Exclusive Ion Recognition Using Host-Guest Sandwich Complexes[†]

Nitesh Kumar*
Department of Chemistry, Washington State University, Pullman, WA, 99163
**E-mail: nitesh.kumar@wsu.edu, kmnitesh05@gmail.com*

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Ion recognition in porous aqueous media utilizing polyethers, involves the formation of 1:1 and higher-order host-guest complexes. The effectiveness of these interactions relies on the optimal size of the host cavity to encapsulate the guest ions. While liquid/liquid extraction based on host-guest interactions offers higher specificity in metal ion extraction, it results in the co-extraction of unwanted coordinating solvents and counter-anions. Therefore, an improved protocol is required by which the ion can be selectively trapped within the host cavity and simultaneously decrease the guest coordination with the outside environment. This study delves into the microscopic mechanisms underpinning the exclusive ion recognition through the formation of 2:1 host-guest sandwich complexes, which reduce metal coordination with solvent or counter-ions, ensuring selectivity. Our analysis shows that ions with a radius larger than the host cavity, such as cesium (Cs$^+$), form stable host-guest sandwich complexes at elevated host concentrations. In this study, we performed molecular dynamics simulations to investigate the microscopic details of Cs$^+$ interactions with open-chain and preorganized polyethers, namely podand, crown, and cryptand in electrolyte media. Our findings reveal that the formation of stable Cs$^+$-Crown sandwich complexes significantly reduces Cs$^+$ coordination with H_2O and NO_3^-. This loss of solute coordination leads to exclusivity in bound metal ions, offering a potential strategy for efficient solvent extraction.

Keywords: Ion Recognition, Sandwich Complex, Free Energy, Molecular Dynamics Simulations, and Cesium Separation.

I. INTRODUCTION

The extraction of undesired solutes, such as water or background electrolytes, presents a major challenge in host-guest complexation-based separation methods.[1] This results in increased processing costs and reduced efficiency. Numerous supramolecular strategies based on host-guest complexation have been developed to address these limitations, which utilize cyclic polymeric hosts with size-specific cavities to selectively bind desired ions based on their fit within the cavity.[2–5] These novel hosts exhibit exclusivity, reducing coordination with unwanted counterions and solvents.[6] Herein, using classical molecular dynamics simulations, subensemble graph theoretical analysis, and enhanced sampling methodologies, we provide microscopic details and demonstrate that the ions too large to fit into the host cavity can form sandwich complexes at elevated host concentrations, promoting selective separation of specific ions from a mixture.

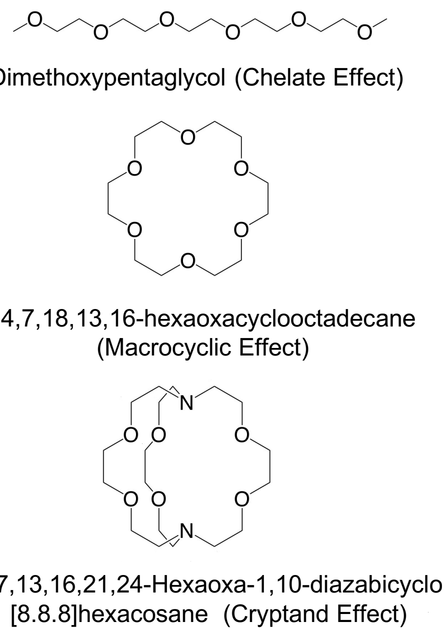

FIG. 1: Structures of the host molecules (pentaglyme, 18-crown-6, [2.2.2]-Cryptand) used in this study. The ligands are arranged with an increasing extent of molecular organization.

