

**A Synergy Between the Catalytic and Structural Zn(II) Ions and the Enzyme
and Substrate Dynamics Underlies the Structure-Function Relationships of
Matrix Metalloproteinase Collagenolysis**

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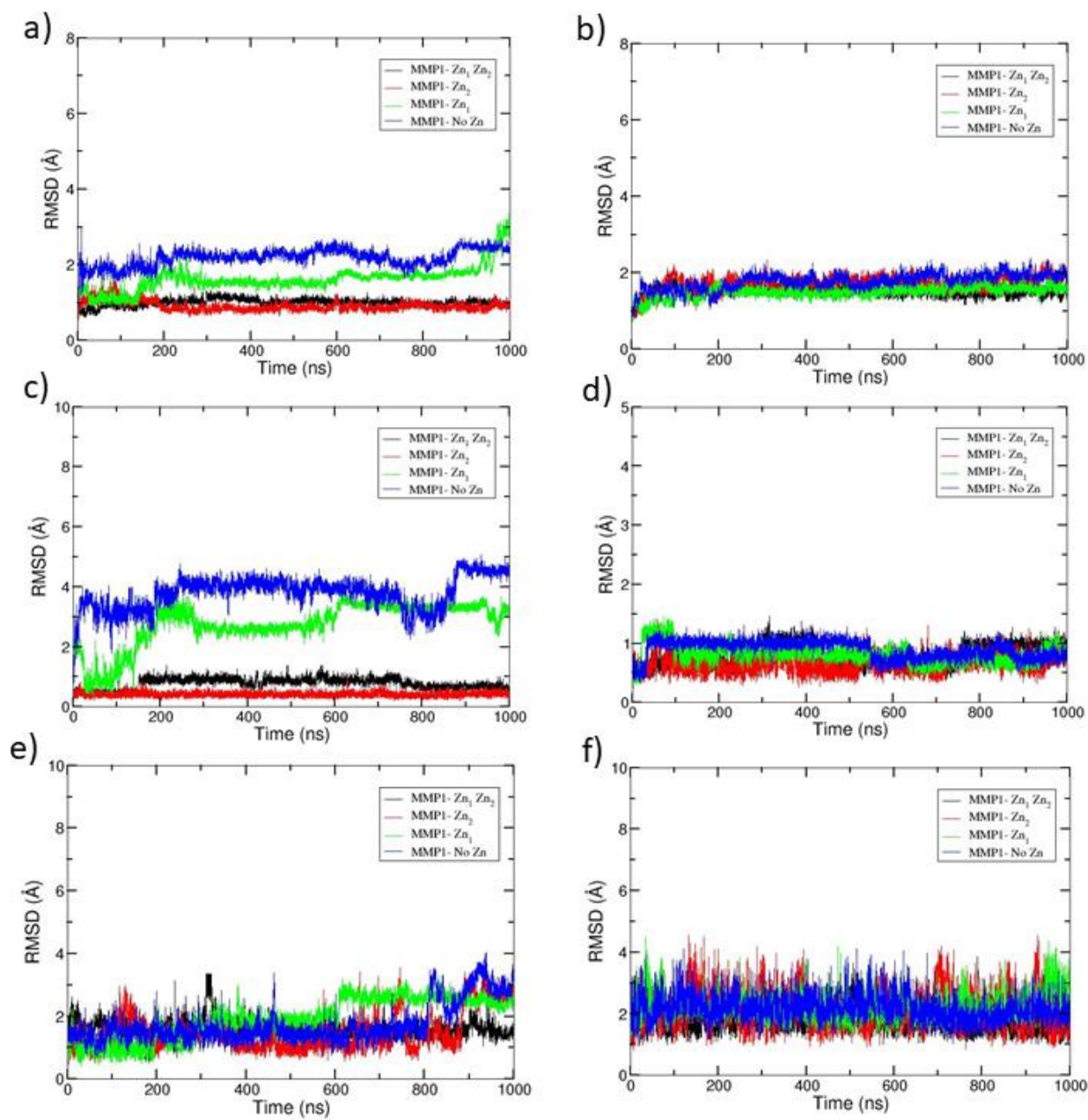


Fig. S1 Superimposed RMSDs of MMP-1 analogs: (MMP1 Zn₁ Zn₂) (black), (MMP1 Zn₁) (green), (MMP1 Zn₂) (red), and (MMP1 no Zn) (blue). a) RMSD of CAT domain. b) RMSD of HPX domain. c) RMSD of the S-loop. d) RMSD of the V-B loop. e) RMSD of the linker. f) RMSD of the THP.

