Electronic Supplementary Material (ESI) for Physical Chemistry Chemical Physics.


# Supporting Information

## Key Determinants Governing a Metal-Bound Water is Deprotonated in Proteins

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**Supplementary Table S1**. Number of 90°, 109.5°, 120°, or 180° angles for an ideal geometry as a function of the number of metal-bound ligands.

| Geometry | # of ligands | # of 90° angles | # of 109.5° angles | # of 120° angles | # of 180° angles |
|---|---|---|---|---|---|
| $O_h$ | 6 | 12 | | | 3 |
| | 5 | 8 | | | 2 |
| | 4 | 5 | | | 1 |
| | 4 | 4 | | | 2 |
| | 3 | 2 | | | 1 |
| | 3 | 3 | | | |
| | 2 | 1 | | | |
| | 2 | | | | 1 |
| $T_d$ | 4 | | 6 | | |
| | 3 | | 3 | | |
| | 2 | | 1 | | |
| TBP or TP | 5 | 6 | | 3 | 1 |
| | 3 | | | 3 | |
| | 2 | | | 1 | |

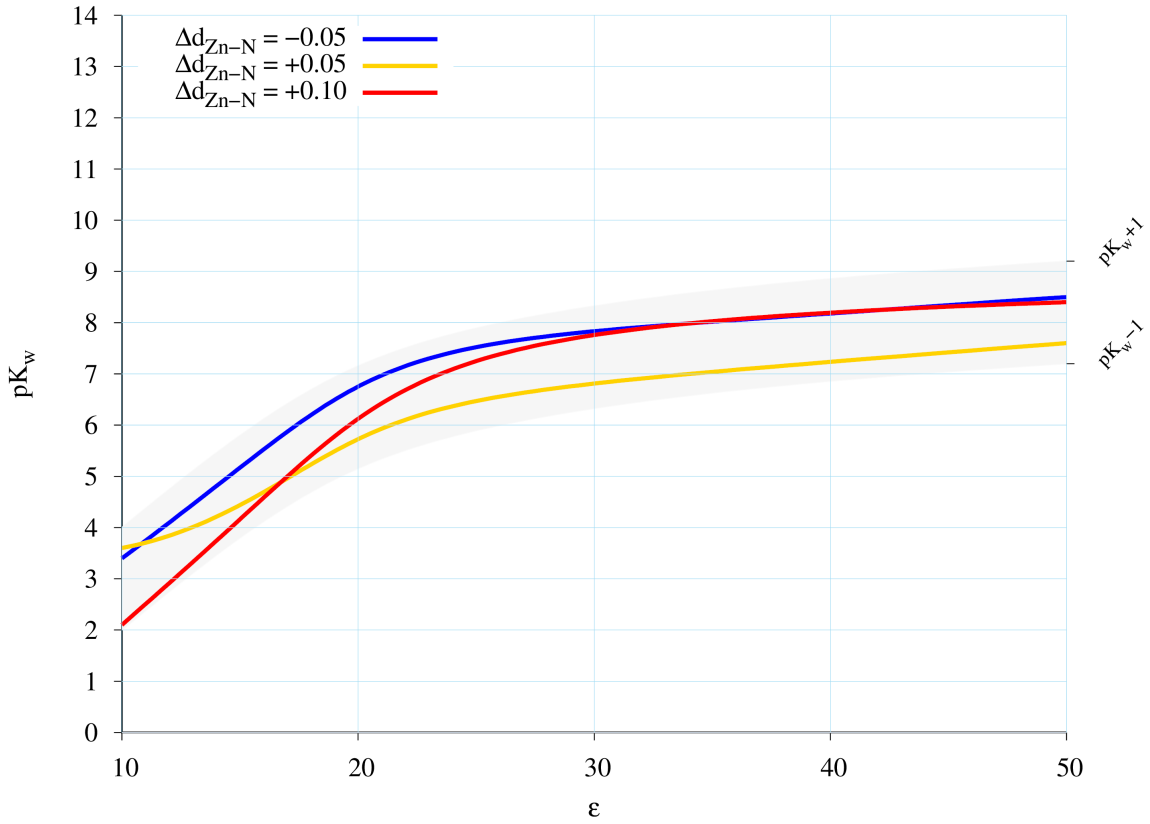



**Figure S1. Effect of changes in the $Zn^{2+}$–N distances on $pK_w(\varepsilon)$ of Zn-HHHw sites**. The grey region corresponds to ±1 $pK_w$ unit of the Zn-HHHw $pK_w$ values; the mean equilibrium $Zn^{2+}$–N distances is 2.01 Å for HHHw and 2.03 Å for HHHh in water, which remained