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Cation– π Interactions of Bare and Coordinatively Saturated Metal Ions: Contrasting Structural and Energetic Characteristics

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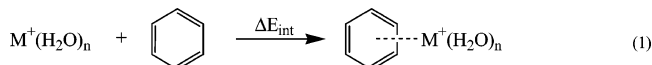
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In the present work, we address an apparent disparity in the structural parameters of the X-ray structures and theoretical models of cation– π complexes in biological and chemical recognition. Hydrated metal ion (Li^+ , Na^+ , K^+ , Mg^{2+} , Ca^{2+}) complexes with benzene (cation– π) are considered as model systems to perform quantum mechanical calculations in evaluating the geometrical parameters and interaction energies of these complexes. The computations disclose that there is a variation in the structural parameters as well as in the interaction energies of these complexes with the multiple additions of water molecules. The distance between the cation and the π -system increases with the addition of water molecules, delineating the influence of solvent or the neighborhood atoms on the structural parameters of cation– π systems present in crystal structures.

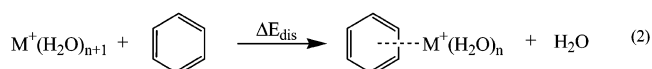
Introduction

Cation– π interactions between metal ions and arenes recently emerged as one of the fundamental bonding motives of key importance in molecular recognition.^{1–4} In the gas phase these ion–molecule interactions are among the strongest possible noncovalent interactions in molecular systems,^{5–9} a finding that has been substantiated by experimental measurements as well as theoretical calculations.¹⁰ In fact, a pairwise interaction energy comparison between the alkali earth metals with benzene and water molecule reveals the former to be stronger than the latter. These interactions are of importance in designing organic nanotubes, biological receptor models, and ionophores and are also expected to play an important role in the protein structure and stability.^{11,12} Computations are expected to provide valuable support in delineating the role of cation– π interactions in the design of new molecular entities, which has wide ranging applications. Recent efforts to explore the structure and strength of cation– π interactions reveal that both density functional theory and conventional ab initio approaches yield rather similar results.⁷ The computed cation– π distances for the alkali and alkaline earth metals range around 1.8–1.9 Å for the first row elements such as Li^+ and Mg^{2+} . The second row ions, Na^+ and Ca^{2+} , have bond lengths of around 2.4–2.5 Å, and the third row element K^+ has an optimal distance of around 2.9 Å to the centroid of benzene or other aromatic systems. These distances seem to vary in a very narrow range of less than 0.3 Å, when the metal binds to benzene or substituted benzenes,⁷ the stacked dimer of benzene,¹³ heteroaromatics,¹⁴ or curved polycyclic aromatic motifs.¹⁵ A cursory look at various experimental crystal structures where one observes the metal ions involved in the close proximity to arenes further supports the role, nature, and ubiquity of cation– π interactions in chemistry and biology.^{16–19} Chipot et al. examined the interaction between the ammonium cation and the aromatic face of toluene in water by means of

SCHEME 1



$\text{M} = \text{Li}^+, \text{Na}^+, \text{K}^+, \text{Mg}^{2+} \text{ and } \text{Ca}^{2+}; n = 1-6$



$\text{M} = \text{Li}^+, \text{Na}^+, \text{K}^+, \text{Mg}^{2+} \text{ and } \text{Ca}^{2+}; n = 1-4$

potential of mean force (PMF) calculations and the obtained comparison of free energy profiles in vacuum and in water suggests that “contact” configurations should be stabilized in nonpolar environments.²⁰ Gallivan and Dougherty have shown that cation– π interactions are frequently found on the surfaces of proteins and exposed to aqueous solvation.²¹ By determining the solvent accessible surface area of individual amino acids and pairs, computationally it is shown that cation– π interactions are rarely buried within proteins in the Protein Data Bank and, more often than not, are exposed to water. According to their analysis, from 2878 energetically significant cation– π interactions present in the data set of 593 nonhomologous proteins, only 20% of the aromatic amino acid residues have at least 20% of their surface exposed to solvent, whereas, on the other hand, 70% of all cationic amino acids expose more than 20% of their surface to water. However, cation– π interactions are rarely completely buried within proteins, and only 11% of cation– π interactions are completely buried. The study projects the importance of solvent on cation– π interactions. Vaden and Lisy investigated the hydrated Na^+ , K^+ ion complexes with benzene and phenol using infrared spectroscopy, wherein hydrated ions interact with the π -system of benzene as well as the phenol oxygen atom.²² According to their analysis in hydrated environments, cation– π interactions are size-selective toward the hydrated ions. Computational studies on the influence of water molecules on cation– π interactions revealed that the strength

