Metal Influence on the Histidine Acidity

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Introduction

Histidine is often found as a ligand in metalloenzymes.\(^8,9\) The imidazole side group has two nitrogen atoms capable of being participated in metal binding. Hence, histidine can take on various metal-bound forms. Alkali metal ions such as Na\(^+\), K\(^+\) and to a lesser extent Li\(^+\) are so important in living organism. They have significant role in structure stability and reactivity of biomolecules.\(^11,12\) Based on theoretical studies, it appeared that the positions of metal ion binding sites play critical roles in determining the location of bond formations and disruptions in biochemical process.\(^13\)

In this paper, we have carried out a detailed study on a) the coordination modes and geometrical structures; b) binding energies of the complexes formed by Li\(^+\), Na\(^+\), K\(^+\) ions with different active sites in histidine; c) gas phase absolute metal ion affinities of histidine and its zwitterionic form; d) acidity of imidazole and carboxylic sites and the influence of metal ions on these two acidic sites.

Methods

Initial search of minima on the potential energy surface were carried out using SPARTAN software.\(^24\) the possible complexes were selected by considering the different coordination modes of ions on the most stable free conformers/tautomers of histidine. They were optimized using B3LYP /6-311++G**.

Results and Discussion

The Li\(^+\), Na\(^+\) and K\(^+\) affinities for histidine were determined by the density functional method using the hybrid B3LYP exchange correlation potential and the 6- 311++G (d, p) basis set. His-M\(^+\) bond energies decrease as the size of the metal ion
becomes larger. The affinities for histidine increase in the order $\text{Li}^+ > \text{Na}^+ > \text{K}^+$. The preferred metalation site for $\text{Li}^+$, $\text{Na}^+$ appears to be that in which the metals interact with oxygen and two nitrogen atoms of the histidine in a tricoordinated fashion. But $\text{K}^+$ cation preferred the oxygen atoms of histidine in its zwitterionic form. The presence of large cation such as $\text{K}^+$ reduces the energy gap between the complexes obtained by the zwitterion compared with canonical forms of histidine. The absolute metal ion affinity trend suggests that the interaction is influenced by the ionic contribution to the metal ion-ligand bond and thus the largest MIA corresponds to $\text{Li}^+$.

Regarding our current computational study, the proton dissociation energies of systems are dramatically reduced when they coordinate with metal ions. To ensure the increase in the acidity values of each acidic site of histidine upon metal complexation, we carried out DFT calculation employing the same method and basis set ($\text{B3LYP}/6-311++G**$). As expected, acidity values in the presence of metal ions become less endothermic by about 80 kcal/mol compared to those in the absence of metal ions in the absence of metal cation the acidity value for the system in which carboxylic acid is deprotonated (denoted by His- [COO\textsuperscript{-}]) is 340.9 kcal/mol, while corresponding value for the system in which imidazole nitrogen is deprotonated (denoted by His- [Im\textsuperscript{-}]) is 326.0 kcal/mol.

As illustrated in Fig. 3 (part B), it is interesting to mention that during the optimization process of His-[Im\textsuperscript{-}], a spontaneous proton transfer was occurred from the hydroxyl group to the imidazolate. Because of this proton transfer, Certainly 326.0 kcal/mol is not the actual acidity value for imidazole site. To confirm the value of 13 kcal/mol we decided to design a system very similar to histidine in which the proton transferred is restrained. Histidine methyl ester (denoted by His-OMe) was a good target. Interestingly, $\Delta H^\circ_{\text{acid}}$ value for imidazole group of His-OMe was computed to be 341.0 kcal/mol. This observation strongly suggests that the acidic strength of two acidic sites of histidine (i.e., imidazole and carboxylic group) is almost equal.

It is worth mentioning that upon metal complexation the above-discussed proton transfer is not observed because imidazolate as a monodendate ligand is involved in complexation through cation-n interaction. Our results obtained in the gas phase are the first theoretical indication that concerns the acidity of histidine in the absence and presence of metal ion. As expected results suggested that histidine proton dissociation value dramatically reduce upon metalation. The acidity values upon the metal complexation strongly reduce to 362.2, 364.1, and 362.8 for His- [Im\textsuperscript{-}]-$\text{Li}^+$, His- [Im\textsuperscript{-}]-$\text{Na}^+$ and His- [Im\textsuperscript{-}]-$\text{K}^+$, respectively. The corresponding values for His-[COO\textsuperscript{-}] are: 350.1, 352.6, 354.0 for his-[COO\textsuperscript{-}]-$\text{Li}^+$, his-[COO\textsuperscript{-}]-$\text{Na}^+$ and his-[COO\textsuperscript{-}]-$\text{K}^+$,
respectively. In fact, in some metalloenzymes, the presence of deprotonated histidine ligand has been suggested.\textsuperscript{36,37,38} These data imply that a histidine ligand is quite suitable for functioning as a proton donor or acceptor in metalloenzymes.

References

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