From Subtle to Substantial: Role of Metal Ions on $\pi-\pi$ Interactions

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Quantum chemistry calculations reveal that the subtle $\pi-\pi$ interactions, usually in the range 2−4 kcal/mol, will become substantially significant, from 6 to 17 kcal/mol, in the presence of metal ion. The metal ions have higher affinity toward a $\pi-\pi$ dimer compared to a single π-moiety. Considering the widespread occurrence of cation$-\pi-\pi$ motifs in chemistry and biology, as evident from the database analysis, we propose that the two key noncovalent forces, which govern the macromolecular structure, cation$-\pi$ and $\pi-\pi$, work in concert.

Interaction between the arene systems ($\pi-\pi$) has been recognized as a key stabilizing force in wide-ranging fields spanning molecular biology, crystal engineering, and material design.[1,2] Despite being subtle in terms of their strength, $\pi-\pi$ interactions have been one of the most widely recognized molecular recognition forces, which sculpt the nucleic acid and protein three-dimensional structures and also crystal packing of organic molecules. It has been observed that 60% aromatic side chains of proteins are in pairs, and these interactions are major stabilizing forces for the globular protein structures.[3−5]

Extensive experimental and theoretical studies on benzene dimer, the prototype arene, reveal that the parallel displaced (**PD**) and T-shaped (**T**) orientations are preferred in comparison to a range of other orientations including a parallel sandwich (**S**) orientation (see Scheme 1).[6,7] However, the available exhaustive theoretical studies corroborate that the interaction potential between the benzene molecules is quite flat, with interactions energies varying in the range 2−4 kcal/mol.[4,7] In contrast, the metal ion$-\pi$ (M$-\pi$) interactions are arguably the strongest noncovalent interactions. [8−11] Thus, the $\pi-\pi$ and cation$-\pi$ interactions seem to be the two key noncovalent forces, in addition to hydrogen bonding, which govern the three-dimensional structure of biomolecules. In this communication, we would like to explore how common the coexistence of M$-\pi$ and $\pi-\pi$ interactions in biology and chemistry is and how these fundamental forces mutually influence each other.

We have analyzed the occurrence of M$-\pi-\pi$ (M = Li$^+$, K$^+$, Na$^+$, Mg^{2+}, and Ca^{2+}) interactions in the Cambridge Structural Database (CSD, CSD V5.26) and Brookhaven Protein Data Bank (PDB) databases.[12] The PDB was searched for metal ion containing structures with less than 3 Å resolution and *R*-value < 0.3. To remove redundancy, the structures with greater than 90% sequence identity were eliminated from the above dataset. This resulted in a total of 1941 protein structures containing the 5 metal ions, which were subjected to analysis. On the basis of the normalized distance distribution function derived from aromatic pairs in protein structures, earlier studies defined an interacting aromatic $\pi-\pi$ motif as one in which the

SCHEME 1: The Various Cation$-\pi-\pi$ Configurations Considered[a]

S-M   PD-M   TA-M

TB-M   SW1   SW2
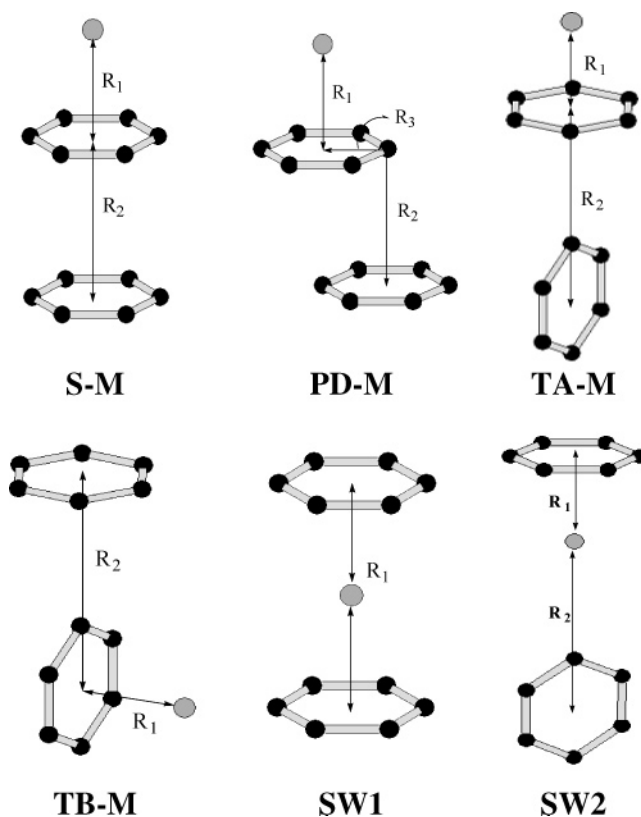
[a] S−M: parallel sandwich orientation of the two benzene rings with metal (M) above one of the rings. PD-M: parallel displaced benzene rings with M above one of the rings. TA-M: T-shaped alignment of the benzene rings with M above the T. TB-M: T-shaped alignment of the benzene rings with M beside the T. SW1: M sandwiched between two parallel benzene rings. SW2: M placed between T-shaped alignment of two benzene rings.

