Nature of Metal Ion Mediated Second Shell Hydrogen Bonds

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Abstract

We investigate the role of induction effects in a zinc ion mediated second-shell hydrogen bond that plays a critical role in the mechanism of allosteric regulation in the paradigm sensor protein *Staphylococcus aureus* CzrA. These effects have been observed at other metal binding sites (MBSs). Natural Bond Order (NBO) and Symmetry-Adapted Perturbation Theory (SAPT) calculations on MBSs adopted from various proteins find that charge transfer (CT) effects withdraw greater charge from atoms participating in hydrogen bonding in the presence of Zn(II) than in the apo state. Polarization may play a significant role in helping strengthen the metal ion mediated hydrogen bond in CzrA and other metal sensor proteins. Furthermore, we find that ligand identity has an effect on second-shell hydrogen bonds.

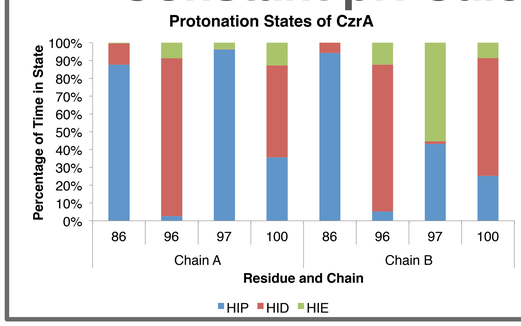
Introduction

- Metal ion binding attenuates the conformational sampling of the paradigm zinc sensor protein *Staphylococcus aureus* CzrA, helping regulate its allosteric mechanism of trascriptional repression.
- This effect is propagated from the MBS to the DNA binding site via a hydrogen bond network only observed in the metal bound state
- A second shell hydrogen plays a critical role in this mechanism.
- The role of electrostatics and induction in the formation of these bonds in CzrA and other metal binding proteins is examined.
- We aim to identify MBS motifs in nature that are likely to utilize similar effects in their mechanisms of function.

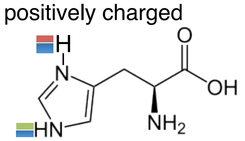
Methods

- Charge Transfer NBO calculations via Gaussian09
- SAPT0-CT Calculations performed by psi4 program
  - B3LYP-D/jun-cc-pvdz and 6-31g** used for CzrA
  - DF-HF and 6-31g** used for all other motifs
- MBS ligands are modeled in the metal binding protonation states
- 10 ns constant pH calculations performed using AMBER 15

Constant pH Calculations



- Experiments indicate that Zn(II)-binding results in a +1 change in charge at the MBS
- We find that Chain A His97 is commonly positively charged



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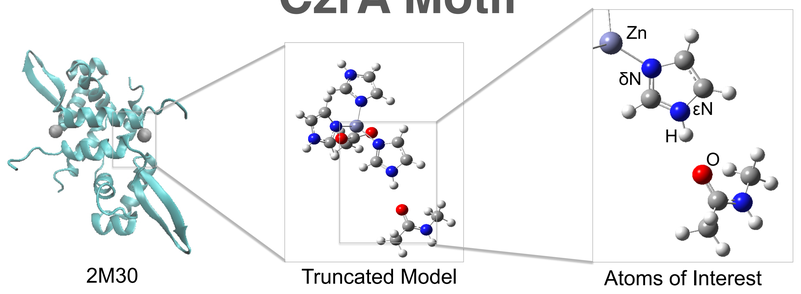
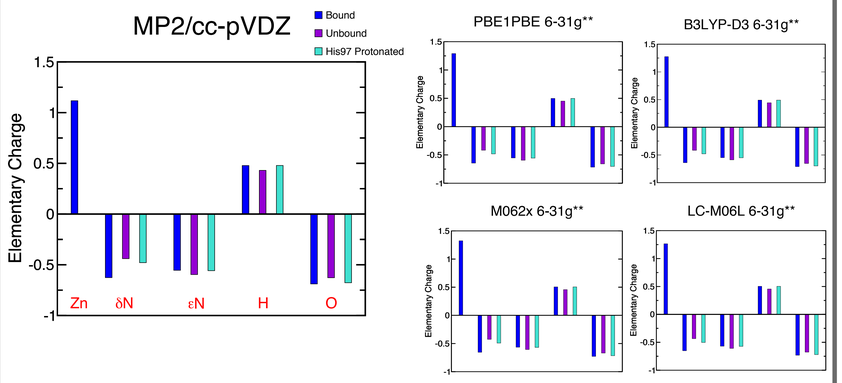
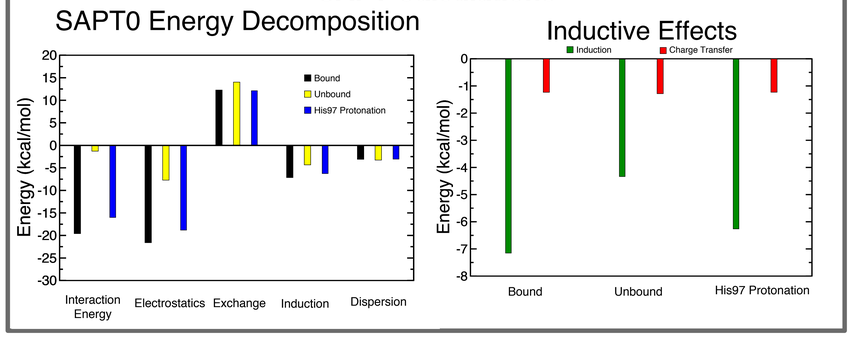
CzrA Motif



