacial complexes that should be of general application in the field and guide future advances in analytical techniques based on molecular recognition.

1 Introduction

Supramolecular recognition at interfaces lies at the heart of a broad range of molecular sensing, separation and catalysis technologies. [1–6] The rationalization of the underlying mechanisms is nevertheless quite challenging due to the heterogeneous solvation scenario within which the interactions occur. The present study focuses on cation recognition by a benchmark calixarene macrocycle at the air-solution interface.

Calixarenes have played a central role among the different families of molecular cavitands presenting host-guest chemistry, in the development of Supramolecular Chemistry in the past decades. Calixarenes are annular oligomers of methylene-bridged phenolic rings, whose *à la carte* functionalization can provide architectures with specific physicochemical and binding properties of technological potential. [7–16] For this study, we have considered the benchmark macrocyle 4-*tert*-butylcalix[6]arene-hexaacetic acid hexaethyl ester (or Cesium Ionophore II, henceforth CI), represented in Fig.1. The *tert*-butyl groups and the ester chains pending in opposite sides of the cavity confer this calixarene both ionophoric properties and the amphiphilic character required to self-assemble in ordered films at the air-water interface. [17–24]

Despite the noticeable efforts devoted to the investigation of macrocycles at air-solution interfaces, the elucidation of binding selectivities still demands approaches directly probing and quantifying the relative abundance of the non-covalent complexes formed at the interface. Previous studies of calixarenes at the air-water interface have typically inferred supramolecular properties from thermodynamical analysis of compression/expansion isotherms, UV and IR spectroscopic techniques, x-ray diffraction or NMR spectroscopy. [24–34] We introduce here a methodology that relies on the determination of the molecular species present at the interface by means of matrix-assisted laser desorption mass spectrometry (MALDI-MS). Firstly, competitive binding of cations from the aqueous subphase to macrocycles prepared in Langmuir monolayers is allowed. Subsequently, the interfacial complexes are transferred as Langmuir-Blodgett (LB) films for MALDI-MS analysis. It will be shown that the method, henceforth alluded to as LB-MALDI-MS, provides a route for the direct identification of supramolecular complexes formed at air-solution interfaces and the quantification of relative binding affinities.

In this study, the application of the LB-MALDI-MS method to films of the CI calixarene has served to expose a marked enhancement on Cs^+ selectivity when competitive binding of alkali cations takes place at the air-water interface, in comparison to binding in bulk solution. This result constitutes a valuable benchmark example for how the partial solvation conditions of the interface may promote supramolecular recognition.

2 Methodology

2.1 Materials

The macrocycle calixarene employed in this study, 4-*tert*-butylcalix[6]arene-hexaacetic acid hexaethyl ester (97% pu-

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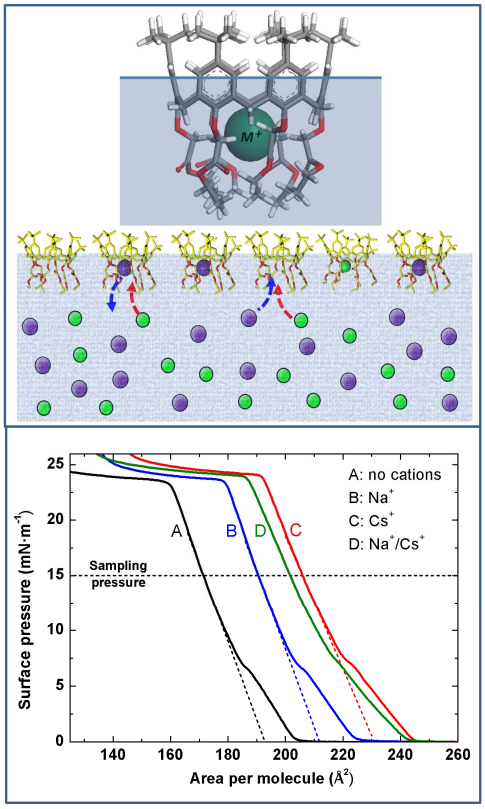