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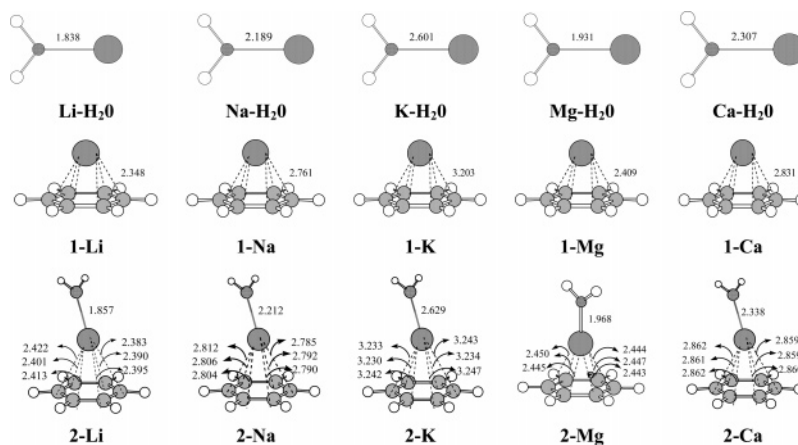


Figure 1. Geometries of the $M-H_2O$, $M-\pi$, and $M-H_2O-\pi$ complexes ($M = Li^+$, Na^+ , K^+ , Mg^{2+} , or Ca^{2+}) at the B3LYP/6-31G(d,p) level of theory. All distances are given in angstroms.

of the cation- π interactions gets substantially reduced when solvated with water.²³ During the crystallographic analysis of tetragonal hen egg-white lysozyme (HEW) at 2.0 Å resolution, Wouters observed a cation- π interaction between a sodium cation and the six-membered ring of the indole of Trp123.¹⁶ The distance between the centroid of the six-membered ring of the indole and the sodium ion amounts to 4.07 Å in this case. The database analysis performed on the structures of Protein Data Bank (PDB) and Cambridge Structural Database (CSD) clearly demonstrates that a higher number of cation- π interactions exist in the distance range of 3–4 Å from the cation to the centroid of the aromatic system.¹⁶ While structural parameters obtained by X-ray analysis are normally in excellent agreement with computations on single molecules in the gas phase, the role of the environment on the geometric parameters appears to be rather critical for cation- π interactions. A quick look at the recently built cation-aromatic database reveals that the frequency of cation- π interactions is relatively high in cation- π distances around 3.5–4.5 Å. These bond lengths are well over 1–2 Å longer than the optimized geometries obtained for smaller model systems using reliable quantum chemical methods.^{17–19} This disparity in the distances has recently raised some general doubt about the relevance of cation- π interactions in biology.¹⁹ To identify possible reasons for this disparity, we consider here the effect of explicit solvation of the cation- π system where the first solvation shell of cations is saturated with water. This will not only provide a realistic description of the first solvation shell, in a manner also relevant for biomolecules, but also mimic the saturation of metal ion coordination. We have considered the alkali and alkaline earth metal cations complexed with water molecules and benzene $[M(H_2O)_n-BEN]$; where $M = Li^+$, Na^+ , K^+ , Mg^{2+} and Ca^{2+} , $n = 1-6$] as model systems and investigated the interaction energies and structural parameters with an increasing number of water molecules. The most relevant energetic parameters for these systems is the interaction energy (ΔE_{int}) between metal cation and benzene is defined by eq 1 (Scheme 1) and the displacement energy (ΔE_{dis}) is evaluated by eq 2 and is only considered for complexes where $n = 1-4$.

Theoretical Methods

All conformations of both hydrated and nonhydrated π -complexes have been optimized at the B3LYP/6-31G(d,p) level, and the nature of the resultant stationary points has been ascertained with frequency calculations. Single-point energy calculations have then been performed at the B3LYP/6-311++G(d,p) and

MP2(FULL)/6-311++G(d,p) levels of theory. The 6-31G(d,p) basis set is of split-valence double- ζ quality with one set of polarization functions added on all atoms, whereas the 6-311++G(d,p) basis set is of triple- ζ quality and includes diffuse functions on both heavy and hydrogen atoms. All interaction energies mentioned in the text (at B3LYP/6-311++G(d,p) or MP2(FULL)/6-311++G(d,p) level of theory) have been corrected for basis set superposition errors (BSSE) using the Boys and Bernardi's counterpoise method.²⁴ The "Counterpoise=N" keyword is used to calculate the BSSE corrected total energy of a complex, where N holds for the total number of fragments composing the complex. BSSE corrected energies are used in the calculation of interaction energies.²⁵ The ΔE_{int} is the difference between the total energies (corrected for BSSE) of the products and reactants as given in eqs 1 and 2. All the calculations have been performed using the Gaussian 03 suite of programs.²⁶

Results and Discussion

As a point of reference we will use here the complexes including only one ligand (water or benzene). The structural details of these complexes (for the benzene system taken from ref 7) displayed in Figure 1 confirm the expected trend of longer metal-ligand distances for heavier alkali or alkaline earth metals. The bond energies collected in Table 1 also show the expected trends, the bond energies of bare metal cations to benzene being rather similar than the corresponding hydration energies for alkali metals, but significantly larger for the alkaline earth metals. Addition of one water molecule to the cation- π complexes **1-M** ($M = Li^+$, Na^+ , K^+ , Mg^{2+} , and Ca^{2+}) leads to minor lengthening of the metal-ligand bond distance. Due to the low symmetry of the monohydrated complexes, we have chosen to give the metal to carbon (of the ring) distances rather than the centroid. Similarly, the metal-water distance is slightly larger in the combined complexes **2-M** than in the pure metal-water complex. Another conformation of the same isomer (**2'-M**) exists with higher metal-ligand distance through intervention of the water molecule between the metal and aromatic ring. It is also observed that metal-oxygen distance is also considerably less in **2'-M** complexes than **2-M** due to the interaction of water molecule with the aromatic system.