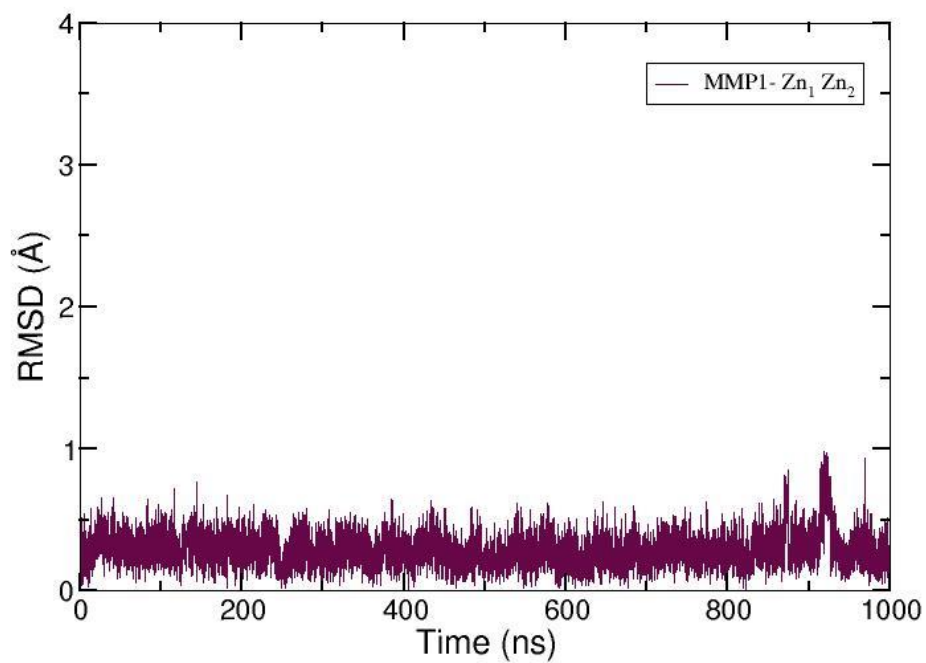


Fig. S2 RMSDs of the Ca(II) ions present in the CAT and HPX domains of (MMP1 Zn₁ Zn₂).