Fig. 1 Top: Sketch of an alkali cation complex of the CI calixarene at the air-solution interface and illustration of the competitive binding with the cations of the subphase. The balance between the hydration of the cation and its coordination with the bulky ester side chains of the calixarene, leads to the observed Cs^+ ionophoric behavior (see text for details). Bottom: Compression isotherms measured for monolayers of CI calixarenes at the air-water interface (A) and at air-solution interfaces with either Na^+ (B), Cs^+ (C), or an equimolar concentration of both cations (D) in the subphase. The interfacial monolayers were transferred to solid plates at $15\,mN{\cdot}m^{-1}$ for mass spectrometry analysis.

rity), the alkali cation precursors (chloride salts of 99% purity) and the MALDI matrix (α-cyano-4-hydroxycinnamic acid, ultrapure, <1 ppm metal cation traces, henceforth α-CHCA) were purchased from Sigma-Aldrich and used as received. The experiments were performed with freshly prepared solutions in ultrapure water of mili-Q quality ($>18M\Omega{\cdot}cm$) or chlorophorm (HPLC quality).

2.2 Langmuir monolayers

Monolayers the CI calixarene were prepared at the air-water interface on a NIMA 302LL Langmuir trough of dimensions 30 cm$\times$ 10 cm, made of PTFE, and equipped with two movable barriers. The calixarene was spread on the water surface from a 0.1 mM chloroform solution with a microsyringe. For characterization purposes, initial experiments were performed with aqueous subphase of either miliQ water or of a single alkali chloride solution at a 40 mM concentration. For the competitive binding experiments, pairs of alkali chlorides, each salt at 40 mM concentration, were employed for the subphase. Test measurements with alkali bromides led to indistinguishable results for the isotherms and recorded mass spectra. The system was allowed to equilibrate for at least 30 min to ensure complete evaporation of the chloroform solvent and formation of the interfacial complexes. No appreciable changes were observed in the recorded isotherms when higher cation precursor concentrations (up to 100 mM) or longer equilibration times (up to 200 min) were employed before starting the compression cycles. The isothermal compression of the Langmuir monolayers was performed up to pressures around 30 mN/m at a barrier speed of 20 mm/min, and the surface pressure was measured assuming a zero contact angle with a 10 mm wide Wilhelmy balance made of Whatman Chr1 chromatography paper. The temperature was kept at 294$\pm$0.5 K with a thermostat enclosure.

2.3 LB-MALDI-MS Method

Each one of the calixarene monolayers investigated was deposited on a conductive glass plate (an ITO coated slide of $75\times25\times0.9$ mm^3 size) for mass spectrometry analysis of the complexes formed with the alkali cations of the subphase. For this purpose, a freshly prepared Langmuir film was allowed to equilibrate with the solution subphase and was subsequently compressed to a surface pressure of 15 mN/m. The glass plate (already immersed into the solution before spreading the calixarene) collected the film in rising/diping cycles at a 10 mm/min rate. A total of 16 collecting cycles were performed in each case, with typical transfer ratios of 0.6 per half-cycle.

The relative abundance of the calixarene-alkali complexes in the film was determined by matrix-assisted laser desorption mass spectrometry (MALDI-MS) in an UltrafleXtreme equipment (Bruker-Daltonics) equipped with a 355 nm laser, and a time-of-flight spectrometer that was operated in positive ion reflectron mode. Ion signal was accumulated for $\sim$2000 laser shots at a repetition rate of 500 shots/second. The mass resolution achieved in the spectra was of set to M/ΔM$\sim$10000, and mass calibration was performed with polydispersed mixtures of polyethylene glycol polymer standards (Sigma-Aldrich), with average molecular weights 500-2000.

