Electronic Supplementary Information

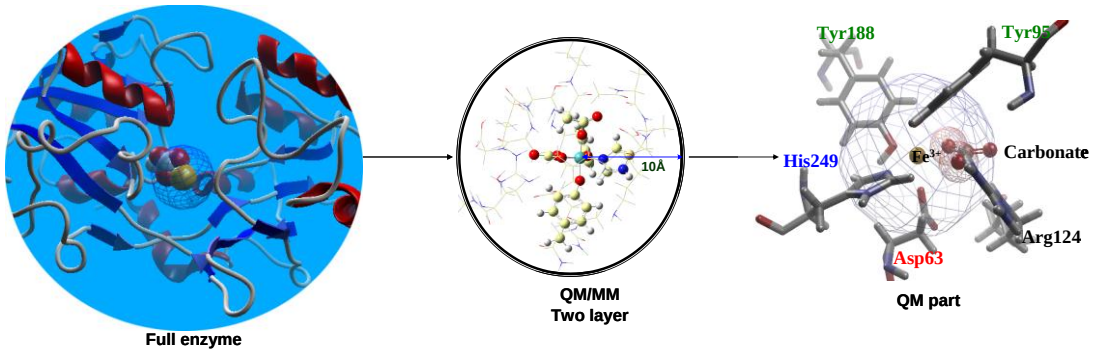
Reductionist Approach

Many problems especially in biology are less understood and this has made modeling these phenomena much more difficult. Problems of this sort have been chosen here and the available experimental information have been used to build the model with a view to gain further insights on them partycularly on the key step. The second main aspect to be mentioned here is the size of the biological systems. Still, even with a available technology, they are too big to be handled, therefore active sites are modeled at strategies like QM/MM have been used.

ESI-I (Computational Methods).

The high resolution N-lobe of human serum transferrin have been considered here for modeling as the metal ions in the C-lobe are rapidly replaced by Fe(III) than in the N-lobe. The structure of human serum transferrin (Tf) have been taken from Protein Data Bank (ID = 1A8E). Enzyme structure has been truncated at 10Å as a layer for ONIOM optimization with iron as a central point. The truncated enzyme structure used for ONIOM optimization is shown below (ESI-I). In this calculation, important active site residues Tyr188, Tyr95, His249, Asp63 and Arg124 with iron co-factor have been treated Quantum Mechanically (QM) and rest of the truncated part of enzyme has been treated using Molecular Mechanics (MM) method. Here Iron atom is replaced by bent metallocene metals (Ti, V, Nb and Mo)(ESI-I).

Geometry optimizations of the transferrin enzyme have been carried out by QM/MM approach using ONIOM method at B3LYP/LANL2DZ:UFF level. That is the metal-transferrin (MTf) coordination sphere Tyr188, Tyr95, His249, Asp63, Metal, the carbonate anion and the Arg124 residue have been treated quantum mechanically while the rest of the enzyme have been treated by molecular mechanics method at UFF level. The transition metal atoms have been treated using ECP and the valance shells including the 3d orbitals are descried by double-ζ basis sets with diffuse 3d functions.