the same when the HHH(w/h) systems were freely optimized at ε = 10. The blue, orange and red curves correspond to $Zn^{2+}$–N distances that deviate from equilibrium by –0.05, 0.05, and 0.10 Å, respectively.

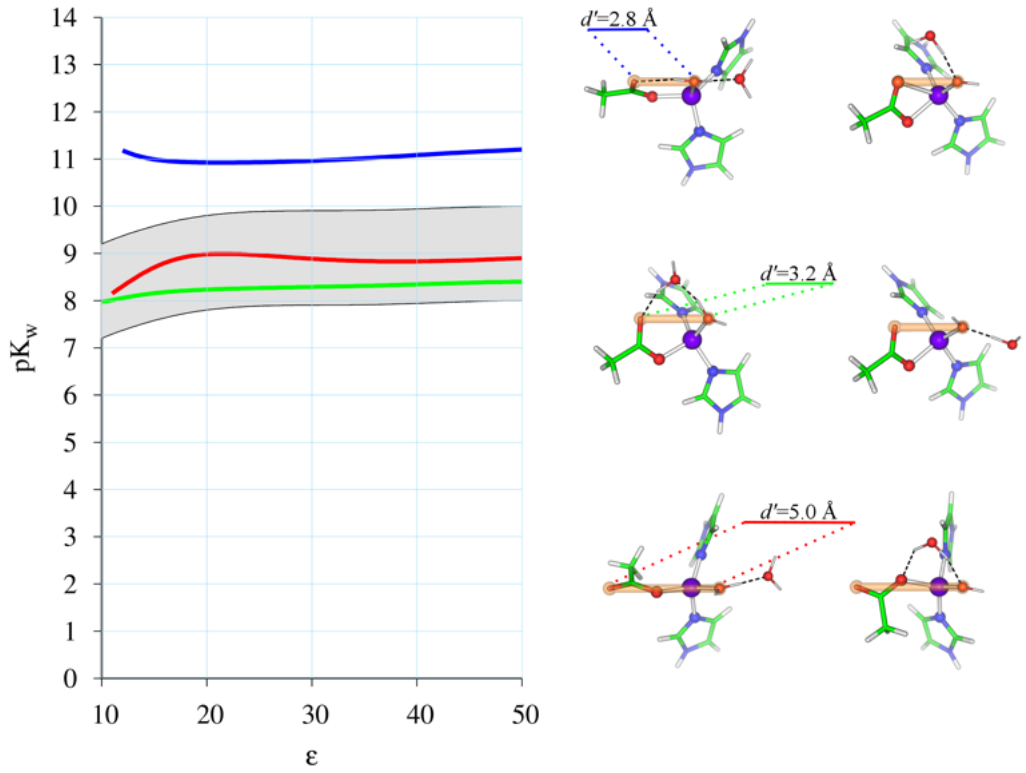



**Figure S2. Effect of the carboxylate orientation in DHHw sites on the $Zn^{2+}$-$pK_w$(ε).** To see how the carboxylate orientation may affect the $pK_w$ in DHHw sites, the distance between the non-coordinating carboxylate O and the water/hydroxide O (denoted as *d'*) was frozen at values ranging from 2.8 to 5.0 Å in increments of 0.2 Å. The blue, green, and red curves were derived by constraining the distance *d'* to 2.8, 3.2 and 5.0 Å, respectively. The optimized structures with *d'* constrained at these values are shown on the right. The grey area corresponds to the average $pK_w$±1 values obtained for *d'* greater than 2.8 Å. For various orientations of the carboxylate relative to the $Zn^{2+}$-bound water/hydroxide, the $pK_w$ exceeds 8, and when the metal-free carboxylate O is close to the hydroxide O (*d'* = 2.8 Å), the $pK_w$ curves shifts upwards by ~3 units