The MALDI matrix α-CHCA to assist the laser desorption process was applied on top of the LB film as a fine solid powder. Such solvent-less method avoids any potential rearrangement of the film that may be induced by the application of solvents[23]. This procedure led to intense signals for the calixarene-alkali complexes in the mass spectra, as can be appreciated in Fig 2, which shows six of the mass spectra recorded for different pairs of alkali cations in the subphase. This is remarkable considering the reduced amount of material that is analyzed (only a few monolayers of the calixarene complexes are transferred to the sample plate). Each spectrum probes the relative abundance of the complexes of the interfacial CI calixarene with the corresponding pair of cations, yielding the relative affinities listed in Table 1. The standard deviation in the relative intensities is smaller than 15%, leading to a sufficiently small statistical error in the average determinations after 3-5 repetitions. In contrast, it must be remarked that every attempt to apply the conventional dried-droplet method, in which the matrix is deposited on the sample as aqueous or methanol a solution, resulted in markedly inhomogeneous signal distributions throughout the sample plate and in a low degree of reproducibility in the average signals recorded.

One practical challenge of the LB-MALDI-MS method is related to the presence of 'empty' (*i.e.* non-complexed) calixarenes in the film, even after long waiting times for equilibration. It was observed that those calixarenes tend to bind the Na^+ and K^+ impurities present in the α-CHCA matrix. It must be noted that eventhough a desalted matrix was employed (< 1 ppm of Na^+/K^+), the concentration of those cations outnumbers that of the calixarenes in the sample. Our way to surpass this difficulty was the incorporation to the sample of a 'cationic sink' to account for all the calixarenes that remain uncomplexed in the film. For this goal, either LiCl or NaCl was mixed and ground with the α-CHCA matrix. Due to the large affinity of the CI calixarene for the small cations in the gas phase (see Fig. 3), the signal arising from gas-phase complexation of the initially empty interfacial macrocycles was confined to the mass of the complex with the added cation, either Li^+ or Na^+, depending on the pair of cations investigated. Note that this approach has the cost of ruling out the direct measurement of the Li^+/Na^+ interfacial affinity, which was determined through the comparison with the larger cations (K^+ and Rb^+, see Fig. 2).

2.4 ESI measurements

In order to explore the binding behaviour in the bulk of an aqueous solution, electrospray ionization (ESI) was performed in an ion trap spectrometer (HCT, Bruker-Daltonics), for a solution with 10 mM concentrations for each of the alkali cations and saturated on the calixarene. The relative abundances of the complexes formed in solution are neatly monitored in the recorded mass spectrum, without any relevant contribution from complexation occurring in the gas-phase during the electrospray process.

2.5 Quantum calculations

Simulated annealing with the universal force field was applied, as implemented in the Materials Studio package [41], as a first step to generate an ensemble of low energy conformations for the CI-M^+ complexes with the five alkali cations (M= Li^+–Cs^+). Density functional (DFT) quantum calculations at the B3LYP/6-31G* level, were employed to optimize those conformations. Isolated solvent-less complexes and complexes microhydrated by three, four and six water molecules around the bound cation were investigated. For the Rb^+ and Cs^+ cations, the core electrons were substituted by the common Stuttgart/Dresden effective core potentials. The calculations were run with the Gaussian09 code[41].