centroids of the aromatic rings are separated by less than 7 Å.[3] Therefore, we choose to present the results for 7 Å cutoff, and essentially the same trends were observed even with 6 Å cutoff.
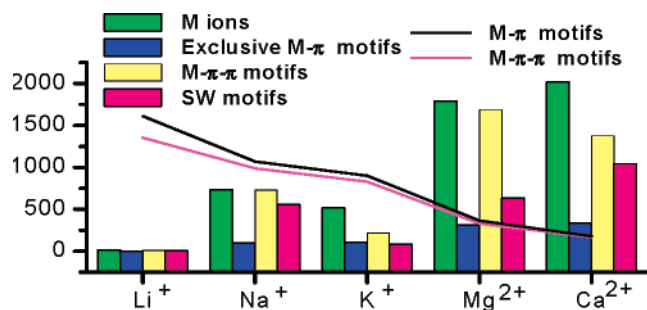
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Figure 1. Number of hits obtained for each metal ion from the statistical analysis of PDB (histogram) and CSD (solid lines). Green bars: Total number of M ions. Blue bars: Exclusive M$-\pi$ motifs which are not part of M$-\pi-\pi$. Red bars: Motifs in which the centroid of the second ring is within the cutoff distance from the metal. Black line: Number of structures containing M$-\pi$ motifs which may be part of M$-\pi-\pi$. Pink line: Number of structures having M$-\pi-\pi$ motifs. It should be noted that a metal ion can be involved in more than one M$-\pi$/M$-\pi-\pi$ motif. Therefore, the sum of exclusive M$-\pi$ and M$-\pi-\pi$ need not be less than or equal to the number of M.

TABLE 1: $\pi-\pi$ Interaction Energies (in kcal/mol) of the Various Benzene Dimers in the Presence of Metal Ions

M	S$-$M	PD-M	TA-M	TB-M
absent	−1.91	−2.91	−3.00	
Li$^+$	−6.54	−7.14	−2.28	−8.32
Na$^+$	−5.48	−6.17	−2.13	−7.26
K$^+$	−5.08	−5.68	−2.18	−6.76
Mg^{2+}	−16.18	−17.26	−5.97	−16.93
Ca^{2+}	−13.00	−13.80	−5.45	−14.81

At the outset, the search procedure involves identifying protein structures containing aromatic rings, which include benzene, indole, phenol, and imidazole, whose centroid is within 7 Å of the metal ion. Of these, structures with a second aromatic ring whose centroid is within 7 Å of either the metal ion or the centroid of the first ring were searched. The various M$-\pi-\pi$ configurations are characterized by considering the orientation of the π-rings and M. Similarly, the CSD was searched for structures containing M$-\pi$ and $\pi-\pi$ motifs with a 7 Å cutoff, where the centroids of the benzene ring were taken as reference. Structures with less than 3 Å cutoff distances were not considered in both CSD and PDB, to eliminate the covalent complexes. While the number of motifs is considered in the proteins of PDB, the CSD search gave the number of structures containing the motifs.

Figure 1 illustrates the ubiquity of M$-\pi-\pi$ motifs in chemistry and biology. The database analysis reveals the following points: (a) There is a high occurrence of M$-\pi$ and M$-\pi-\pi$ interactions in chemistry and biology. (b) The prevalence of M$-\pi-\pi$ is seen to be higher *in most cases* or comparable to that of exclusively M$-\pi$ configurations. (c) The number of M$-\pi-\pi$ motifs present is only marginally lower than the number of metal ions available. The nonavailability of enough metal ions appears to be a reason that a small percentage of $\pi-\pi$ interactions are metal ion assisted (Supporting Information). (d) In proteins, the aromatic amino acid side chains seem

to prefer the PD-M and TB-M orientations (Scheme 1). As all the histidine interactions need not be essentially of π-type with the metal ion, we have also considered the situation where the M$-$histidine interactions are removed. Essentially similar trends were observed.