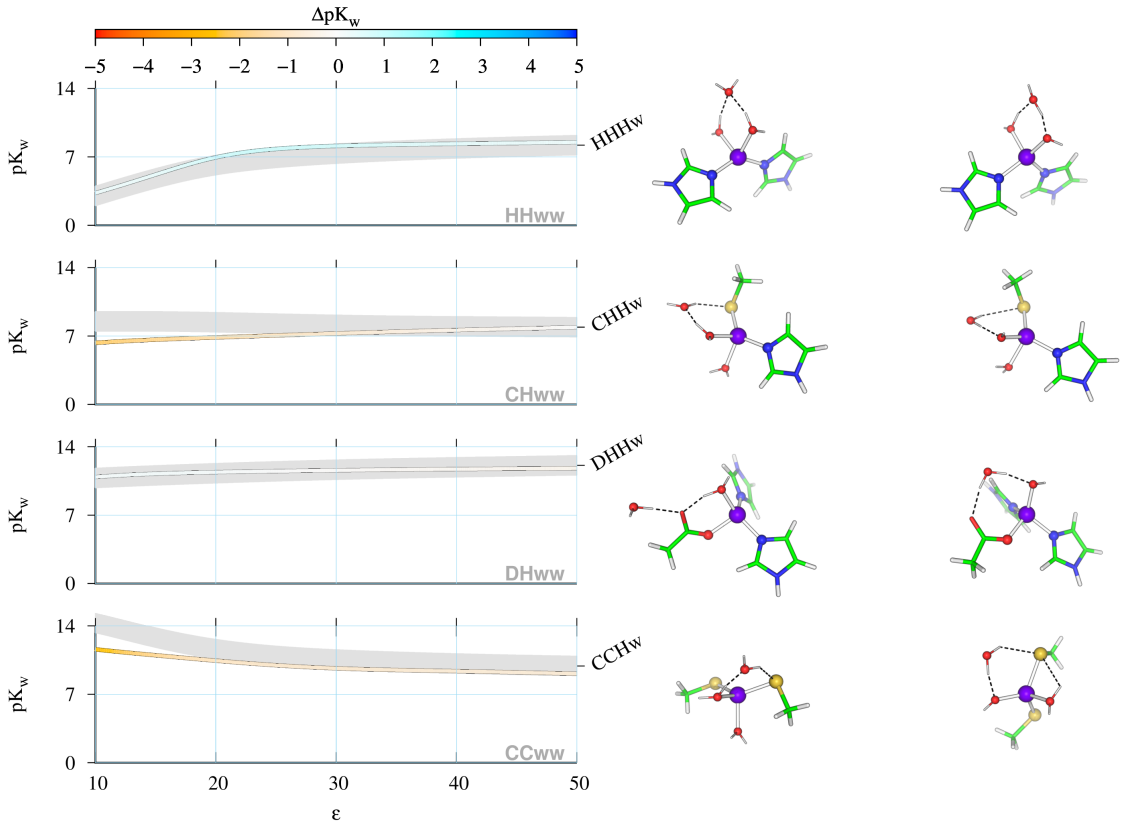



**Figure S3. Effect of substituting a His with water on the $pK_w(\varepsilon)$ of $[Zn\text{-}HHHw]^{2+}$, $[Zn\text{-}DHHw]^{+}$, $[Zn\text{-}CHHw]^{+}$, and $[Zn\text{-}CCHw]^{0}$ complexes.** The grey region corresponds to the $pK_w \pm 1$ values of the unsubstituted complexes. The $pK_w$ curves in each panel were derived from fully optimized structures shown on the right.