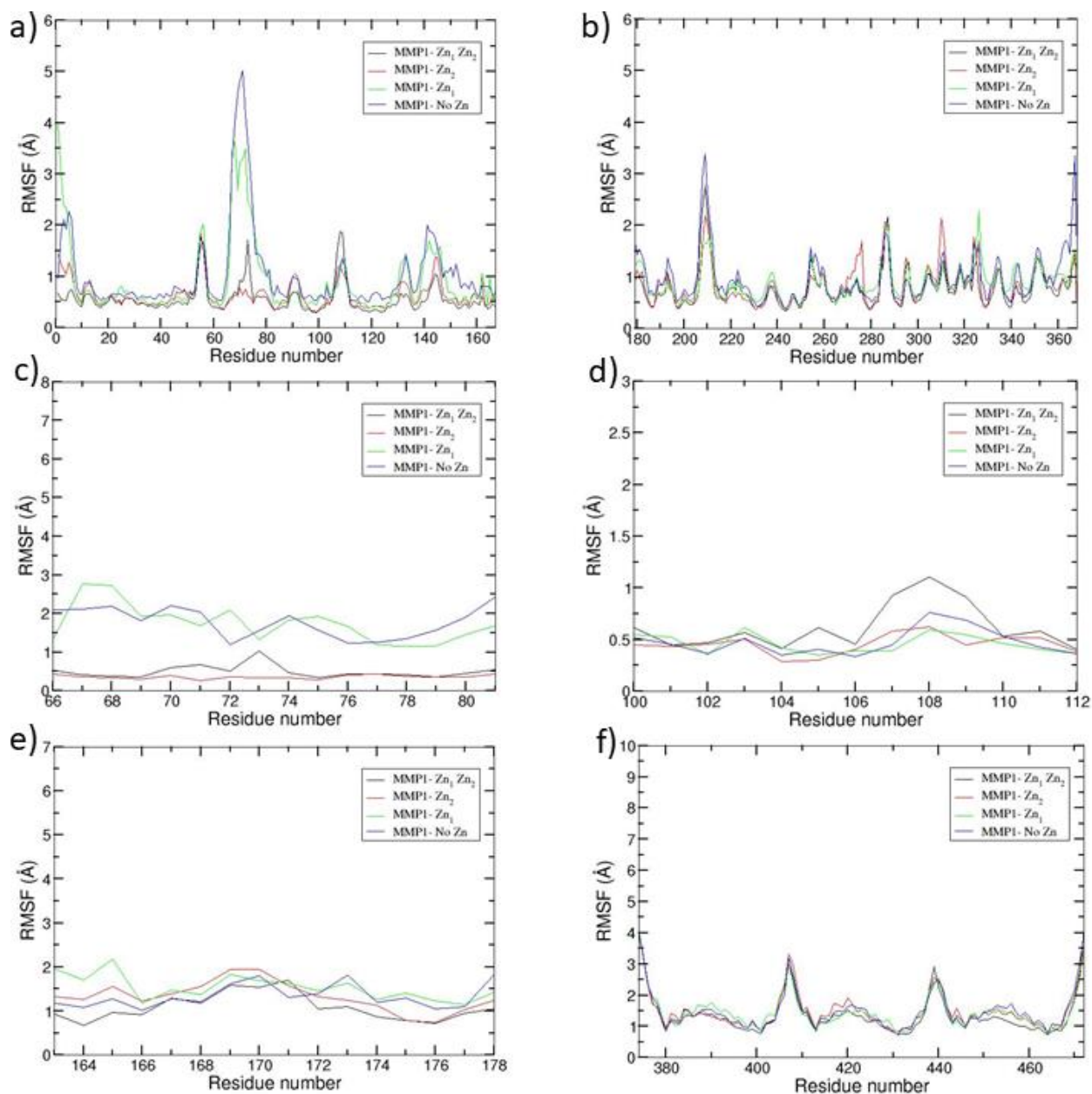


Fig. S3 Superimposed RMSFs of MMP-1 analogs: (MMP1 Zn₁ Zn₂) (black), (MMP1 Zn₁) (green), (MMP1 Zn₂) (red), and (MMP1 no Zn) (blue). a) RMSF of CAT domain: the x-axis numbering (residue numbers) corresponds to the crystal structure (PDB ID: 4AUO) numbering 81-242 and incorporating the Zn(II) and Ca(II) ions. b) RMSF of HPX domain: the x-axis numbering (residue numbers) corresponds to crystal structure numbering 259-447 and incorporating the Ca(II) ion; for uniformity, the HPX numbering for MMP-1 analogs have been modified to that of (MMP1 Zn₁

Zn₂). c) RMSF of the S-loop: the x-axis numbering (residue numbers) corresponds to 146-161. d) RMSF of the V-B loop: the x-axis numbering (residue numbers) corresponds to crystal structure numbering (residue numbers) 180-192. e) RMSF of the linker: the x-axis numbering corresponds to crystal structure numbering 243-258. f) RMSF of the THP: the x-axis numbering corresponds to crystal structure numbering (residue numbers) 963-995; for uniformity, the THP numbering for MMP-1 analogs have been modified to that of the (MMP-1 Zn₁ Zn₂)•THP.