The field of supramolecular chemistry observed a significant advancement following the awarding of the Nobel Prize to Cram, Lehn, and Pedersen in 1987 for their pioneering work in the development of supramolecular structures capable of selective ion binding. This recognition led to further research and diversification of applications for these supramolecular systems, which have since been employed in a myriad of applications, ranging from separation sciences to the synthesis of molecular machines.[1, 7, 8] Recent trends in the field have shown a growing interest in leveraging supramolecular-

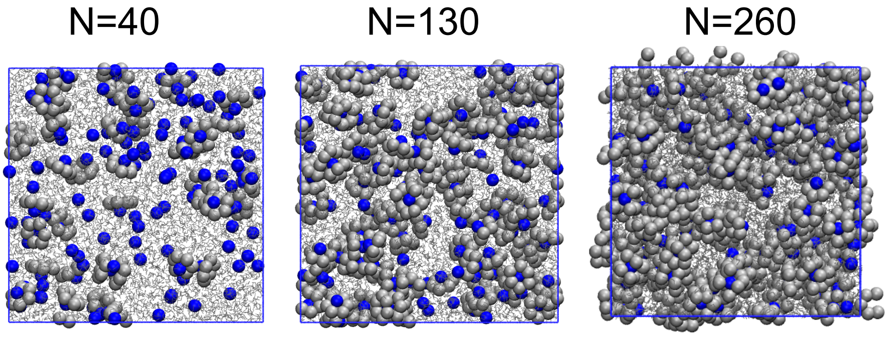

FIG. 2: A schematic illustration of host-guest (Cs^+-crown) systems with 40, 130, and 260 crown ethers. Note that 130 Cs^+ atoms were placed randomly in each system. The Cs^+ atoms are shown in blue, crown oxygen in silver. The water molecules are drawn using a line model and colored in grey.

based ligands for the selective separation of critical materials, underscoring their potential in addressing contemporary material challenges.[9, 10]

Ion-polyether host-guest interactions occur non-covalently through ion-dipole supramolecular interactions, where the selectivity of ion binding correlates with host cavity size, composition, and ion radius (r).[11, 12] For example, the selectivity of 18-crown-6 for K^+ relative to Cs^+ results from the optimal K^+ size to fit properly into the crown cavity, similar to a key in a lock, whereas Cs^+ lies on top of the host molecules.[13] However, ion binding is significantly limited by factors such as ion hydration and coordination with counteranions. Ions with less favorable (less negative) free energies of hydration or complexation are more likely to lose coordination, leading to entropic favorability of ion binding compared to ions that possess stronger solvation shells. The binding constants are highly sensitive to the dimensions and preorganization of host cavities, where organized hosts with low conformational entropy result in enhanced guest selectivity and ion recognition.[5, 14, 15] For instance, the open-chain flexible linear counterparts of crown ethers, i.e., the podand molecules, chelate with ions, whereas the closed-ring crown ether can bind guest ions directly into the cavities, resulting in an increase in metal-ligand (ML) binding constants. Due to enhanced flexibility, a podand can undergo numerous geometric transformations, causing an increase in the entropy of complexation. The preorganization of polyethers, also known as the macrocyclic effect, leads to a significant decrease in conformational entropy and, consequently, an increase in binding selectivity.[16] Furthermore, highly organized 3-dimensional cryptands (shown in Figure 1) can significantly improve selectivity over the crown by encapsulating ions within their spherical cavity, limiting the excess of solvent and counter-anions to the bound cation, known as the cryptand effect.[17, 18]

The formation of 1:1 and 2:1 and higher host-guest complexes with cyclic polyethers have been observed in bulk aqueous media.[19, 20] Most of the simulations and theoretical studies are pertinent to the validation of the experiments. Experimental proof of the sandwich concept (cesium-crown) came from the recent paper by Chu et al.[21] in which it is reported that the propensity of alkali metal and crown molecules to form 2:1 sandwich complexes follows a linear relationship with the crown cavity size and the cation radius. The microscopic aqueous phase chemistry of sandwich compound formation, as it relates to changes in a host organization (shifting from podands to cryptands) and concentration, remains unexplored. This work demonstrates that a systematic increase in host concentration leads to the formation of a 2:1 host-guest (i.e., Cs^+-2 Host) sandwich complex, which traps the Cs^+ between two host rings, resulting in a decrease in the average coordination with the solvent and counter-anions. Three host molecules, namely podand, 18-crown-6, and [2.2.2]-cryptand, which exhibit increased preorganization of the ether polymer, are considered. In each of the three host-guest systems, elevated host concentration promotes an increase in ion recognition through the formation of 2:1 host-guest sandwich complexes, leading to improved ion recognition.