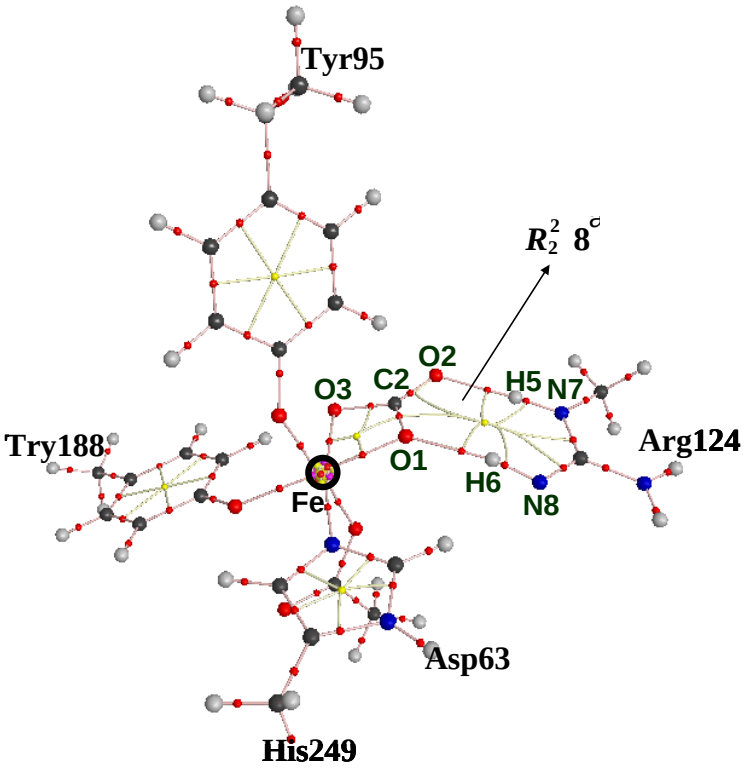
ESI-I. *Schematic representation of QM/MM layer selection of the M-Tf Sphere from the full enzyme*

From the QM/MM optimized transferrin, the M-Tf coordination sphere and the Arg124 residue has been taken to model the cleavage. B3LYP hybrid functional-Becke's three parameter non-local exchange functional with GGA correlation functional of Lee, Yang and Parr has been used. Stationary points located have been characterized as either minima or TS by computing their harmonic vibrational frequencies. TSs has a single imaginary frequency while all minima have real frequencies. In order to find out the weak interactions, the NBO