3 Results and Discussion

The first stage of the procedure involves the preparation and characterization of a calixarene monolayer at the air-water interface. Fig 1 depicts surface pressure-area compression isotherms recorded for monolayers of the CI calixarene with different subphases. Results for a miliQ water subphase and for solutions of alkali cations are presented. The cases of Na^+, Cs^+ solutions and of an equimolar Na^+/Cs^+ solution are shown for illustration. The isotherms recorded in this study are consistent with those reported from earlier experiments and with space-filling models for the compressed monolayer with a "cone" configuration of the calixarenes, where the hydrophilic rim (ester side chains) is immersed in the aqueous phase, as sketched in Fig. 1. [19,21,24] Upon compression, the surface pressure in the monolayer eventually rises steeply with decreasing surface area. A smooth liquid expanded-liquid condensed phase transition is observed in the form of a shoulder in each of the isotherms at ca. 7.0 mN/m[21]. The liquid condensed phase constituted the working regime for the present analysis in the mass spectrometer. In particular, the interfacial monolayers were transferred to solid substrates for the mass spectrometry analysis at 15 mN/m pressure. It can be noted that at pressures above 23 mN/m the film area decreases abruptly due to orientational rearrangements of the calixarenes, which are discussed in ref. [21] and are not of interest to this work.

Noticeably, the limiting area per molecule grows steadily from the monolayer of the bare uncomplexed calixarene, 193 ± 11 Å^2, to the monolayers of the calixarene complexed with alkali cations of increasing size, *e.g.* 212 ± 10 Å^2 for Na^+

and 231±12 Å^2 for Cs^+, as obtained from the linear extrapolation of the isotherms in the liquid condensed regime (dashed straight lines in Fig. 1). In principle, such differences in the limiting area displayed by each of the alkali cation complexes in the film may be used as a probe for the binding selectivity of the calixarene. Indeed, Fig. 1 shows that when equimolar concentrations of Na^+ and Cs^+ are present in the subphase, the isotherm and the corresponding average limiting area per molecule obtained in the experiment lie consistently in between those measured for the solutions of each of the cations alone. The greater proximity of the isotherm of the Na^+/Cs^+ mixture to that of the Cs^+ solution can be taken as a measure for the preference of the macrocycle for the binding of this latter cation. The quantitative accuracy of this approach is however limited by differences in the compressibility of monolayers prepared under identical conditions due to unavoidable domains of defects in the ordering of the calixarene molecules.[38,39] In our experiments, despite the careful deposition and slow compression rate, the absolute position of the isotherms was affected by a statistical error after up to ten repetitions of not less than ±10 Å^2, which is of the order of the changes in area associated with the different complexes.

In can be concluded that the analysis of isotherms provides a valuable approach to expose binding selectivities of the macrocycle films at the air-solution interface, and constitutes the first step towards alternative methods capable of probing more directly and with greater quantitative accuracy the relative abundances of the complexes formed at the interface. In this study, we introduce the LB-MALDI-MS method to analyze the composition of the interfacial films. Fig. 2 depicts an illustrative set of mass spectra recorded for systems in which pairs of alkali cations were present at equimolar concentration in the solution subphase. Neat signals are observed for the two possible CI-M^+ complexes in each case, with integrated intensities that reflect the corresponding relative abundances in the film. The experiments were performed for the following cation pairs: Li^+/K^+, Li^+/Rb^+, Na^+/K^+, Na^+/Rb^+, K^+/Rb^+, K^+/Cs^+ and Rb^+/Cs^+. For these combinations, the integrated intensity ratios measured for the corresponding complexes in the mass spectra are 0.11±0.01, 0.11±0.01, 0.36±0.02, 0.35±0.02, 1.05±0.04, 0.18±0.01 and 0.17±0.01, respectively. It can be appreciated that the choice of cation pairs is to some extent redundant, which served to test the consistency of the method with positive results. The general trend is observed that the heavier of the two cations brought into competitive binding in each experiment, interacts more favourably with the interfacial calixarene, with the only exception of the similar intensities found for the K^+ and Rb^+ complexes. The joint analysis of the mass spectra leads to the relative affinities of the calixarene for the alkali cations Li:Na:K:Rb:Cs with values 0.02:0.06:0.17:0.16:1 (see Table 1). Clearly, the interfacial calixarenes bind preferentially the Cs^+ cations.