II. METHODOLOGY

A. Simulation Details and Force Fields Implementation

Molecular dynamics (MD) simulations were carried out employing an all-atom approach using the GROMACS-2016.2 software package.[22]. We constructed simulation systems within cubic unit cells of side length 60 Å. Each system was designed with a consistent $CsNO_3$ concentration of 1 M. The concentration of host molecules was systematically increased by varying the number of host molecules. As such, for 18-crown-6, the concentration ranged from $n = 40$ (0.26 M) to $n = 260$ (1.36 M). Detailed system compositions are provided in Table S1. The molecular motions were integrated at 298 K using the Leap-Frog Verlet integrator, with a 2 fs time step and periodic boundary conditions in all three dimensions. Energy minimization was performed using the steepest descent algorithm. Initially, each system underwent a 40 ns equilibration in the NPT ensemble, subsequently transitioning to a 20 ns NVT ensemble equilibration utilizing the Nose-Hoover thermostat[23] and the Parrinello-Rahman barostat.[24]. The data analyses were performed on production runs within the NVT ensemble, each lasting for a minimum of 40 ns. The simulated host-guest simulation systems, showing the interactions of Cs^+ with a crown in an aqueous phase, are presented in Figure 2. To model the Cs^+ and $NO_3{}^-$ ions, we employed the force fields by Joung[25] and Wipff et al.[26], respectively. The chosen combination aims to accurately reproduce aqueous phase structural properties such as the pair correlation function and specific coordination environments. The TIP3P model was chosen for water molecules[27]. Three distinct host molecules, namely, podand, 18-crown-6, and [2.2.2]-cryptand (refer to Figure 1), were modeled using the General Amber Force Field (GAFF)[28]. We analyzed and compared the structural properties between GAFF, OPLS-AA[29], and CHARMM36[30, 31] force fields for these host molecules (*vide infra*). Non-bonded short-range interactions were computed using a 16 Å cutoff. For long-range electrostatic interactions, the Particle Mesh Ewald (PME) method was employed[32].

Force Fields Benchmarking A detailed comparison and rigorous benchmarking of various force fields are critical to ensure the accuracy of computational models for host-guest interactions. Such an evaluation is imperative to identify the most reliable force fields that can faithfully replicate the intricate interactions and energetics inherent in these complex systems. Therefore, to elucidate the influence of different force fields on ion recognition, we calculated the atomic pair-correlation functions, $g(r)$, and coordination numbers for Cs^+-crown ether interactions as depicted in Figure S1, employing three distinct force fields: OPLS-AA, CHARMM, and GAFF. [28, 31] The $g(r)$ correlation between Cs^+ and O_C manifested a predominant peak at approximately (3.1 Å), with the mean coordination number of O_C adjacent to the coordinated Cs^+ ions consistently averaging around 6 across all evaluated force fields (Figure S2). This consistency suggests that the nature of host-guest interactions remains largely unaffected by the specific force field implemented. Notably, Kollman and colleagues showed that the host-guest binding dynamics remain largely invariant to the charge, polarization, and Van der Waals parameters of the guest alkali cations.[33] Consequently, these observations support the notion that Cs^+-crown ether host-guest interactions can be proficiently captured using standard classical force fields.

B. Data Analysis

Network Analysis of the Host-Guest Interactions Supramolecular interactions were characterized using network theory based sub-ensemble analysis. The host-guest intermolecular interactions were reduced to a graph representation consisting of vertices and edges. Host (N or O) and the Cs^+ atoms were considered vertices, and the edges between any two vertices were defined based on the presence and absence of an ion-dipole interaction.[34, 35] Geometric criteria based on the first minima in the inter-atomic radial distribution functions were used to define the ion-dipole interactions. Similarly, the methodology is used to obtain the coordination of H_2O and $NO_3{}^-$ in the primary shell of Cs^+ ions.

