

Supporting information

**The Influence of Zinc(II) on Thioredoxin/Glutathione Disulfide Exchange:
QM/MM Studies to Explore How Zinc(II) Accelerates Exchange in Higher
Dielectric Environments**

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Table S1: Comparison of structural parameters in full protein PDB structure, optimized structure, Zn-bound Trx, Glutathione-bound Trx, and isolated active site.

	Angle parameters (°)	Protein PDB structure	ONIOM optimized structure	Zn bound Trx	Glutathionyl ated Trx	Isolated active site		Bond parameters (Å)	Protein PDB structure	ONIOM optimized structure	Zn bound Trx	Glutathionyla ted Trx	Isolated active site
Cys32	S-C ₃ -C ₂	107.9	116.22	115.08	114.16	113.12	Cys32	S-C ₃	1.805	1.853	1.862	1.84	1.84
	C ₃ -C ₂ -C ₁	112.57	115.99	114.25	111.05	113.15		C ₃ -C ₂	1.524	1.558	1.549	1.533	1.537
	C ₃ -S-Zn			109.63				C ₂ -C ₁	1.528	1.543	1.547	1.533	1.522
	S-Zn-Cl			141.77				S-Zn			2.21		
	C ₂ -C ₃ -S-Zn			92.06			Gly33	N-C ₂	1.463	1.447	1.452	1.449	1.453
Gly33	N-C ₂ -C ₁	116.04	114.51	115.04	119.01	118.73		C ₂ -C ₁	1.537	1.534	1.536	1.531	1.54
Pro34	N ₁ -C ₂ -C ₃	104.89	104.15	103.65	103.76	103.39	Pro34	N ₁ -C ₅	1.461	1.481	1.486	1.484	1.469
	C ₃ -C ₄ -C ₅	103.92	103.51	103.76	103.92	103.29		N ₁ -C ₂	1.476	1.470	1.473	1.471	1.475
	N ₁ -C ₅ -C ₄	103.44	103.37	103.21	103.76	103.36	Cys35	S-C ₃	1.806	1.832	1.836	1.843	1.846
Cys35	S-C ₃ -C ₂	110.69	115.32	115.2	114.48	113.66		C ₃ -C ₂	1.53	1.535	1.537	1.532	1.531
	C ₃ -C ₂ -N	111.67	110.69	112.99	111.49	112.2		C ₂ -N	1.462	1.462	1.457	1.462	1.448
							Cys32-Cys35	S-S	3.67	3.54	4.09	3.51	3.78
								Cl1-Cl1	4.67	4.19	5.76	5.15	4.76

Table S2 : QM/MM transition state for the reaction between Trx (active site) and GSSG in water