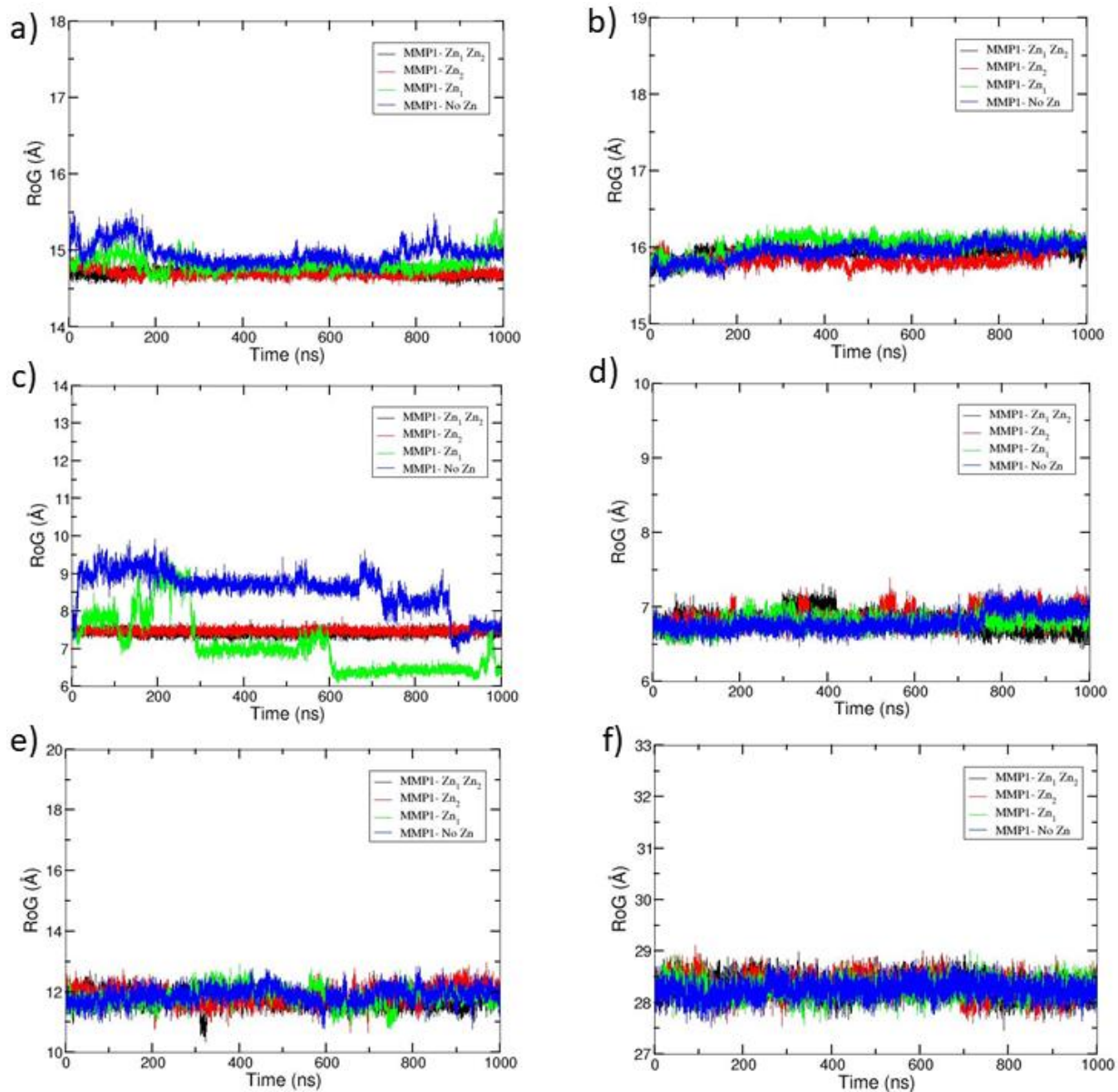


Fig. S4 Superimposed Radius of Gyration (RoG) of MMP-1 analogs: (MMP1 Zn₁ Zn₂) (black), (MMP1 Zn₁) (green), (MMP1 Zn₂) (red), and (MMP1 no Zn) (blue). a) RoG of CAT domain. b) RoG of HPX domain. c) RoG of the S-loop. d) RoG of the V-B loop. e) RoG of the linker. f) RoG of the THP.