Umbrella Sampling The one-dimensional potential of mean forces (PMFs) along the Cs-18-crown-6 radial distance were obtained using umbrella sampling methodology.[36, 37] The potential of mean force systems were generated by randomly placing $CsNO_3$ and 18-crown-6 in 2134 TIP3P H_2O. Starting with the initial bound host-guest configuration, Cs^+ is pulled away from the crown center of mass with a force constant of 5000 kJ mol^{-1} nm^{-2}. Constrained simulations have been performed in a total of 40 windows. Each window was equilibrated for 2 ns, followed by production runs of length 2 ns each in the NPT ensemble. The PMFs were constructed using the weighted histogram analysis (WHAM) method.[38] Statistical errors were computed using Bayesian bootstrapping analysis.[39]

Metadynamics Simulations The two-dimensional free energy surfaces along Cs^+-H_2O coordination and Cs^+-18-crown-6 (COM) radial distance collective variables were obtained using metadynamics methodology.[40, 41] The coordination number was computed using

$$CN = \sum_i \frac{1 - (\frac{r_i - d_0}{r_0})^n}{1 - (\frac{r_i - d_0}{r_0})^m} \tag{1}$$

where r_i is the distance between Cs^+ atom and water O-atoms. The parameter r_0 was set to 4.10 Å, and a d_0 value of 5.0 Å was chosen such that any r values greater than d_0 were designated as 0. The parameters

n and m were assigned values of 12 and 24, respectively. The use of a four-parameter equation for CN, including n, m, r_0, and d_0, provides a robust approach over the regular enumeration method with a spherical cutoff. This formula allows for a gradual, rather than abrupt, decline in the weighting of water molecules based on their distance from the Cs^+ ion. This method aligns more closely with the actual physical interactions by capturing the diminishing influence of distant molecules. To obtain the free energy surface corresponding to 2:1 host-guest complex, one Cs^+-Crown complex was constrained using a harmonic potential of form $V(r) = \kappa(r - r_0)^2$ with $\kappa = 20{,}000$ kJ mol^{-1}nm^{-2} and the other crown is moved along the Cs^+-Crown COM radial distance. Well-tempered Metadynamics simulations were performed in NPT ensemble for 40 ns each using GROMACS software package patched with PLUMED[42] using a bias factor of 5 K. Gaussians with width and height 0.5 Å and 1.0 kJ/mol were deposited every 100 time-steps.

III. RESULTS AND DISCUSSION

A. Host-Guest Sandwich Complexes

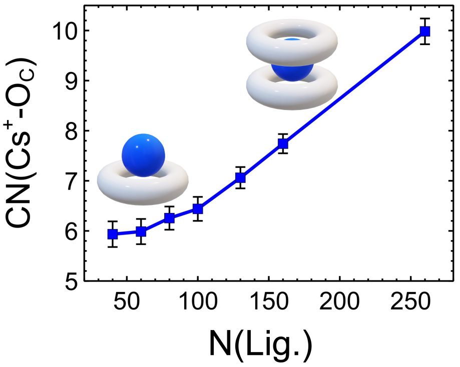

FIG. 3: Coordination number of O_C (crown oxygen atoms) around central Cs^+ ions with increase in the crown ether concentration. Note that the coordination number is calculated for the Cs^+ ions interacting directly with the host molecules. The standard deviations of coordination distributions of each host-guest system are shown as error bars.

The abundance of host molecules can alter host-guest interactions and lead to the formation of sandwich complexes, particularly in the presence of cations like Cs^+ that do not fit into the host cavities of 18-crown-6 and [2.2.2]-cryptands. To obtain the microscopic details, Cs^+-crown interactions are studied as a function of crown concentration in terms of $Cs^+{-}O_C$ coordination, as shown in Figure 3. The number of O_C atoms interacting with Cs^+ in the primary coordination shell increased with crown concentration. At low host concentrations, the Cs^+ ions interacted primarily with one crown ether, with a coordination number of ~ 6 formed with O_C. The O_C coordination number increased to an average of ~ 10 at a Crown:Cs^+ ratio of 2:1 (N=260), indicating the favorability of sandwich formation at elevated crown concentrations. Interestingly, a similar linear increase in the $Cs^+{-}O_C$ coordination is observed for podands and cryptands (Figure S3), showing the dominance of sandwich complexes at higher concentrations, irrespective of molecular pre-organization. An illustration of the sandwich complex formed by podand and cryptand with cesium ion is provided in Figure S3.