On sequential solvation of the cation- π complexes with additional water molecules the conformational space becomes much larger, and only the energetically most favorable complexes are assembled in Figure 2. The complexes containing two water molecules and benzene as a ligand **3-M** and **3'-M**

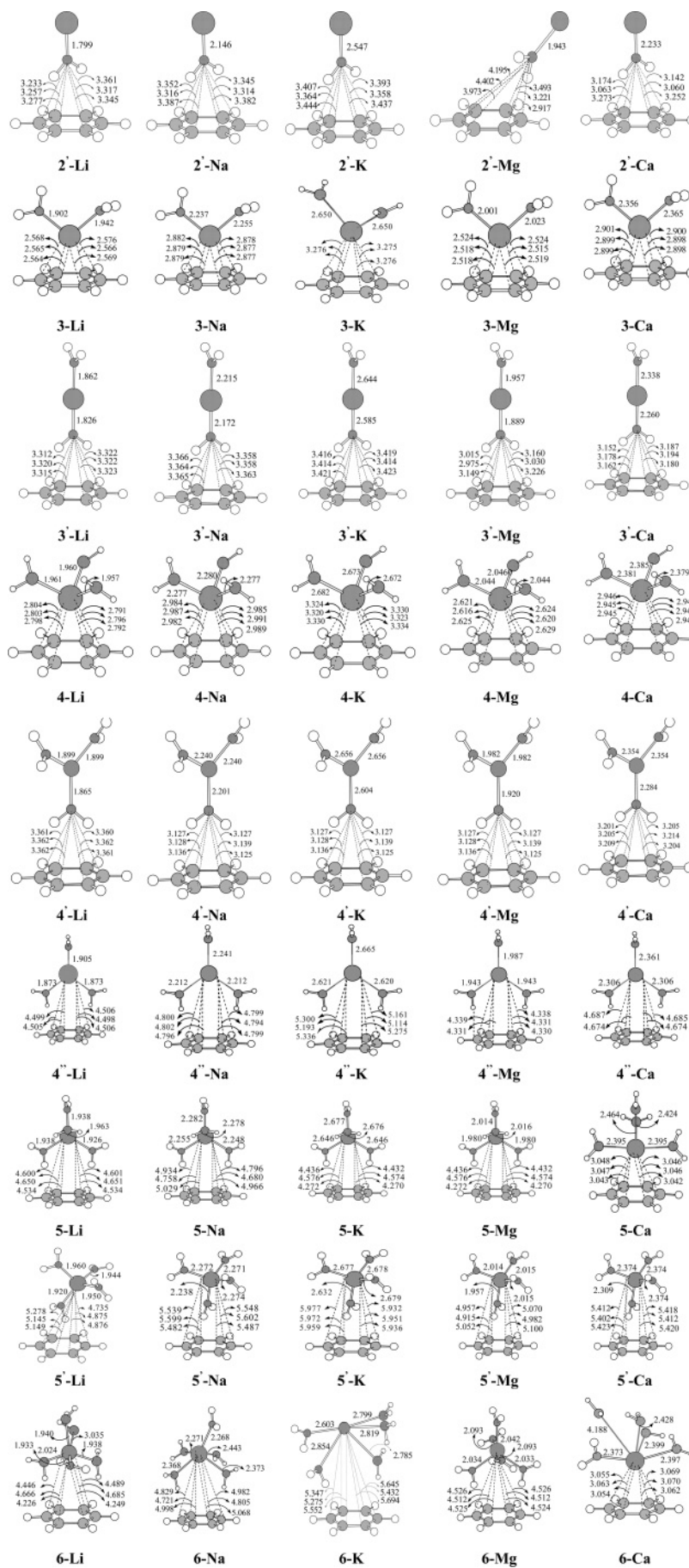


Figure 2. Continued

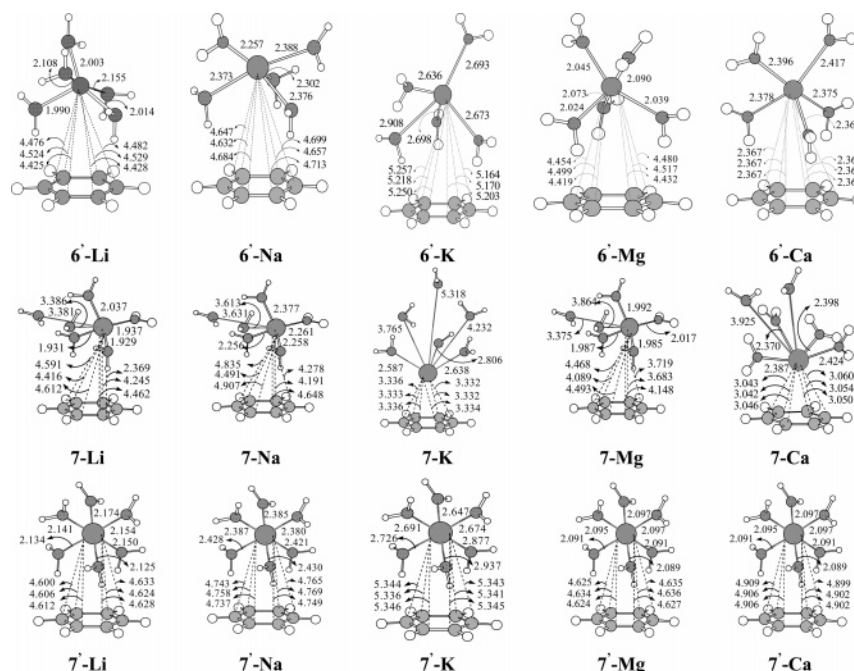


Figure 2. Geometries of the considered hydrated metal ion π -complexes ($n = 2-6$) as optimized at the B3LYP/6-31G(d,p) level of theory. All distances are given in angstroms.

TABLE 1: BSSE Corrected ΔE_{int} Interaction Energies^a (kcal/mol) of the Considered Hydrated Cations ($M(\text{H}_2\text{O})_n$, $n = 0-3$) with Benzene at B3LYP/6-311++G(d,p)/B3LYP/6-31G(d,p) and MP2(FULL)/6-311++G(d,p)/B3LYP/6-31G(d,p) Levels of Theory

structure	n	B3LYP/6-311++G(d,p)					MP2(FULL)/6-311++G(d,p)				
		Li^+	Na^+	K^+	Mg^{2+}	Ca^{2+}	Li^+	Na^+	K^+	Mg^{2+}	Ca^{2+}
1	0	-37.77	-23.14	-15.88	-117.24	-79.08	-35.41	-21.31	-16.99	-108.76	-72.83
2	1	-25.22	-19.38	-13.08	-96.86	-65.31	-28.26	-18.17	-14.58	-92.40	-62.47
3	2	-18.07	-14.24	-10.40	-74.00	-53.66	-19.76	-14.63	-12.29	-73.23	-53.12
4	3	-9.94	-10.28	-7.98	-54.58	-41.36	-12.69	-11.51	-10.33	-56.58	-44.85
W ^b	1	-35.53	-24.89	-18.38	-81.24	-57.36	-33.44	-23.12	-17.83	-76.02	-53.51

^a Interaction energies are calculated according to eq 1. ^b Corresponds to the interaction energy of water molecule with metal ion.

are structurally similar to those containing only one water, but again show slightly longer metal-ligand distances as before. In **3-M** the water molecules are away from the aromatic ligand, whereas in **3'-M** one water molecule is located between the metal and ligand, increasing the metal-ligand distance. After addition of one more water