Table 1 Relative alkali cation binding affinities of the CI calixarene, as determined from the measurement of the abundance of CI-M^+ complexes formed at the air-water interface (LB-MALDI-MS method), in bulk aqueous solution (ESI-MS method) and in the gas phase (solvent-free MALDI-MS method[23])

environment	Li^+	Na^+	K^+	Rb^+	Cs^+
air-water interface	0.02	0.06	0.17	0.16	1
water solution	0.04	0.24	0.41	0.49	1
solvent-less	51	7	2.6	2.0	1

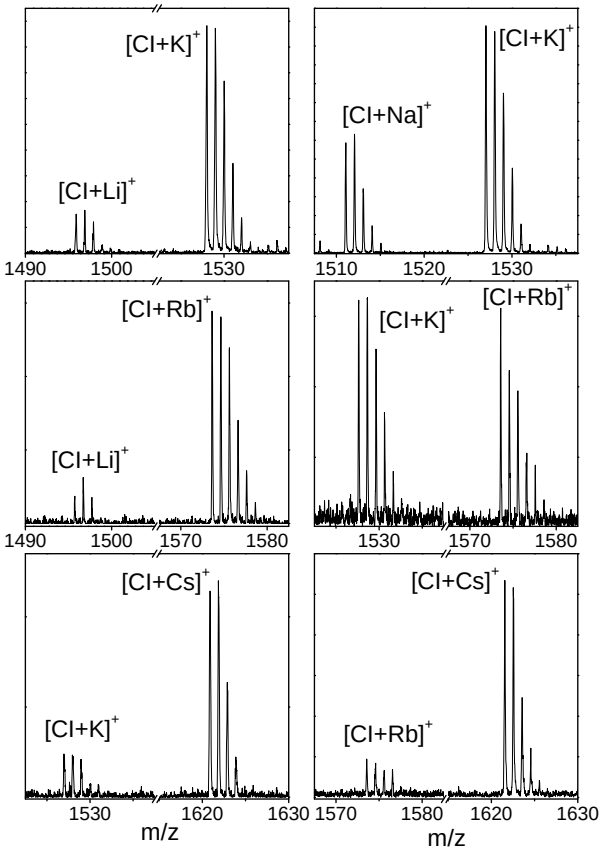

Fig. 2 Mass spectra recorded with the LB-MALDI-MS method for alkali cation complexes of the CI calixarene formed at the air-solution interface. In each experiment, a pair of cations are present in the aqueous subphase and bind competitively with the calixarenes. The integrated intensities of the peaks in each mass spectrum provide the relative abundances of the corresponding complexes at the interface.

In order to rationalize these results, it is timely to contrast the relative cation affinities of the calixarene at the air-solution interface, with the corresponding behavior observed in the two