At lower host concentrations, not all Cs^+ ions form sandwich complexes; hence, it is crucial to compute the fractions of unbound, 1:1, and 2:1 complexes at varying concentrations. The percentage of Cs^+ ions coordinating 0, 6, or 12 with O_C(crown) indicates the proportion of unbound cesium, and the cesium ions forming 1:1 or 2:1 host:guest complexes. To achieve this, we calculated the probability distribution of $Cs^+{-}O_C$ coordination, as shown in Figure S4, to explore the likelihood of sandwich complex formation at increasing host concentrations. The figure reveals that at very low host concentration (N=40), the Cs^+ ions were predominantly unbound (approximately 70%) or part of 1:1 complexes. Notably, the likelihood of forming sandwich complexes escalated from approximately 20% to 80% as the host:guest ratio increased from 1:1 to 2:1.

The stability of 1:1 and 2:1 host:guest complexes was quantified using the potential of mean forces. The free energies of both 1:1 and 2:1 host-guest binding were computed by pulling the Cs^+ ion and crown ring away from the initial complexes, as shown in the schematic illustration at the top of Figure S5. The distance between Cs^+ and the crown center of mass (COM) is used as the reaction coordinate for the 1:1 PMF, while the radial distance between the 1:1 complex COM and the second crown ring COM is employed for the 2:1 PMF. Considering $\Delta G = 0$ as the host-guest interaction energy at infinite separation, the formation of the 1:1 host-guest Cs^+-crown complex is stabilized by approximately -5 kcal/mol. The free energy of 1:1 Cs-crown binding was reported to be around -6 kcal/mol by Bakulin et al.[43] and -3 kcal/mol by Dang et al.[44].These findings underscore the consistency of our results with previously established data, reflecting the reliability of the methodologies employed and providing a cohesive understanding of the Cs-crown interaction energetics. The formation of the 2:1 sandwich complex further stabilizes the host-guest complex by adding nearly -2 kcal/mol of energy. Combining free energies from both PMFs, the free energy of sandwich complex formation of

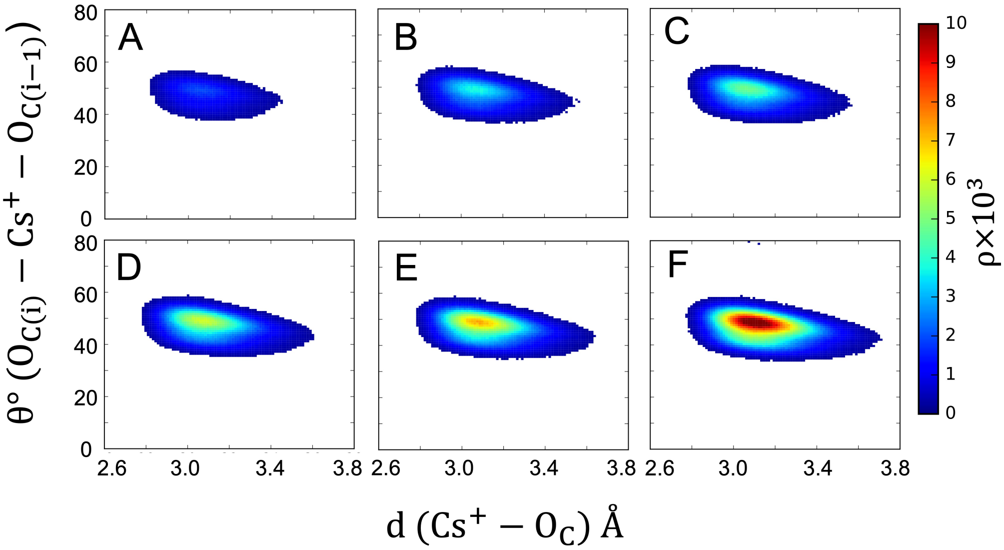

FIG. 4: Combined angular/spatial distributions of $O_{C(i)}$-Cs^{+}-$O_{C(i-1)}$ angle and Cs^{+}-$O_{C(i)}$ distances between Cs^{+} ions and crown oxygen atoms in systems with (A) 40 (B) 60 (C) 100 (D) 130 (E) 160 and (F) 260 18-crown-6 molecules.