molecule ($n = 3$), there are three distinct minima on the potential energy surface, one where the complex is tightly bound (**4-M**) and another two (**4'-M**, **4''-M**) with sharply longer cation aromatic distances (1.5–2 Å) with intervening water molecules. In **4'-M** one water molecule and in **4''-M** two water molecules are present between the benzene and metal ion. However, when the number of water molecules exceeds three, the complexes become much looser with water molecules found occupying the region between the metal and π -ring. Figure 2 depicts all the structures that correspond to cation- π complexes, where metal ion is solvated by more than one water molecule. Figure 2 reveals that in all cases the $M-\text{OH}_2$ distances show a regular trend; these distances are much shorter when H_2O is placed toward the π -motif compared to those distances of water molecules placed on the exterior. The analysis of the optimized geometries of structures, such as **6-Ca**, reveals that in order to obtain an optimal binding with the arene, water molecules are pushed to the second solvation shell. For $n = 6$, while the optimized minimum energy structures could be obtained for $M = \text{K}$ and Ca , **7-K** and **7-Ca**, where the metal- π complexation is rather tight, similar stationary points could not be located for other metals. An examination of earlier

structures also reveals that, for $M = \text{K}$ or Ca , the stationary points obtained are much tighter for $n = 4$ and 5, compared to other metals. For the structures with $n = 6$, the more stable conformation **7-M** reveals that most structures need to push one or two water molecules to the second solvation shell to optimize bonding. Another alternative is to have a fully solvated metal ion interacting with the π -system, **7'-M**.