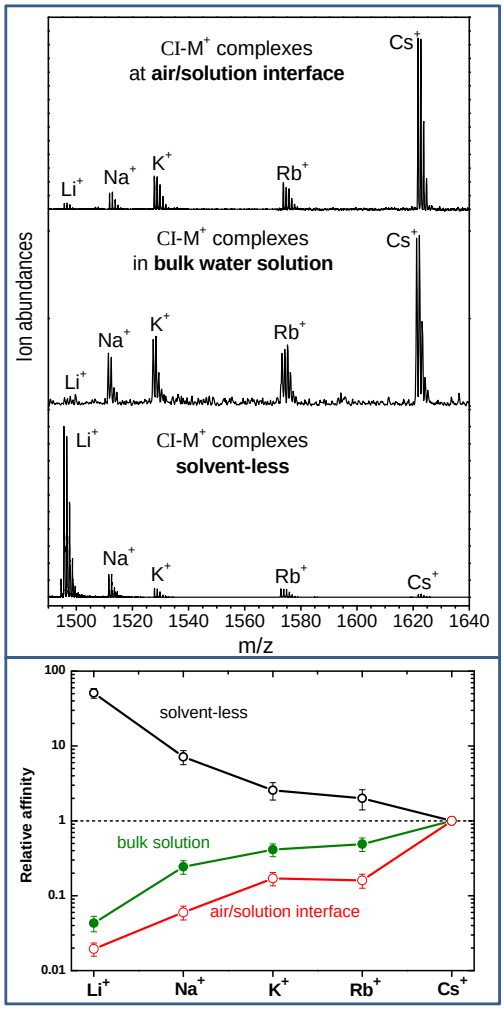

Fig. 3 Mass spectra of the alkali cation complexes of the CI calixarene formed at the air-solution interface, in bulk solution and under solvent-less conditions in the gas phase. The integrated intensities of the peaks in each mass spectrum reflect the relative abundances of the corresponding complexes in each environment, which are represented in the bottom panel. While the bulk solution spectrum is a raw ESI measurement, the representations for the interfacial and solvent-less spectra are built from a scaled composition of the mass spectra registered for pairs of cations in this study (Fig. 2) and in a previous study [23], respectively.

limiting cases of full solvation (bulk solution) and of a solvent-less environment (gas phase). For this purpose, in the present study the relative abundances of the calixarene complexes formed in the bulk of an aqueous solution of the five alkali cations have been determined by Electrospray Ionization (ESI-MS). The procedure is essentially the same followed successfully in numerous previous determinations of binding selectivities in metal-ligand systems.[36] The corresponding affinities in the absence of solvent were determined in a previous work [23] by laser desorption mass spectrometry, and are included here for comparison.

Fig. 3 and Table 1 compare the composite mass spectra and the corresponding relative CI-M^+ affinities obtained in the three environments (interface, solution, gas phase). Noticeably, the interfacial calixarenes display the most marked Cs^+ selectivity, in particular in comparison to bulk solution. For instance, the Cs^+/Na^+ affinity ratio is as large as $\sim$16 at the interface, in comparison to the value of $\sim$4 obtained in solution. The elucidation of the origin of such an enhancement of the Cs^+ selectivity at the interface is not straightforward, as it involves a complex combination of conformational features along with cation-macrocycle and solvation interactions, all of them taking place in a heterogeneous environment. In the following, we attempt to provide an intuitive framework to describe this scenario with the aid of quantum computations.

As starting point, it can be noticed that the solvent-less gas-phase affinities of the CI calixarene follow a decreasing trend with cation size, becoming about 50 times smaller accross the alkali series from Li^+ to Cs^+. This is a remarkable feature, since it means that the intrinsic macrocycle-alkali interactions actually favor the binding of the smaller guest cations, in particular Li^+. Such pronounced preference of the calixarene host for Li^+ in the absence of solvent can be traced back to the greater electronic density of this cation in relation to the larger ones, leading to a tighter coordination with the oxygen atoms of the ether and ester groups of the flexible hydrophilic side chains of the calixarene. [23,35]

Solvation changes dramatically this scenario and leads to a qualitatively reversed trend, with the CI calixarene being prone to binding the larger cations and acting as a particularly efficient Cs^+ ionophore. Such behavior can be attributed in general terms to two main factors with sinergic effects. On

Table 2 Oxygen-cation distances (in Å) in the lowest energy conformations predicted by the B3LYP/6-31G* computation for the CI complexes with Na^+ and Cs^+, under isolated solvent-less conditions and under microsolvation by six water molecules (see Fig. 4). Distances are given between the cation and the oxygen atoms from the carbonyl (bold) and ether (normal) groups of the macrocycle and from water (with asterisk).

complex	O-M^+ distances
CI-Na^+ solvent-less	**2.2**, **2.3**, **2.4**, 2.5
CI-Na^+ microhydrated	**2.4**, **2.4**, 2.5, 2.3*, 2.4*, 2.9*
CI-Cs^+ solvent-less	**3.0**, **3.1**, **3.2**, 3.1, 3.6, 3.6
CI-Cs^+ microhydrated	**3.1**, **3.3**, 3.1, 3.2, 3.1*, 3.2*, 3.2*