Effect of Functional on NBO Calculation

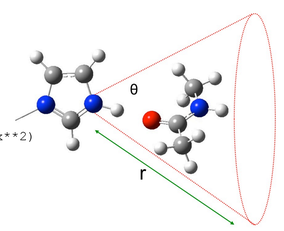


SAPT Calculations



Sampling Conformational Space

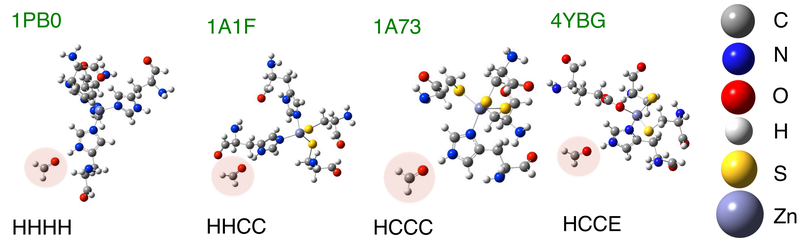
```
for d in range(26, 32):
    d = round((d * 0.1), 3)
    for x in range(0,32):
        x = round((x * 0.1), 3)
        for y in range(0,32):
            y = round((y * 0.1), 3)
            for z in range(0,32):
              z = round((z * 0.1), 3)
              if (((x**2) + (y**2) + (z**2)) <= (d**2)) and (((x**2)
              + (y**2) + (z**2)) >= (d**2)):
                print "This is the x value : %f" % (x)
                print "This is the y value : %f" % (y)
                print "This is the z value : %f" % (z)
```



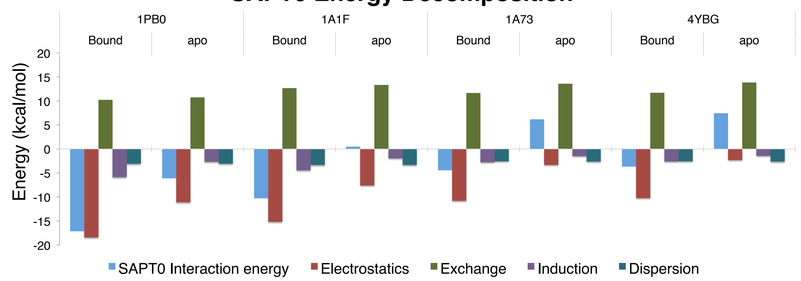
- Optimize hydrogen bond angle and distance for maximum charge transfer and inductive effects
- Wrote a python code that varies r and theta

Motif Analysis

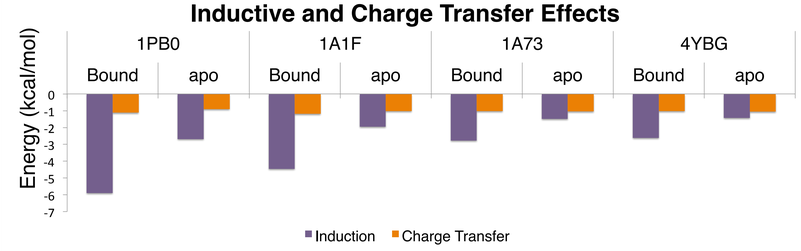
- Analyzed several other motifs for similar effects



SAPT0 Energy Decomposition



Inductive and Charge Transfer Effects



Summary

- Metal ion binding tends to promote second shell hydrogen bond interactions in these metal binding site motifs.
- CzrA Motif
  - Electrostatics and Exchange are dominant effects in interaction energy
  - CT effects do not account for the entirety of inductive effects
  - Key trends in CT and natural charge unaffected by functional and basis set
- Additional Motifs
  - Cys residues tend to reduce second-shell hydrogen bond interactions
  - Electrostatics and Exchange also dominate these motifs
  - Inductive effect varies greatly between bound and apo state
  - Dispersion effects remain relatively constant across states
- Second-shell CT effects fail to capture the entirety of the induction effect and may be overshadowed by polarization or first shell CT effects

References

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