The foregoing analysis clearly reveals that the cation- π distances are critically dependent on whether the metal ion is coordinated with other ligands or not. Interestingly, the cation- π distances observed in the optimized geometries of metal ion solvated complexes are very typical distances found in the protein structures. Thus, while cations form strong complexes with aromatic moieties in the gas phase, the realistic scenario in aqueous solutions is such that the solvated metal ion interacts with the aromatic motif.

How do the interaction energies in complexes with direct and indirect cation- π complexes compare? The interaction energies of the considered $M(\text{H}_2\text{O})_n$ -benzene complexes at B3LYP/6-311++G(d,p) and MP2(FULL)/6-311++G(d,p) levels of theory are provided in Tables 1–4. The trends obtained at B3LYP and MP2 levels are virtually identical as the water molecules are sequentially added. While the B3LYP method overestimates the binding strength of the unsolvated cation- π complex, the binding strength is underestimated for the interaction of aquated metal ions with the arene. This may be traced to the inadequacy of the current line-up of density functional theory (DFT)

TABLE 2: BSSE Corrected ΔE_{int} Interaction Energies^a (kcal/mol) of the Considered Hydrated Cations ($M(\text{H}_2\text{O})_n$, $n = 1-4$) with Benzene at B3LYP/6-311++G(d,p)//B3LYP/6-31G(d,p) and MP2(FULL)/6-311++G(d,p)//B3LYP/6-31G(d,p) Levels of Theory

structure	<i>n</i>	B3LYP/6-311++G(d,p)					MP2(FULL)/6-311++G(d,p)				
		Li ⁺	Na ⁺	K ⁺	Mg ²⁺	Ca ²⁺	Li ⁺	Na ⁺	K ⁺	Mg ²⁺	Ca ²⁺
2'	1	-10.18	-8.01	-6.52	-39.98	-23.63	-11.28	-9.21	-7.83	-28.43	-22.86
3'	2	-8.57	-7.07	-5.82	-26.82	-20.02	-9.89	-8.38	-7.18	-26.76	-20.27
4'	3	-7.07	-6.38	-5.16	-21.87	-17.34	-8.55	-7.50	-6.58	-22.64	-18.03
5'	4	-6.05	-5.29	-4.59	-18.66	-15.16	-7.76	-6.76	-6.06	-19.50	-16.15

^a Interaction energies are calculated according to eq 1.**TABLE 3: BSSE Corrected ΔE_{int} Interaction Energies^a (kcal/mol) of the Considered Hydrated Cations ($M(\text{H}_2\text{O})_n$, $n = 3-6$) with Benzene at B3LYP/6-311++G(d,p)//B3LYP/6-31G(d,p) and MP2(FULL)/6-311++G(d,p)//B3LYP/6-31G(d,p) Levels of Theory**

structure	<i>n</i>	B3LYP/6-311++G(d,p)					MP2(FULL)/6-311++G(d,p)				
		Li ⁺	Na ⁺	K ⁺	Mg ²⁺	Ca ²⁺	Li ⁺	Na ⁺	K ⁺	Mg ²⁺	Ca ²⁺
4''	3	-9.47	-8.48	-6.93	-28.15	-21.90	-10.93	-9.53	-8.36	-28.12	-22.45
5	4	-8.35	-7.57	-7.16	-23.76	-33.03	-10.07	-8.85	-9.58	-24.36	-35.98
6	5	-8.12	-8.14	-5.82	-20.61	-30.18	-10.39	-9.63	-8.33	-21.71	-33.56
7	6	-6.78	-6.26	-7.12	-17.13	-29.50	-8.95	-8.12	-9.64	-20.10	-32.72

^a Interaction energies are calculated according to eq 1.**TABLE 4: BSSE Corrected ΔE_{int} Interaction Energies^a (kcal/mol) of the Considered Hydrated Cations ($M(\text{H}_2\text{O})_n$, $n = 5-6$) with Benzene at B3LYP/6-311++G(d,p)//B3LYP/6-31G(d,p) and MP2(FULL)/6-311++G(d,p)//B3LYP/6-31G(d,p) Levels of Theory**

structure	<i>n</i>	B3LYP/6-311++G(d,p)					MP2(FULL)/6-311++G(d,p)				
		Li ⁺	Na ⁺	K ⁺	Mg ²⁺	Ca ²⁺	Li ⁺	Na ⁺	K ⁺	Mg ²⁺	Ca ²⁺
6'	5	-8.74	-8.28	-6.65	-21.56	-18.39	-11.26	-10.24	-8.86	-23.50	-20.32
7'	6	-8.42	-7.84	-6.86	-19.27	-16.46	-11.15	-10.21	-9.12	-21.55	-18.53

^a Interaction energies are calculated according to eq 1.