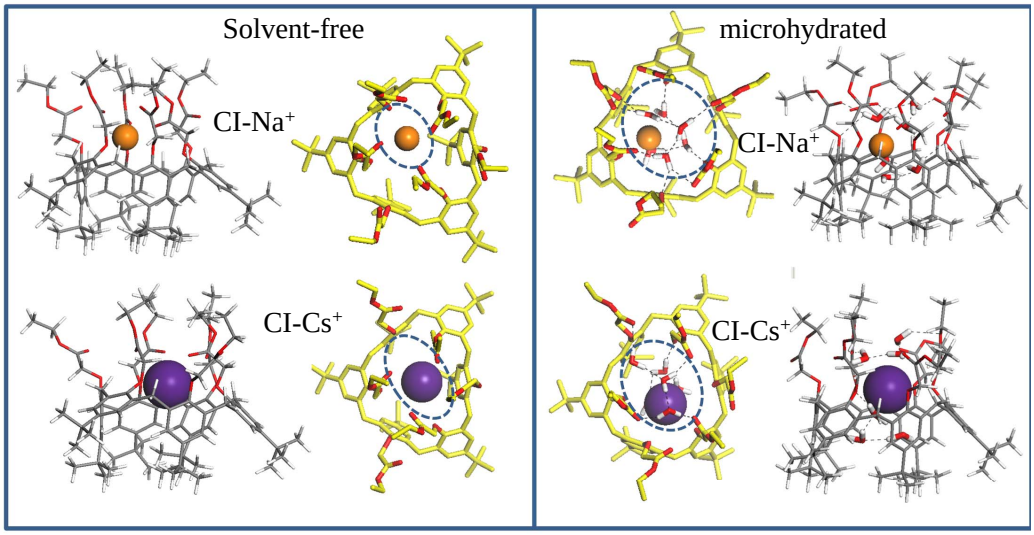

Fig. 4 Lowest energy conformations predicted by the B3LYP/6-31G* calculations for the complexes of the CI calixarene with the Na^+ and Cs^+ cations under solvent-less and microhydrated (six water molecules) conditions. Note the comparably moderate distortion of the macrocycle conformation in the Cs^+ complex upon hydration (unlike the Na^+ complex), which partly explains the enhanced Cs^+ ionophoric activity of the calixarene at the air-solution interface (see text for details).

the one hand, the free energy of hydration of the alkali cations increases with decreasing cation size[37] and, hence, opposes the inclusion of the smaller cations into the macrocycle cavity. This aspect is common to the experiments at the air-water interface and in aqueous solution, since in both cases the uncomplexed cations are solvated in the bulk of the solution. On the other hand, the optimum coordination of the small cations in the absence of solvent involves a significant folding of the calixarene backbone and of its polar side chains, which act as molecular tweezers that trap the cation. The incorporation of water molecules inside the cavity for partial solvation of the cation takes place at the cost of stretching the macrocycle structure, leading to a greater degree of disruption of the intrinsic coordination of the smaller cations with the macrocycle. This is where significant differences between interfacial and bulk solution complexation may arise, as discussed below in more detail.

In order to elucidate the conformational constraints underlying the marked Cs^+ ionophoric behaviour of the CI calixarene, we have performed B3LYP/6-31G* density functional quantum calculations of the complexes, under conditions of isolation (no solvent) and of microsolvation of the bound alkali cation. The microsolvated complexes are modelled with up to six water molecules inside the macrocycle cavity, which seemed adequate to extract sensible information, taking into consideration that the first hydration shell of the alkali cations uncomplexed in solution includes in average between six and eight water molecules[37]. The qualitative considerations that follow assume that the solvation of the external part of the macrocyle remains essentially the same, irrespectively of the alkali cation incorporated to the complex.

