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# Reply to “Comment on ‘From Subtle to Substantial: Role of Metal Ions on $\pi$ – $\pi$ Interactions’”

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Cation– $\pi$  and  $\pi$ – $\pi$  interactions are shown to play an important role in determining the macromolecular structure.<sup>1,2</sup> In a recent letter<sup>3</sup> using the quantum mechanical calculations and database studies, we have shown the M– $\pi$  (where M = alkali and alkaline earth metal ion) and  $\pi$ – $\pi$  interactions work in concert and the subtle  $\pi$ – $\pi$  interaction becomes substantial in the presence of a metal ion. The computational calculations have revealed that the subtle  $\pi$ – $\pi$  interactions that are in the range 2–4 kcal/mol will become substantially significant, ranging from 6 to 17 kcal/mol in the presence of metal ion. Analysis of Brookhaven Protein Data Bank (PDB) and Cambridge Structural Database (CSD, CSD V5.26) reveal that M– $\pi$ – $\pi$  motifs do occur in both chemistry and biology.

In a comment to our paper, Chelli and Procacci expressed concern on the second aspect of the results, that is, the statistical analysis of the motifs found in the PDB.<sup>4</sup> Chelli and Procacci argue that in the metal–aromatic interactions, the metal ion approaches the aromatic moiety along the molecular plane ( $\sigma$ -type) rather than perpendicular to the molecular plane ( $\pi$ -type). From this analysis, they conclude that M– $\pi$  interactions have little role to play in protein stabilization. They also have shown that there is a disparity in the range of equilibrium bond lengths between the quantum chemical calculations and the X-ray structural data.

In a closer look at Figure 1, Chelli and Procacci<sup>4</sup> reveal that a large number of M–aromatic interactions are to be categorized as  $\sigma$ -type of interaction, albeit a nonnegligible number of M– $\pi$  interactions occur in case of each metal. Their analysis reveal that the M– $\pi$  type interactions are higher for Ca<sup>2+</sup> compared to that of Mg<sup>2+</sup>. We do admit that it is not proper to categorize all M–aromatic–aromatic interactions as M– $\pi$ – $\pi$ , but the occurrence of true M– $\pi$ – $\pi$  motifs is a reality (Figure 1). The

**TABLE 1: Percentage of Proteins Which Contain the Aromatic Motifs of the Total Proteins Considered Containing the Respective Metal Cation, and the Percentage of M– $\pi$ – $\pi$  Motifs of the Total Motifs Considering the Histidine Moiety as an Aromatic Motif**

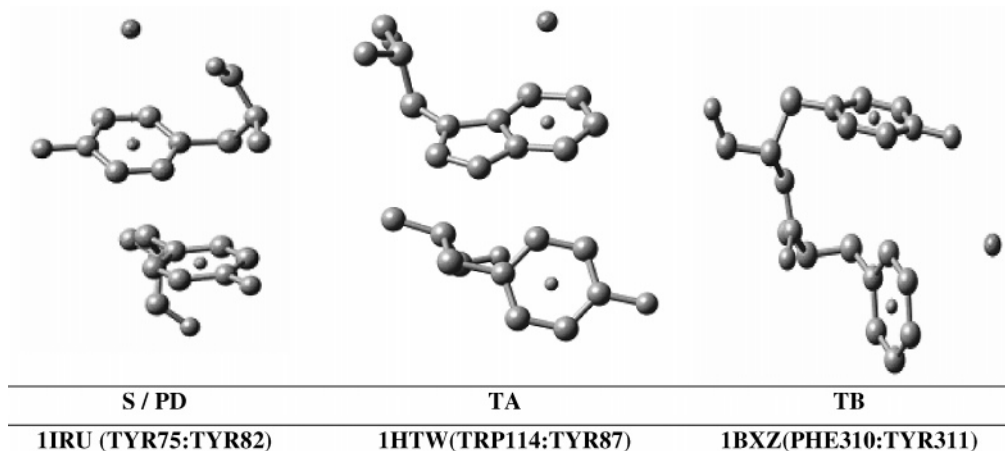
metal	% of protein having motifs	% of motifs with His
Na <sup>+</sup>	39.4	40.5
K <sup>+</sup>	43.5	37.9
Mg <sup>2+</sup>	29.8	68.8
Ca <sup>2+</sup>	48.2	37.6

CSD analysis also indicate that there are several examples of M– $\pi$ – $\pi$  motifs. Although the occurrence of M– $\pi$ – $\pi$  motifs is not ubiquitous in proteins, the analysis reveals that the majority of M– $\pi$  motifs are having an additional stacking interaction with another aromatic motif.

Analysis is carried out with all four metals to examine the argument of Chelli and Procacci on the disproportionately high occurrence of histidine moiety as an aromatic unit, which is invariably bound to the metal in a  $\sigma$  fashion. Table 1 which lists the percentage of His moieties in the M– $\pi$ – $\pi$  motifs, points out that Ca<sup>2+</sup> has a greater number of motifs involving tyrosine and phenylalanine rather than histidine, and therefore, the occurrence of His does not seem to be an issue. We would like to add that our database analysis was based on CSD and PDB. The occurrence of M– $\pi$  interactions is high among the CSD entries, and certainly, they are not rare in proteins. It is rather obvious from the foregoing analysis of ours and that of Chelli and Procacci that M– $\pi$ – $\pi$  interactions do occur in chemistry and biology. According to quantum chemical calculations, in such cases the M– $\pi$  and  $\pi$ – $\pi$  interactions are mutually stabilizing.

The second issue regarding the discrepancy between quantum chemical calculations and the structural database analysis regarding the magnitude of  $\pi$ – $\pi$  distances has already been pointed out earlier.<sup>5</sup> While the quantum chemical calculations are carried out on isolated species in the gas phase, the solvent and the other coordinations of the metal ion may be responsible for the disparity between the theoretical and experimental equilibrium bond lengths. The cutoff distance employed earlier<sup>3</sup> is based on the normalized distance distribution function derived from aromatic pairs in protein structure obtained from earlier studies.<sup>6</sup>

In summary, the proposal that we made in our paper was that the M– $\pi$  and  $\pi$ – $\pi$  interactions are mutually stabilizing



**Figure 1.** Snapshots of some representative S–M/PD, TA, and TB orientations with Mg<sup>2+</sup>. The PDB IDs and the residue number are also given. Several other examples of similar kind exists in the PDB.

and work in concert and their occurrence is common in biological and chemical molecules seem to hold well, and there is no evidence to prove that the above two noncovalent interactions do not work in concert. However, the main contention of Chelli and Procacci that M- $\pi$  interactions are not stabilizing in proteins, as the equilibrium distances are well over 4–5 Å where the interactions energies are negligible, is an important issue which needs to be probed further. We agree that while a good number of M- $\pi$  interactions originally proposed probably should be categorized as  $\sigma$ -type, it is true that several M- $\pi$ - $\pi$  motifs do occur.

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