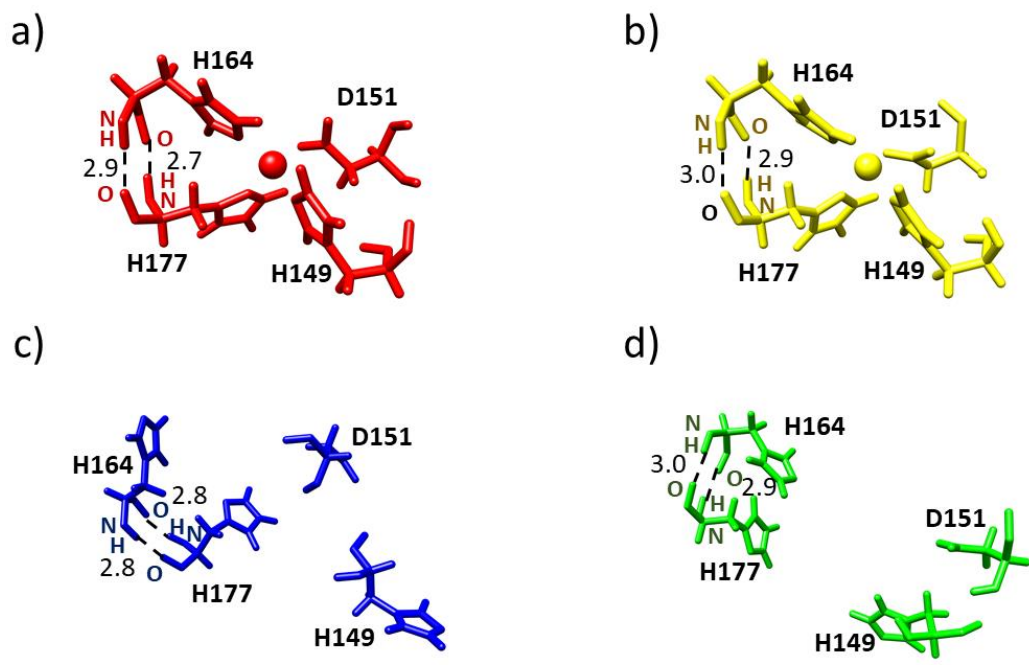


Fig. S5 Representation of hydrogen bonding interactions between H164 and H177 in the structural site of (MMP1 Zn₁ Zn₂) (red), (MMP1 Zn₂) (yellow), (MMP1 Zn₁) (blue), and (MMP1 no Zn) (green).

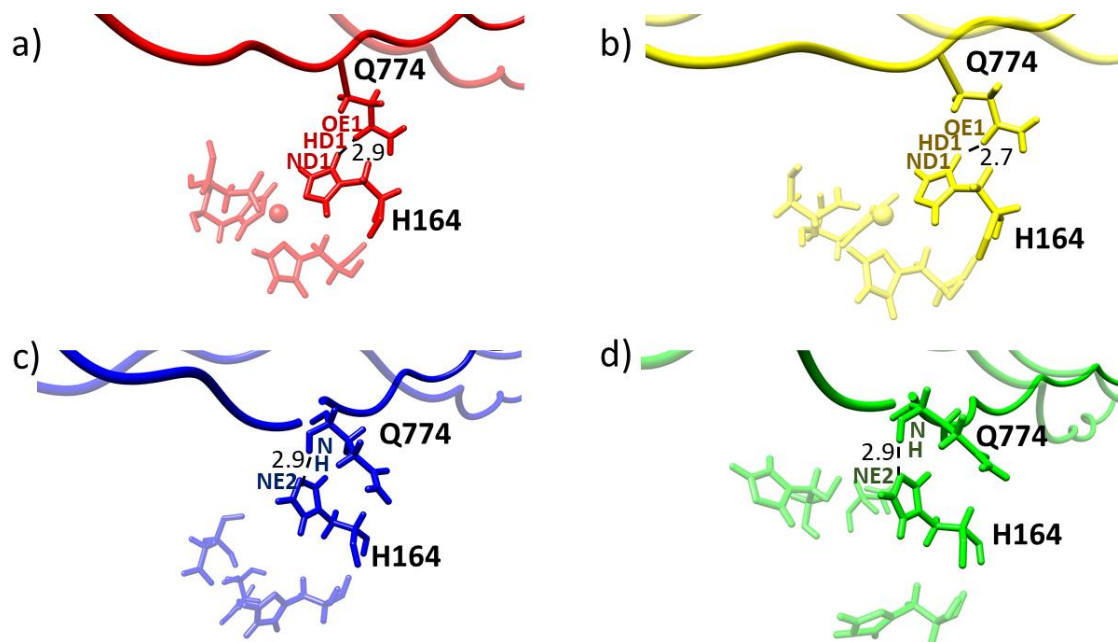


Fig. S6 Representation of hydrogen bonding interactions between H164 and Q774 of the T strand of the THP substrate of (MMP1 Zn₁ Zn₂) (red), (MMP1 Zn₂) (yellow), (MMP1 Zn₁) (blue), and (MMP1 no Zn) (green). The participating atoms in the hydrogen bonding interaction changed when structural Zn(II) is removed from the enzyme. The trend was also seen when the enzyme was devoid of both the Zn(II) ions.