methods, including B3LYP, to model dispersive interactions.²⁷ The subsequent discussion will therefore focus on the results obtained at the MP2(FULL)/6-311++G(d,p) level. For all metal cations studied here there is a gradual decrease in the interaction energy as the metal ion gets solvated. Among the three different conformations of the $M(\text{H}_2\text{O})_3$ -benzene molecule, 4-M complexes, wherein the metal ion is in direct contact with the π -system and all water ligands are facing away from benzene, has a higher interaction energy compared to the other two conformations 4'-M and 4''-M, wherein water molecules are positioned between metal cation and the π -face of benzene. The preference for 4-M compared to 4'-M and 4''-M is on the order of 2–4 kcal/mol for the monocationic systems. Between 4'-M and 4''-M, the later orientation is relatively more stable than the first, because in 4'-M, one water molecule is separating the metal ion with the aromatic benzene ring to a greater extent than in 4''-M, although two water molecules are separating metal ion and aromatic benzene ring. Addition of more than three water molecules leads to a continuous, but not very systematic, reduction of the interaction energy for all metals considered here. Therefore, the orientation and the ambience of the cation- π motif, which is placed in the condensed phase, appear to be important factors in deciding the strength of interaction. Thus, the interaction energies gradually decline up to the addition of three water molecules; the variation in the strength of interaction is more orientation-dependent afterward. A cursory look at the optimized geometries and the interaction energies reveals that among all the metals considered Ca²⁺ appears to have a higher propensity for direct interaction with the arenes.

Feller, in a computational study of the benzene-water complex, has predicted that the conformation wherein the water molecule sits above the aromatic ring with oxygen pointed away from the benzene center of mass is the most stable.²⁸ This study shows that the electronic binding energy in the complete basis

set limit is -3.9 ± 0.2 kcal/mol. The intermolecular distance between the benzene centroid and O of the water, using multiphoton ionization studies, is determined as 3.329 Å.²⁹ The current study reveals that in the presence of a metal, 2'-M, the oxygen-centroid distance gets substantially reduced with all metals, where the effect of shrinkage is directly correlated with the charge and binding strength of the metal ion involved. However, when the metal ions are solvated with further addition of water molecules, its effect on the distance between the oxygen atom and the aromatic ring in 3'-M and 4'-M complexes appears to be rather subdued (Figure 3). On inspection of the interaction energies evaluated at B3LYP, MP2 levels of theory with the 6-311++G(d,p) basis set, the water molecule bound to the metal

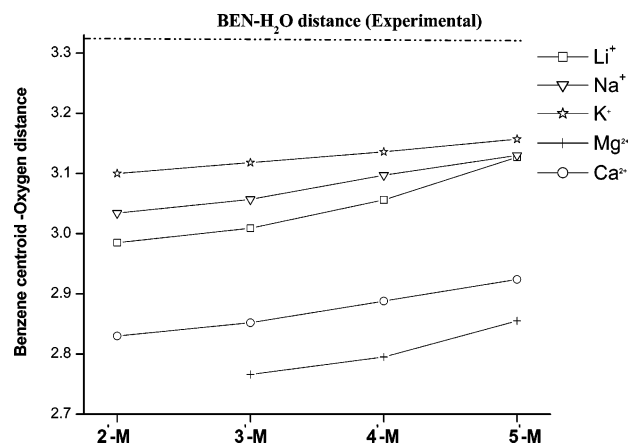


Figure 3. Variation in the distance of the oxygen atom from the centroid of the benzene ring in various hydrated metal complexes with the increase of the number of water molecules at the B3LYP/6-31G(d,p) level of theory. The upper (dotted) line corresponds to the BEN-H₂O molecule. 2'-Mg complex conformation is clearly different from the rest and not considered here (see Figure 2).

TABLE 5: Displacement Energies^a (ΔE_{dis}) of Complexes 1–4 Calculated at B3LYP/6-311++G(d,p)//B3LYP/6-31G(d,p) and MP2(FULL)/6-311++G(d,p)//B3LYP/6-31G(d,p) Levels of Theory Using Equation 2

structure	<i>n</i>	B3LYP/6-311++G(d,p)					MP2(FULL)/6-311++G(d,p)				
		Li ⁺	Na ⁺	K ⁺	Mg ²⁺	Ca ²⁺	Li ⁺	Na ⁺	K ⁺	Mg ²⁺	Ca ²⁺
1	0	−2.24	1.75	2.50	−35.99	−21.72	−1.97	1.81	0.84	−32.74	−19.31
2	1	2.07	1.72	2.71	−31.41	−15.86	−1.86	1.87	0.92	−29.79	−15.26
3	2	4.37	2.87	3.52	−20.72	−8.83	2.05	2.06	1.63	−21.36	−11.67
4	3	7.93	5.83	4.12	1.04	−3.64	5.50	3.89	1.73	−2.98	−6.29