Fig. 4 illustrates the result of the quantum calculations by depicting the conformations of lowest energy predicted for the CI complexes with Na^+ and Cs^+, both without solvent and with six water molecules solvating the cation. Similar qualitative results were obtained with three and four water molecules. The oxygen-cation distances describing the coordination arrangements are given in Table 2. In the solvent-less complexes, the cations coordinate with oxygen atoms from the ether and carbonyl ester groups of the side chains, at distances within 2.2–2.5 Å and 3.0–3.6 Å for Na^+ and Cs^+, respectively. It can be noted that the Na^+ cation coordinates tightly with four oxygen atoms in a compact conformation of the complex. In comparison, the Cs^+ cation achieves a looser coordination with six oxygen atoms, in a more stretched arrangement of the calixarene.

Upon hydration, three water molecules are incorporated to the first coordination shell of the cation, thereby altering its interaction with the macrocycle. The coordination of the Na^+ cation with the calixarene is reduced from four to three oxygen atom sites at increased distances to incorporate the water molecules. In contrast, the Cs^+ cation maintains a roughly

unchanged coordination with four oxygen atoms of the macrocycle in the hydrated complex. Importantly, the inclusion of the water molecules into the cavity stretches the conformation of the macrocycle and leads to a more open configuration of the side chains. This latter effect is particularly noticeable in the Na^+ complex, which undergoes significant conformational changes in order to allow the solvation of the cation. In Fig. 4, the opening of the calixarene cavity resulting from the stretching of the side chains upon solvation is highlighted to visually show the greater perturbation of the host-guest interactions upon solvation in the Na^+ complex in comparison to its Cs^+ counterpart. The net result of this qualitative trend is a stabilization of the Cs^+ calixarene complex, which renders a more facile interaction of the solvent molecules with the bound cation with comparably minor structural changes.

The key question of the enhancement of the Cs^+ selectivity at the air-solution interface can then be traced back to the fact that the complexes of the calixarenes at the interface are more markedly affected by the above mentioned constraints than those formed in bulk solution. At the interface, complexation takes place under conditions of 'half'-solvation, with the hydrophobic face of the macrocycle partly sticking out of the aqueous subphase. Hence, the transport of water molecules in and out of the macrocycle cavity occurs mainly through the hydrophilic side, and solvation of the bound cation relies directly on the conformation of the long ester side chains. In contrast, in bulk solution, the solvent has as well access to the cation through the hydrophobic face, which involves a significantly less hindrance from the comparably short and stretched *tert*-butyl groups and a lesser dependence on the size of the bound cation.

4 Conclusions

The potential of the air-water interfacial environment to enhance supramolecular recognition has been demonstrated for a benchmark calixarene ionophore, by means of a novel mass spectrometry method. Modelling of the macrocycle-cation complexes with quantum mechanic calculations has shed light into the conformational features involved in the binding and partial hydration of the cations at the interface. For the CI calixarene presently investigated, steric effects associated with the bulky hydrophilic side chains are found to constraint the partial hydration of the cation bound in the complex. In consequence, the binding of Cs^+ is favoured as it leads to a comparably stretched arrangement of the calixarene rendering a more facile incorporation of water molecules than the complexes with the smaller alkali cations.

It can be noted that a similar scenario, in which the more open hydrophobic face of the calixarene is effectively blocked to water and only the hydrophilic phase is exposed to the species of the solution, would also emerge in a monolayer of calixarenes fixed on a solid substrate through covalent linkages (in place of the side *tert*-butyl groups). Consequently, an enhancement of the Cs^+ binding selectivity can be expected as well at solid surface/solution interfaces. This is an important realization since it implies that LB-MALDI-MS experiments on air-solution interfacial monolayers can potentially provide a rapid means of screening molecular materials for specific binding of cationic species in solution, prior to more involved procedures in which the host macrocycles are irreversibly incorporated to solid substrates. The extension of the present study with metal cations, to molecular cationic guest species deserves an in-depth research program which is currently underway in our group.

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