analysis has been carried out for all the metal transferrin. The effect of solvent has been evaluated using the single point PCM (Polarizable Continuum Model) calculation at SCRF-B3LYP/LANL2DZ level with water solvent on the gas phase geometries. All calculations have been carried out using the G03 program and Crystal field splitting analysis has been carried out using ADF package. The Topological analysis also carried out for electronic structure characterization using AIM2000.

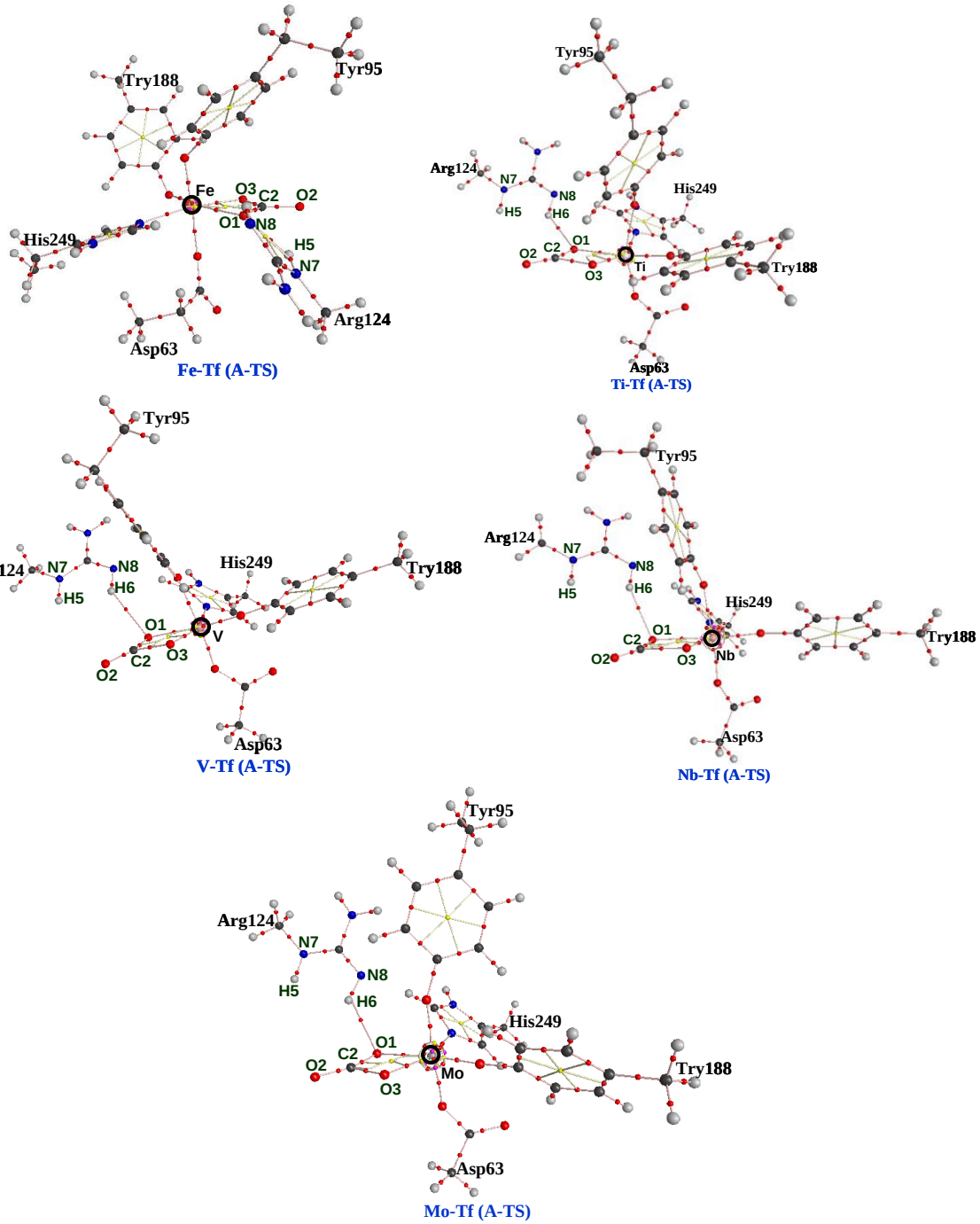
ESI-T1. Essential bond lengths (Å) of reactant, transition state (TS) and metal-oxo product (M-OP) of M-Tf sphere computed at B3LYP/LANL2DZ level