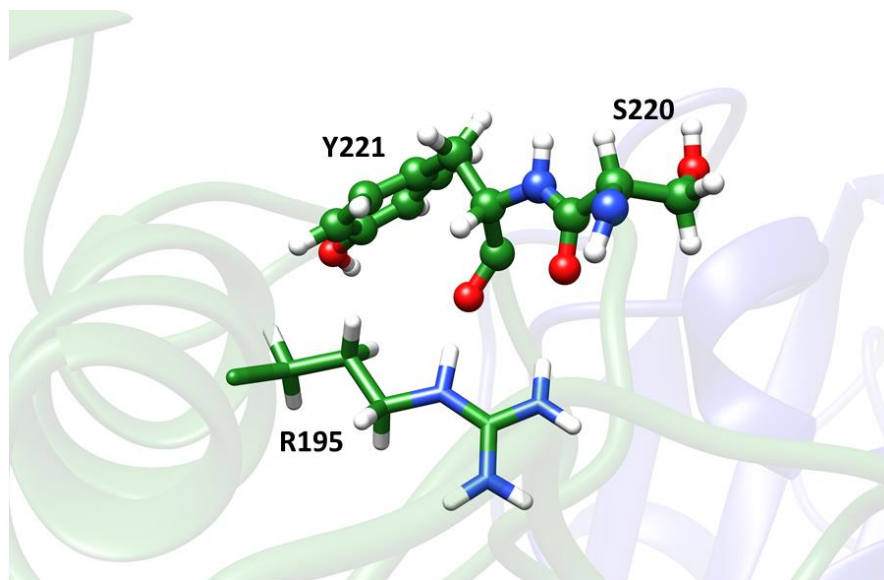


Fig. S7 Interaction of R195 with S220 and Y221 in (MMP1 Zn₁ Zn₂). [Crystal structure numbering]

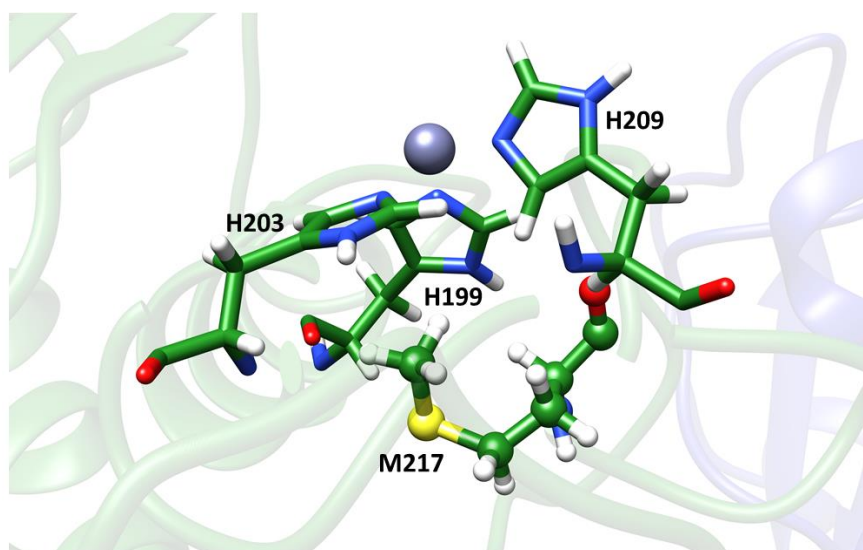


Fig. S8 The hydrophobic pillow formed by M217 below the catalytic site in (MMP1 Zn₁ Zn₂). [Crystal structure numbering]