^a Displacement energies are calculated according to eq 2.**TABLE 6: Total Energies (in Hartrees) of the Complexes at MP2(FULL)/6-311++G(d,p)//B3LYP/6-31G(d,p) Level of Theory**

structure	Li ⁺	Na ⁺	K ⁺	Mg ²⁺	Ca ²⁺
1	−239.002 47	−393.525 79	−830.992 37	−430.819 69	−908.221 92
2	−315.338 31	−469.851 58	−907.310 88	−507.208 72	−984.584 65
2'	−315.310 52 ^a	−469.836 28 ^a	−907.299 45	−507.104 42	−984.519 96
3	−391.660 79	−546.171 83	−983.625 88	−583.571 90	−1060.938 95
3'	−391.648 47	−546.162 08	−983.617 70	−583.503 17	−1060.885 55
4	−467.978 22	−622.487 40	−1059.938 89	−659.921 97	−1137.285 78
4'	−467.976 44	−622.482 55	−1059.923 65	−659.880 48	−1137.244 53
4''	−467.978 56	−622.484 13	−1059.934 37	−659.886 49	−1137.249 80
5	−544.295 75	−698.799 42	−1136.250 82	−736.247 56	−1213.617 52
5'	−544.293 29	−698.798 32	−1136.245 24	−736.242 25	−1213.595 46
6	−620.602 48	−775.106 28	−1212.553 67	−812.583 56	−1289.945 74
6'	−620.598 06	−775.103 14	−1212.554 19 ^a	−812.585 15	−1289.938 65
7	−696.914 48	−851.415 34	−1288.866 21	−888.893 63	−1366.265 44
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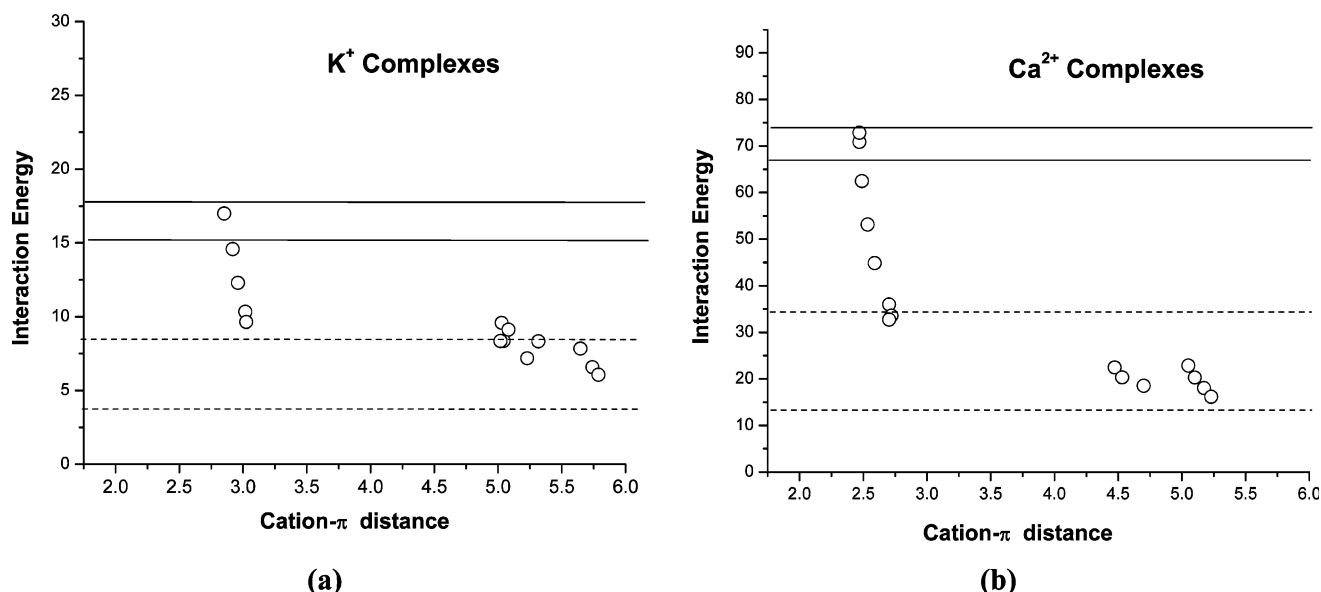
^a Not minima on the potential energy surface; are first-order saddle points.**TABLE 7: Distances (Å) between the Metal Cation and the Centroid of the Benzene Ring in Both Gaseous Phase and Aqueous Media (PCM Method) at the B3LYP/6-31G Level of Theory**

complex	gas phase	PCM
1-Li ⁺	1.945	2.084
1-Na ⁺	2.413	2.666
1-K ⁺	2.672	2.884
1-Mg ²⁺	2.001	2.225
1-Ca ²⁺	2.556	2.719

ion has relatively higher binding affinity with the benzene ring (2'-M) than the simple BEN-H₂O complex. In 3'-M and 4'-M complexes, the presence of higher solvated metal ions decreases the interaction energy by 2–3 kcal/mol. Furthermore, with the

addition of another water molecule, in 5'-M complexes, the interaction energy rise is negligible. But all the above-discussed complexes have a considerably larger amount of interaction energy than the BEN-H₂O complex (Table 2).²⁸

In the complexes 4''-M, 5-M, 6-M, and 7-M there are two water molecules nearer to the aromatic benzene system, moving the metal ion further away from the aromatic system. From 4''-M, with the addition of water molecules there is a 2–3 kcal/mol decrease in the interaction energy to 7-M for monocations and the decrease is higher (2–10 kcal/mol) in the case of dicationic complexes (Table 3). Similarly, the interaction energy difference between the 6'-M and 7'-M molecules is negligible in the case of monocations, whereas it is 2 kcal/mol for dications (Table 4).