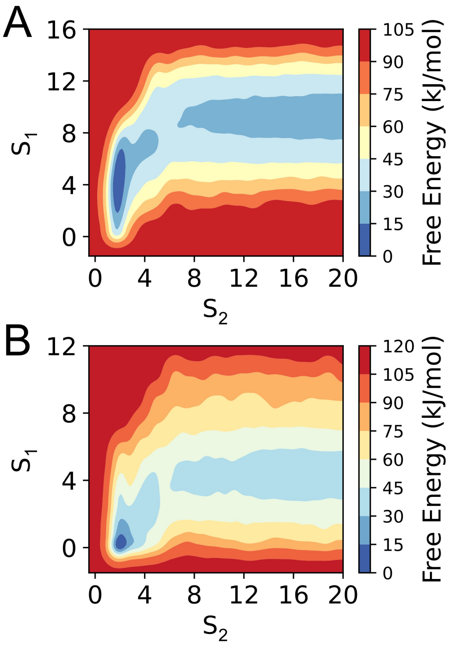

FIG. 5: Free energy surfaces for the formation of (A) 1:1 and (B) 2:1 host-guest (Cs^{+}-crown) complexes in aqueous media. Cs^{+}-H_2O coordination (S_1) and Cs^{+}-Crown (COM) radial distance (S_2) are used as reaction coordinates.

approximately -7 kcal/mol demonstrates the stability of the 2:1 complex over the 1:1 host-guest complex.

To gain detailed insights into the effect of increasing host concentrations on host-guest binding with Cs^{+} ions, we employed combined angular/spatial distributions (CASD) of $O_{C(i)}$-Cs^{+}-$O_{C(i-1)}$ angles and Cs^{+}-$O_{C(i)}$ distances between Cs^{+} ions for each of the three types of host molecules, namely podands, crowns, and crypts, as shown in Figure 4. Here, $O_{c(i)}$ represents the i'th host oxygen atom. CASDs measure the probability of finding a particle at a certain distance d' away from the reference, and interacting at a specific angle with respect to the host molecules. This analysis provides the probabilistic quantification of the propensity of Cs-ligand complexation within the conformational space leading to sandwich complex formation. The CASDs between host-guest molecules showed distances in the range of 2.8 to 3.6 Å, which correlated with angles in the range of 40 to 60°. The correlation intensity increased with an increase in host concentrations, particularly the Cs:Crown ratio from 1:1 to 1:2 (Figure4 E and F). It is evident from Figure4 that, with an increase in host-guest correlations, the probability of Cs^{+} ion recognition and being in the sandwich conformation by the crown ether increases with an increase in crown concentration. Similar behavior is observed for podands and cryptands molecules, except for the density of the correlation (Figure S6). The densities of podand CASDs are significantly lower compared to those of the crown. This is attributed to their high structural and conformational flexibility. Due to the macrocyclic effect, crown ethers exhibited higher correlations compared to the chelate effects displayed by the podand host molecules. Nonetheless, an increase in podand concentrations also led to increased host-guest correlations.

TABLE I: Coordination environment of Cs^+ ions in systems with podands, crowns and cryptands as host molecules. The number of water and ${NO_3}^-$ ions in Cs^+ coordination shells are provided with increase in host concentrations in each of the three types of host-guest systems. The statistical errors were calculated using block averaging methodology.

N(host)	CN(Cs^+-O_w) podand	CN(Cs^+-O_N) podand	CN(Cs^+-O_w) crown	CN(Cs^+-O_N) crown	CN(Cs^+-O_w) crypt	CN(Cs^+-O_N) crypt
40	8.48 ± 0.07	0.95 ± 0.01	7.39 ± 0.05	0.82 ± 0.02	6.97 ± 0.05	0.79 ± 0.01
60	8.22 ± 0.07	0.94 ± 0.01	6.67 ± 0.05	0.74 ± 0.02	5.77 ± 0.04	0.67 ± 0.01
80	8.07 ± 0.06	0.92 ± 0.01	5.90 ± 0.04	0.67 ± 0.02	5.22 ± 0.04	0.63 ± 0.02
100	7.84 ± 0.06	0.91 ± 0.01	5.19 ± 0.06	0.59 ± 0.02	4.50 ± 0.05	0.58 ± 0.02
130	7.48 ± 0.05	0.89 ± 0.02	4.16 ± 0.07	0.48 ± 0.03	3.56 ± 0.06	0.49 ± 0.02
160	7.25 ± 0.05	0.87 ± 0.01	3.26 ± 0.07	0.39 ± 0.02	2.84 ± 0.07	0.42 ± 0.02
260	6.38 ± 0.04	0.84 ± 0.02	0.82 ± 0.02	0.08 ± 0.03	1.55 ± 0.12	0.27 ± 0.03