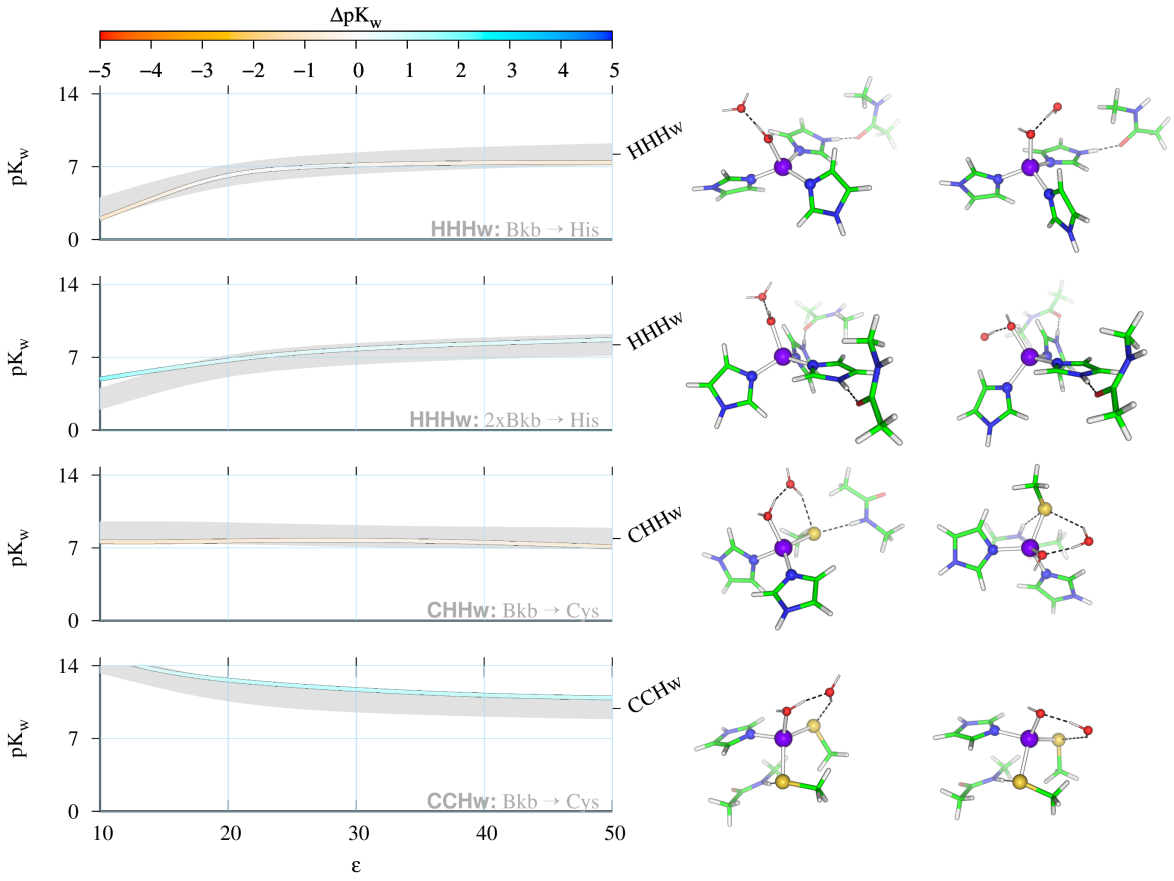



**Figure S4. Effect of HBs from 2$^{nd}$-shell backbone(s) to the $Zn^{2+}$-bound His/Cys in HHHw, CHHw, and CCHw sites on the $Zn^{2+}$-p$K_w$(ε).** Deviations from the p$K_w$±1 values of the isolated $[Zn\text{-}HHHw]^{2+}$, $[Zn\text{-}CHHw]^{+}$, and $[Zn\text{-}CCHw]^{0}$ complexes (grey region) due to backbone H-bonding interactions are shown by a color gradient. The fully optimized structures of the water or $OH^{-}$-bound $Zn^{2+}$ complexes in the presence of one or two backbone amides are shown on the right side.