**Figure 4.** Variation of interaction energy (kcal/mol) versus cation- π distances (Å) through sequential addition of water molecules for various cations, optimized at the MP2(FULL)/6-311++G(d,p)//B3LYP/6-31G(d,p) level of theory. The upper column (solid lines) corresponds to the gas-phase situation, thus the single-ion-molecule scenario, while the lower column (dotted lines) corresponds to the situation in the condensed phase.

Following eq 2, the displacement energies (ΔE_{dis}) are calculated for the complexes **1–4** and reported in Table 5 at the B3LYP/6-311++G(d,p) and MP2(FULL)/6-311++G(d,p) levels of theory. It is seen from the results that benzene can displace the water molecules from a hydrated metal ion complex to form strong cation– π complexes with Li, Mg, and Ca metal cations. The energy released in this exothermic reaction decreases, and the process becomes endothermic, when the number of water molecules attached to the metal ion rises to three. If we compare the hydrated Na^+ and K^+ complexes, which are more abundant in salt bridges, the displacement energy values for Na^+ are more positive than the K^+ ion. From these results it appears that benzene can replace water molecules easier from K^+ complexes than the Na^+ complexes, which is also supported by the first experimental evidence given by Lisy and co-workers, that K^+ selectively interacts with an aromatic complex in aqueous environment, while Na^+ does not.³⁰

From the total energies (Table 6), it is seen that **2-M** complexes are more stable than **2'-M** in which the metal ion is facing directly the π electron density of the benzene ring. The same trend is seen in case of complexes with two water molecules (**3-M** complexes). Out of three conformations of **BEN–M(H₂O)₃**, **4-M** complexes are more stable than the **4'-M** complexes followed by **4''-M** complexes. Similarly **5-M**, **6-M**, and **7-M** complexes are more stable than their corresponding **5'-M**, **6'-M**, and **7'-M** complexes.

To check the influence of solvent on cation– π interactions, we have performed geometry optimizations of **1-M** complexes in aqueous media, using the polarizable continuum model (PCM) at the B3LYP/6-31G level of theory. When comparing the cation– π distances in both gaseous and aqueous phases (Table 7), the cation– π distance is elevated approximately by 0.2 Å in the aqueous medium. But the cation– π distances calculated in aqueous medium are longer than the distances measured in **2-M** and **3-M** complexes in the gaseous phase but shorter than the **4-M** complexes.

The present study reveals that the strength of interaction of an arene, modeled by benzene, with a fully solvated metal ion is nearly half of the gas-phase complex for K^+ , while it reduces to almost one-fifth for the divalent Mg^{2+} . Figure 4 depicts the variation of interaction energies as a function of cation– π distances. While the figure depicts those for K^+ and Ca^{2+} as representative cases, the results for the other metals are very similar (see Supporting Information). There is a stepwise decrease in the strength of cation– π interactions as the metal ion is solvated and thus the cation– π strength is actually much smaller in the condensed phase. However, all energies are still higher than the interaction energy of the water–benzene complex of about 3 kcal/mol.²⁷ Further coordination of metal ions with water molecules results in lengthening the cation– π distance. Interestingly, while the potential in the gas phase for the cation– π may be very tight, it appears to be loose in the condensed phase. This is precisely the reason for the adaptation of a large span of cation– π distances that are observed in protein databases.

Conclusions

In summary, the present paper successfully addresses the disparity in cation– π motifs, between the quantum mechanically calculated structural parameters and the crystal structural parameters by using appropriate model systems. The study resolves an apparent discrepancy, which is traced to the structural comparison of models with different numbers of ligands. Calculations reveal that the strength of both cation– π

interactions gets substantially reduced when the metal ion is solvated or coordinated. Thus the high binding strength of the pairwise interaction of a metal ion with an aromatic motif gets substantially attenuated followed by a remarkable elongation of the bond length. Cation– π interactions traditionally exhibiting their greatest effect in nonpolar environments, such as in the gas phase, in the interior of proteins, or within the lipid bilayer membrane. Nonetheless these forces are expected to be of key importance in controlling the macromolecular structure and function.

Supporting Information Available: Tables of optimized Cartesian coordinates and total energies of all optimized structures considered. Figure of geometries of B3LYP/6-31G-(d,f.) level of theory and interaction energies of other explored conformations; figure of variation of interaction energy versus cation– π distances. This material is available free of charge via the Internet at <http://pubs.acs.org>.

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References and Notes

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