Cryptand molecules exhibited similar behavior. Due to larger size Cs^+ ions cannot go into the cryptand cavity and interact primarily with the 4 peripheral oxygen atoms (as shown in Figure S3), and the two remaining cryptand oxygen atom did not contribute to the cesium binding, therefore, the correlation densities in cryptand CASDs (Figure S6) are primarily due to angle computations involving the four central ring oxygen atoms that directly interacted with the Cs^+ atoms.

B. Perturbations in Cesium Coordination Environment on Host-Guest Complex Formation

Selective ion extraction requires the removal of unwanted molecular extraction, which includes the extraction of water and acid or background electrolytes. The formation of 2:1 host-guest sandwich complexes increases both larger ion selectivity and specificity by excluding unwanted molecular interactions, trapping the ions between the cavity formed by two sandwiching host molecules. The exclusivity of ion recognition is studied using perturbations in Cs^+-water interactions calculated in terms of average Cs^+-O_w coordination, as shown in Table I. The systems with crown and cryptand molecules showed a significant decrease in Cs^+-water coordination compared to the podands. The CN decreased from approximately 8 to 6 in the systems with podand on the increase in host concentration from 40 to 260, whereas the Cs^+-water CN decreased from approximately 7 to 1 in similar systems with crown or cryptand molecules. In the cryptand system with N=260, we observe an increase of approximately 0.73 in Cs-water coordination compared to the crown system. This effect is attributed to the steric hindrance imposed by the cryptands, which causes the water molecules to remain trapped within the Cesium coordination shell. This phenomenon is evidenced by the increased lifetime of water in the cesium coordination shell. Specifically, for the cryptand systems, the lifetime of water in the coordination shell of cesium is found to be ~ 18.7 ps (N=240), in comparison to ~ 11.7 ps for the analogous crown system.

This suggests that increased host pre-organization is crucial for the increase in ion exclusivity. This phenomenon is further elucidated by examining the 2D free energy surfaces along the Cs-water and Cs-Crown COM as collective variables (Figure 5). Upon binding with one crown ether, Cs^+ ions are observed to lose nearly half of their primary coordination shell (Figure 5 A). Moreover, interaction with a second crown ring causes the Cs^+ ion to almost entirely lose its primary coordination with water. The findings from the free energy calculations corroborate the Cs^+ coordination environment obtained from the unconstrained molecular simulation, as discussed previously.

With the hypothesis that the exclusivity of ion recognition involves a reduction in ion-pair interactions after the formation of sandwich complexes, Cs^+-nitrate complexation in host-guest systems is assessed in terms of ensemble average Cs^+-O_N contact ion pairs in the primary Cs^+ coordination shells. The variations in Cs^+-nitrate complexation are examined in terms of Cs^+-O_N contact ion pairs (CIPs) (Table I). Both crown and cryptand systems possessed approximately 0.80 CIPs in the system with 40 host molecules, which decreased respectively to 0.08 ± 0.03 and 0.27 ± 0.03 in the system with 260 host molecules. In this case, crown ethers are quantified to be more efficient than cryptands in terms of Cs^+-O_N coordination perturbations with an increase in host concentration. The podand systems, on the other hand, showed minor changes in the Cs^+-O_N coordination (0.95 ± 0.01 at N=40 to 0.84 ± 0.02 at N=260). The data explain the efficiency of crown and cryptand in exclusivity over the flexible podand hosts.