Bond*	Fe-Tf			Ti-Tf			V-Tf			Nb-Tf			Mo-Tf		
	R	TS	OP	Re	TS	OP	Re	TS	OP	R	TS	OP	R	TS	OP
M-O1	1.88	2.16	-	2.00	2.34	-	2.14	2.20	-	2.22	2.41	-	2.02	2.25	-
O1-C2	1.38	1.23	-	1.38	1.24	-	1.35	1.27	-	1.36	1.25	-	1.40	1.28	-
C2-O3	1.34	2.07	-	1.36	1.90	-	1.35	1.70	-	1.35	1.89	-	1.39	1.73	-
M-O3	1.96	1.68	1.62	1.93	1.72	1.65	1.93	1.71	1.58	2.08	1.83	1.74	2.02	1.83	1.71
C2-O4	1.25	1.19	-	1.24	1.19	-	1.26	1.20	-	1.25	1.19	-	1.22	1.19	-
O1-H5	1.88	2.53	-	1.68	2.49	-	1.73	2.51	-	1.71	2.37	-	1.96	2.56	-
O4-H6	1.79	2.63	-	1.52	3.51	-	1.53	3.49	-	1.57	3.49	-	2.94	4.i	-

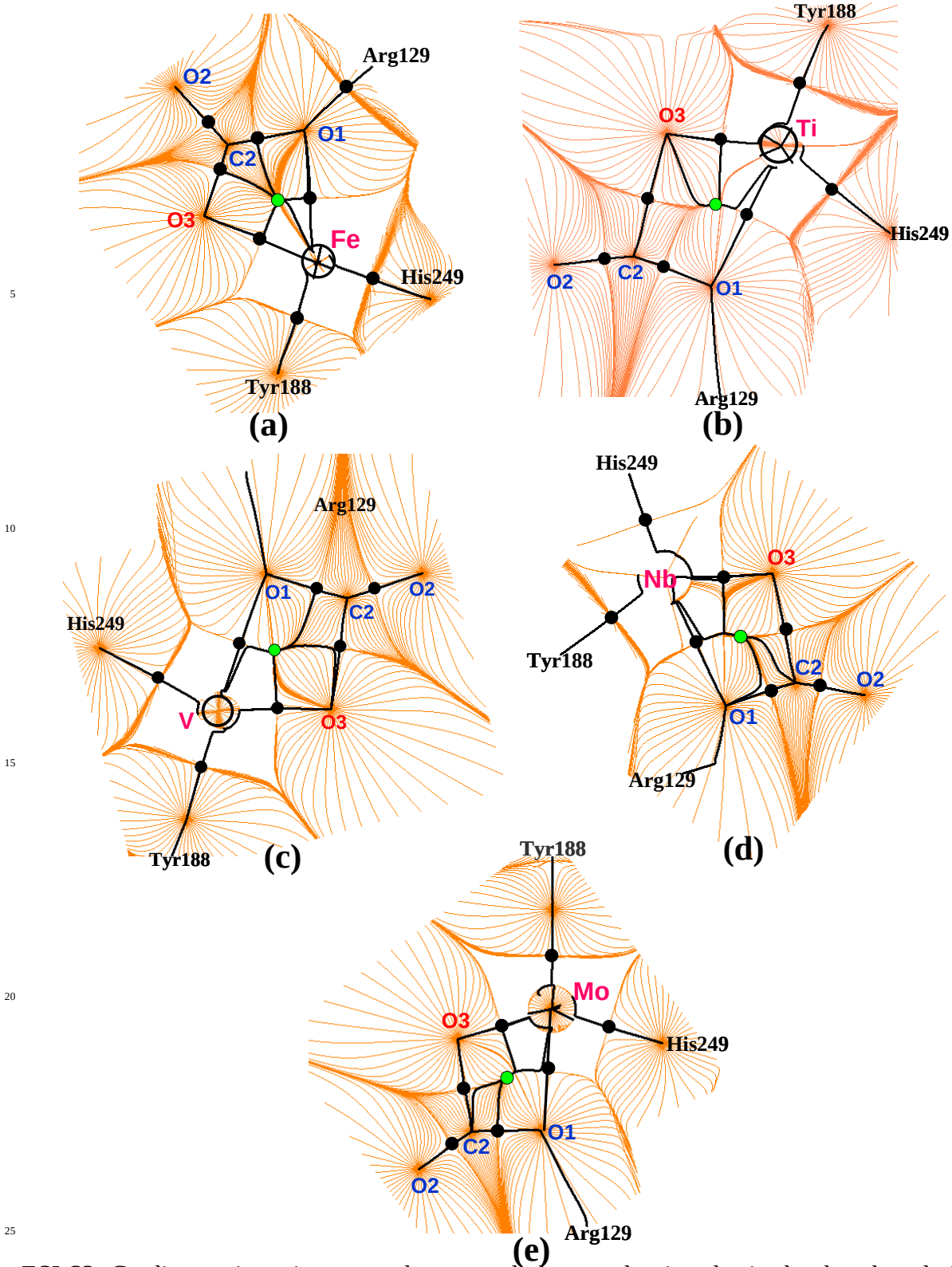
(*Atom numbering refers Fig. ESI-II)



ESI-S1. Molecular graph for metalloenzyme coordination part of transferring enzyme with active sites residues. The black, gray, red and blue spheres are carbon, hydrogen, oxygen and nitrogen atoms and small red and yellow spheres are (3, -1) bond critical points and (3, +1) ring critical points respectively.



ESI-S2. Molecular graph for transition state of decarboxylation reaction of Fe-Tf(A-TS), Ti-Tf(A-TS), V-Tf(A-TS), Nb-Tf(A-TS) and Mo-Tf(A-TS) complex with active sites residues. The black, gray, red and blue spheres are carbon, hydrogen, oxygen and nitrogen atoms and small red and yellow spheres are (3, -1) bond critical points and (3, +1) ring critical points respectively.



ESI-S3. Gradient trajectories mapped on a total electron density plot in the decarboxylation low energy transition state (A-TS) plane of Fe-Tf(a), Ti-Tf(b), V-Tf(c), Nb-Tf(d) and Mo-Tf(e), showing the atom basins, bond path's (black lines), bond critical point's (black solid circles),and a ring critical point (green solid circle).