Ab initio calculations are performed in this study to address the following questions: What is the effect of a metal ion on the subtle $\pi-\pi$ interactions? How do the two primary noncovalent interactions, namely, M$-\pi$ and $\pi-\pi$ interactions, influence each other? All calculations were done using the *Gaussian 03* program.[13] All the initial geometry optimizations were done at the MP2/6-31G* level followed by single-point calculations at the MP2/6-311++G** level. The Boys$-$Bernardi counterpoise method[14] was used for estimating the basis set superposition error (BSSE). The calculations were carried out with the C$-$C and C$-$H bond lengths fixed at 1.3915 and 1.0800 Å, respectively, as described by Gauss and co-workers.[15]

The interaction of the metal ion with the π-face of the three representative orientations, **S**, **PD**, **T**, of the benzene dimer results in four possibilities (Scheme 1). Table 1 gives the values of interaction energies between the free benzene and the benzene complexed with metal ion. Interestingly, when M = Li$^+$, there is a substantial increase in the $\pi-\pi$ interactions for the **S** and **PD** type, while the **T**-shaped stacking has a higher interaction energy only in the **TB-M** orientation. Essentially the same trends have been noticed for M = Na$^+$ and K$^+$, albeit to a minor extent. To our surprise, the enhancement of $\pi-\pi$ interaction in the presence of metal ion is quite substantial, especially when the metal has a higher charge. Table 1 reveals that a Mg^{2+} ion enhances the strength of the $\pi-\pi$ interactions by almost more than fivefold in three configurations, **S-M**, **PD-M**, and **TB-M**. Thus, with the $\pi-\pi$ interaction energy values around 17 kcal/mol, their strength of stabilization is quite substantial. Hence, the strengths of subtle $\pi-\pi$ interactions transform to substantial, under the influence of a dicationic metal. Importantly, the interaction between the two benzene rings in most orientations is enhanced to almost a comparable extent, except in **TA-M**. It indicates that the metal ions stabilize the $\pi-\pi$ interactions in most orientations. The influence that the M ion has on the first ring could be the major source of the enhanced interaction. Interestingly, interaction of the metal ion with a single benzene molecule is much lower compared to the interaction of the metal ion with a benzene dimer (Supporting Information and Table 2). Therefore, the metal ion has a preferential binding to a $\pi-\pi$ rather than a single π system. Thus, the present computational study clearly establishes that M$-\pi$ and $\pi-\pi$ interactions work in concert, augmenting each other. The relative influence of individual metal ion on the $\pi-\pi$ system in each considered cation$-\pi-\pi$ conformation is also been gauged with the calculated charges and total atomic charges (Supporting Information) of the carbon atoms.

After analyzing the role of metal ion in various configurations of the benzene dimers, we intend to explore the relative strength of metal ion binding to the two-benzene system. Table 2 collects the values of the interaction energies of the metal ion with the

TABLE 2: Interaction Energies (in kcal/mol) of the Metal Ion with the Benzene Monomer and Dimers

	S$-$M	PD-M	TA-M	TB-M	SW1[a]	SW2[a]	BM1[b]	BM2[b]
Li$^+$	−38.76	−38.36	−33.41	−39.45	−57.88	−33.98	−34.13	−4.73
Na$^+$	−23.83	−23.52	−19.39	−24.52	−35.57	−18.57	−20.26	−2.10
K$^+$	−19.81	−19.37	−15.82	−20.40	−28.78	−14.56	−16.64	−1.31
Mg^{2+}	−120.05	−120.13	−108.75	−119.71	−179.08	−127.60	−105.78	−40.59
Ca^{2+}	−82.66	−82.46	−74.03	−83.38	−125.49	−83.04	−71.57	−21.20

[a] In SW1 and SW2, both benzene rings have direct interaction with metal ion. [b] See Supporting Information.

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two $\pi-\pi$ units, which include two additional possibilities **SW1** and **SW2**, with a metal sandwiched between the π systems, and they are devoid of direct $\pi-\pi$ interactions (Scheme 1).[16] The computations reveal that, irrespective of the metal ion, the double-decker sandwich complexes of type **SW1** are most stable. The strength of interactions for the **SW2**-type isomer is lower for complexes with $\pi-\pi$ interactions for monovalent ions. In the case of dicationic complexes, the strength of **SW2** is comparable to or higher than that of M$-\pi-\pi$ interaction.

In summary, the combined database and computational study reveal that M$-\pi$ and $\pi-\pi$ interactions work in concert, and the subtle $\pi-\pi$ interaction become substantial in the presence of a metal ion. Quantum chemical calculations indicate that the metal ion assisted $\pi-\pi$ interaction strengths may become comparable in magnitude to that of the hydrogen bonding interaction. Interestingly, metal ions have a higher propensity to bind to an arene$-$arene dimer complex compared to a single arene. This cooperative effect of noncovalent interaction should be explored further to understand its role in the 3D aggregation of supramolecular entities and biomolecules.

Supporting Information Available: The reference codes, number of PDB and CSD structures containing M$-\pi-\pi$ motifs, the interaction energies of the various M$-\pi-\pi$ configurations at the MP2/6-31G* level, and the total energies at the MP2/6-31G* and MP2/6-311++G** levels. This material is available free of charge via the Internet at http://pubs.acs.org.

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