C. Solvent Effects on Host-Guest Interactions

Sandwich complex formation not only affects the Cs^+ coordination environment, but also reduces host-solvent interactions (water, in this case) by decreasing the effective area of interaction. This reduction in effective area can be directly observed by analyzing the Solvent Accessible Surface Area (SASA) per crown, as shown in Figure S7. The average SASA decreased from approximately 4.5 nm^2 to 2.5 nm^2 with an increase in the number of crown molecules from N=40 to N=260, respectively. To delve into the details of crown-water interactions, we computed the probability distribution of the number of water molecules directly interacting with the oxygen atoms (O_C) of the 18-crown-6 molecules (Figure S8). The results indicate that each crown oxygen interacted primarily with one H_2O in the first coordination shell at all host concentrations. However, the probability of non-interacting O_C atoms increased by approximately 10% from N=40 to N=260, directly correlating to the decrease in effective SASA of host-solvent interactions at high host concentrations.

The dynamics of interacting solvents and counter-anions can be altered by the formation of sandwich complexes. To analyze this phenomenon, we calculated the residence times of H_2O ($\tau(H_2O)$) in Cs^+ coordination shells (in the system with 18-crown-6 as the host molecule), as illustrated in Figure S9-S10. The results depict a decrease in the dynamics of H_2O in Cs^+ coordination shells. The ($\tau(H_2O)$) increased linearly from approximately 5 ps at N=40 to approximately 12 ps at N=240. The observed increase in water lifetime with an increase in host concentration is attributed to increased steric hindrances. The diffusion constant of water, D_{H_2O}, decreased from 3.29 ± 0.05 to $2.17 \pm 0.02 \times 10^{5}$ cm^2/s at N=130 and 260, respectively (Figure S11). The dynamics of NO_3^- in the Cs^+ solvation shell, which is quantified to be in the range of approximately 7 to 10 ps, remained fast and uncorrelated to the increase in the density of crown ethers. This is related to weak Cs^+-NO_3^- interactions relative to Cs^+-H_2O, further supported by the Cs^+-H_2O and Cs^+-NO_3^- potential of mean forces (Figure SI 12).

IV. CONCLUSIONS

The trapping of guest ions in host cavities has proven to be an effective method for the selective separation of metal ions. However, supramolecular extractant molecules are commonly employed for chemical separation, often involving solvent and counter-anions co-extraction. In this study, we present a framework involving host-guest sandwich complexes with the potential to trap metal ions between two host molecules exclusively, consequently reducing the costs of processing co-extracted solvents and counter-anions. We employed molecular dynamics simulations to investigate the speciation, dynamics, and thermodynamics of 2:1 host-guest sandwich complexes in the aqueous phase, utilizing polyethers such as 18-crown-6, pentaglyme, and [2.2.2]-cryptands as host molecules and cesium as the guest. Our results show that cesium ions have a relatively strong affinity for 18-crown-6 or cryptands, but their size makes them imperfect fits for these host molecules, leading to the formation of 2:1 sandwich complexes, particularly at high host concentrations. The formation of sandwich complexes creates an environment devoid of water or counter-anions in the primary Cs^+ coordination shells. Sandwich formation involves significant perturbations in Cs^+ coordination with H_2O and counter-anions. Both crown and cryptand show greater exclusivity in Cs^+ recognition relative to podand due to their lower conformation flexibility. Our thermodynamics analysis of the stability of 1:1 and 2:1 Cs^+-crown complexes using the potential of mean force reveals the sandwich complex to be nearly -2 kcal/mol more stable than the 1:1 complex. The microscopic understanding of 2:1 sandwich complexes will help broaden ion recognition and extraction horizons using host-guest chemistry in separation science. The results described in this study will aid the design and optimization of solvent extraction systems that facilitate the selective and efficient separation of metal ions. By minimizing the co-extraction of solvents and counter-anions, these extraction systems could reduce the environmental impact and operational costs associated with traditional separation methods, while enabling the recovery of valuable metal resources from complex mixtures.

Supplementary Information

System Configuration and simulation protocol; Force fields benchmarking; Pair correlation functions; Average coordination numbers and distributions; Solvent accessible surface area; Average residence times; Potential of mean forces; Mean square displacements; Water structure, and topology.

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Conflicts of Interest

None.

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