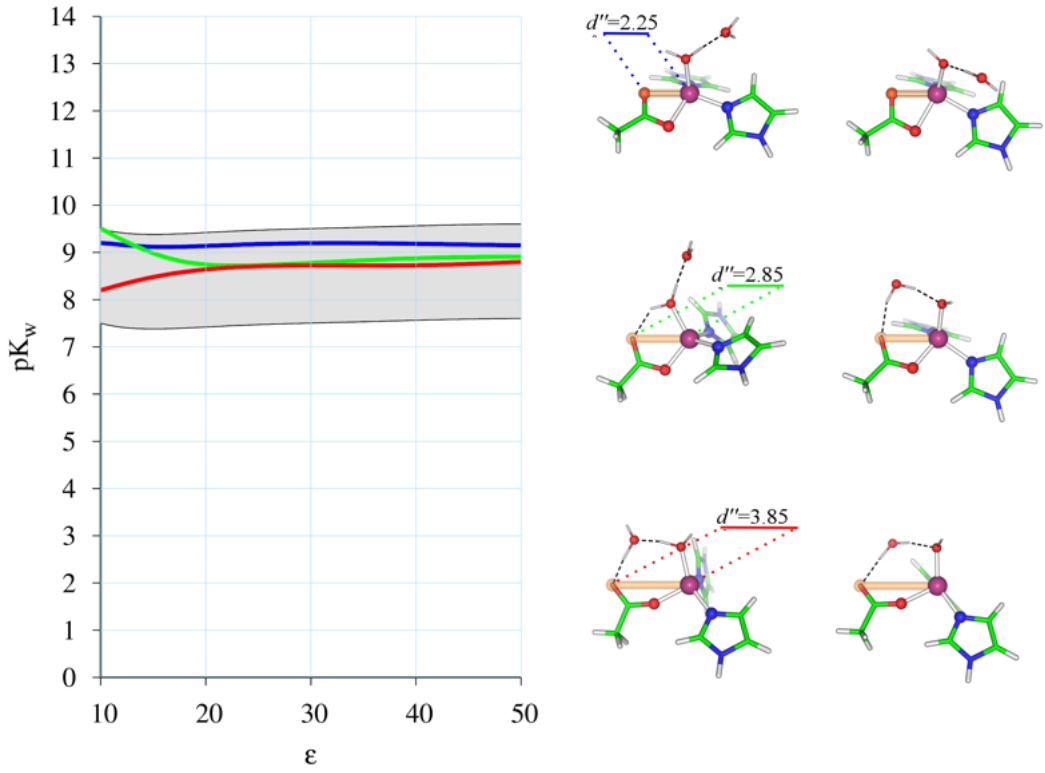
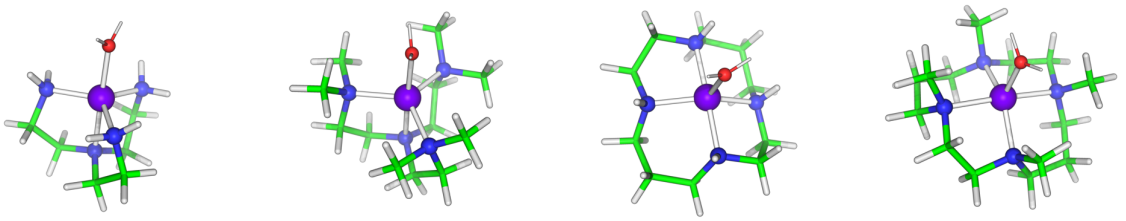



**Figure S5. Effect of the carboxylate-binding mode in DHHw sites on the $Zn^{2+}$-$pK_w(\varepsilon)$.** The blue, green, and red curves were derived by constraining the distance *d″* between the metal-free carboxylate O and the $Zn^{2+}$ to 2.25, 2.85 and 3.85 Å, respectively. The optimized structures with *d″* constrained at these values are shown on the right. The grey area corresponds to the average $pK_w$±1 values obtained for *d″* ranging between 2.25 and 2.85 Å, using an increment of 0.05 Å.



TREN (10.2) | $Me_6$TREN (8.9) | [14ane]-$N_4$ (9.8) | tetramethylcyclam (8.4)

**Figure S6. The $pK_w$ values of pairs of $Zn^{2+}$ complexes with and without methyl groups**