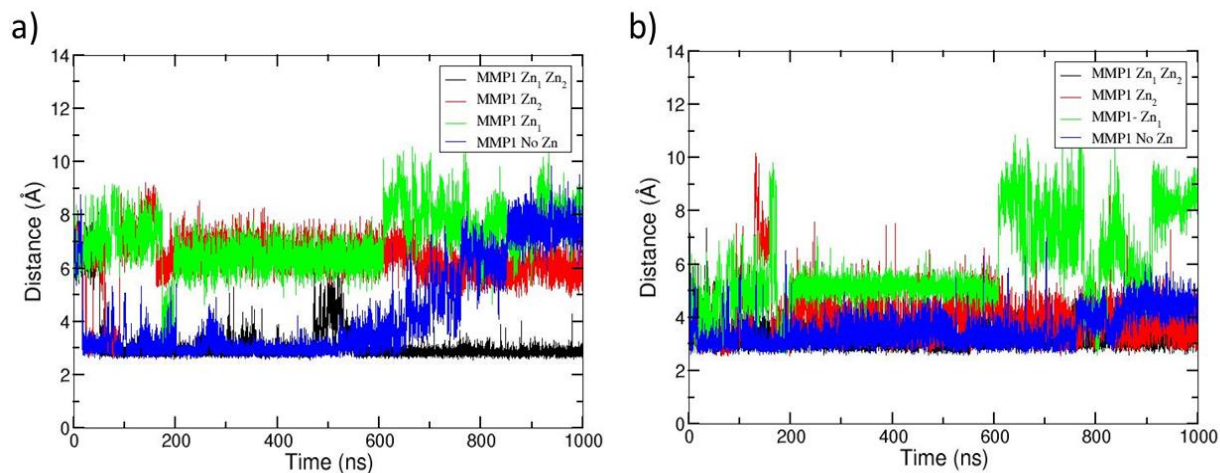


Fig. S9 a) Distances between donor nitrogen (NE) of R195 with acceptor oxygen (O) of Y221 in (MMP1 Zn₁ Zn₂) (black), (MMP1 Zn₁) (green), (MMP1 Zn₂) (red), and (MMP1 no Zn) (blue). R195 – Y221 hydrogen bond is lost when the Zn(II) ion is removed from the structural site. b) Distance between donor nitrogen hydrogen (NH₂) of R195 with acceptor oxygen (O) of S220 in (MMP1 Zn₁ Zn₂) (black), (MMP1 Zn₁) (green), (MMP1 Zn₂) (red), and (MMP1 no Zn) (blue). MMP-1 large fluctuations in hydrogen bonding distance occur with the removal of structural Zn(II) suggesting the necessity of the ion to maintain the bonding.

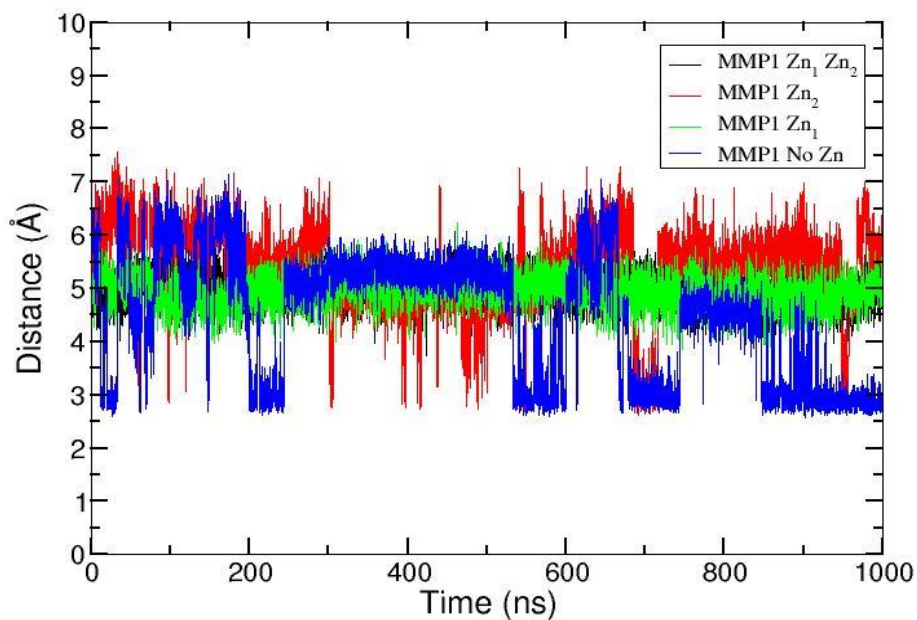


Fig. S10 Distances between the acceptor oxygen (O) of M217 and donor nitrogen (ND1) of catalytic site residue H209 in (MMP1 Zn₁ Zn₂) (black), (MMP1 Zn₁) (green), (MMP1 Zn₂) (red), and (MMP1 no Zn) (blue). Hydrogen bond formation takes place when both of the Zn(II) ions are removed from the system, which may alter the structural orientation of the catalytic site.