C-C_3	19.266043240000	-13.406784030000	6.229732340000 H
C-C_R	18.717238380000	-14.523444540000	7.109639010000 H
O-O_R	18.529024850000	-15.666096240000	6.656448590000 H
C-C_3	18.222310430000	-12.723121420000	5.324628310000 H
S-S_3+2	17.015482190000	-11.656800790000	6.210086950000 H
H-H_	19.767717400000	-12.649340930000	6.837262270000 H
H-H_	18.754848120000	-12.126081530000	4.579239980000 H
H-H_	17.644318810000	-13.487382750000	4.790385300000 H
N-N_R	18.472360280000	-14.191248550000	8.392706450000 H
C-C_3	18.160060030000	-15.145869550000	9.445502000000 H
C-C_R	17.154140760000	-16.260707740000	9.128326750000 H
O-O_R	17.446565690000	-17.426533260000	9.411816690000 H
H-H_	18.601775290000	-13.211499150000	8.671075070000 H
H-H_	19.063204520000	-15.674152430000	9.768834640000 H
H-H_	17.798925770000	-14.565205570000	10.300510290000 H
N-N_R	15.949769160000	-15.939957370000	8.582731040000 H
C-C_3	14.957328560000	-16.998612760000	8.352667530000 H
C-C_R	15.145402550000	-17.782617320000	7.036783950000 H
O-O_R	14.335100100000	-18.669847960000	6.749618870000 H
C-C_3	13.617530670000	-16.239969070000	8.375910790000 H
C-C_3	13.988073490000	-14.865692790000	7.800406930000 H
C-C_3	15.378048970000	-14.587423450000	8.392831760000 H
H-H_	15.024916190000	-17.742830760000	9.150162940000 H
H-H_	12.847378000000	-16.765838320000	7.808185150000 H
H-H_	13.274525220000	-16.141252480000	9.411970790000 H
H-H_	14.050492220000	-14.918376350000	6.707339040000 H
H-H_	13.270437060000	-14.080685960000	8.052291120000 H
H-H_	15.998290110000	-13.974519670000	7.737867760000 H
H-H_	15.297605620000	-14.075568340000	9.359036820000 H
N-N_R	16.200255270000	-17.440179580000	6.262837880000 H
C-C_3	16.546724020000	-18.158098060000	5.045690380000 H
C-C_3	16.966609230000	-17.211174740000	3.921376160000 H
S-S_3+2	15.608697390000	-16.152461670000	3.259809490000 H
H-H_	16.882801790000	-16.765317880000	6.608225310000 H
H-H_	15.682912700000	-18.760340770000	4.758550880000 H
H-H_	17.788032710000	-16.570049670000	4.251925520000 H
H-H_	17.312539380000	-17.793716390000	3.062908790000 H
H-H_	15.314585380000	-15.524212970000	4.417125710000 H
O-O_R	26.020912920000	-6.461955690000	13.671281160000 M
C-C_R	25.997397980000	-7.670920800000	13.862892690000 M
C-C_3	26.241413990000	-8.614901740000	12.707707810000 M
C-C_3	25.028688810000	-9.532736710000	12.465789980000 M
H-H_	26.418517550000	-8.022213690000	11.781391660000 M
N-N_3	27.434130560000	-9.427483460000	12.954984190000 M
C-C_3	23.792100320000	-8.751069630000	11.998401320000 M
H-H_	24.790145070000	-10.094588110000	13.396260700000 M
H-H_	25.296696870000	-10.274968230000	11.681042610000 M
H-H_	28.256935670000	-8.790513650000	13.065380300000 M
H-H_	27.321035750000	-9.951719570000	13.853759520000 M
C-C_R	22.649893610000	-9.685965010000	11.708410020000 M
H-H_	24.047366380000	-8.170745120000	11.085626500000 M
H-H_	23.472363230000	-8.031725710000	12.782636450000 M
N-N_R	22.154887830000	-9.831200400000	10.364217940000 M H-H_ 56
O-O_R	22.146798980000	-10.317929430000	12.626159160000 M
H-H_	22.605209360000	-9.274373110000	9.602271920000 M
C-C_3	21.061851000000	-10.730294030000	10.004825630000 H
H-H_	20.654509240000	-11.196518400000	10.907926660000 H
C-C_3	19.918981760000	-9.929186410000	9.345892110000 H
C-C_2	21.585466540000	-11.804362560000	9.097464130000 M H-H_ 56
H-H_	19.642734940000	-9.084504790000	9.986914670000 H

H-H_	20.222926570000	-9.501782220000	8.381898960000 H
O-O_2	22.093573280000	-11.494451860000	8.029011610000 M H-H_ 7
N-N_3	21.502839270000	-13.187615640000	9.487334360000 M H-H_ 6
H-H_	21.036555530000	-13.433354920000	10.389901030000 M
C	22.049196630000	-14.279197810000	8.682478680000 M H-H_ 6
C-C_R	23.197207510000	-14.914400220000	9.404836900000 M
H-H_	21.261546830000	-15.042697130000	8.516986060000 M
H-H_	22.378490140000	-13.917437530000	7.684371060000 M
O-O_R	24.315857840000	-14.891196220000	8.908259130000 M
S	18.379116660000	-10.910758130000	9.061765620000 H
O-O_R	14.652703230000	-12.527393840000	14.025698570000 M
C-C_R	15.030264000000	-12.821722540000	12.902731480000 M H-H_ 73
C-C_3	14.958014270000	-11.792859040000	11.813152930000 H
N-N_R	15.498131250000	-14.071078010000	12.635989050000 M
N-N_R	13.574616720000	-11.348458790000	11.649339660000 M H-H_ 73
C-C_3	15.884912620000	-10.590787250000	12.104598570000 H
H-H_	15.293068030000	-12.225863660000	10.862779750000 H
C-C_3	15.556747900000	-15.152814570000	13.620363780000 M
H-H_	15.834824030000	-14.291948390000	11.673032930000 M
C-C_R	12.609693440000	-12.131105690000	11.066786520000 M
H-H_	13.288565250000	-10.432149170000	12.065076390000 M
H-H_	15.647179790000	-10.108887650000	13.062867980000 H
H-H_	15.755550480000	-9.819193580000	11.336839060000 H
S	17.677917590000	-10.993602260000	12.163491500000 H
C-C_R	14.695682430000	-16.292274380000	13.165478670000 M
H-H_	15.233099340000	-14.810662430000	14.627605470000 M
H-H_	16.605706590000	-15.506624020000	13.707350040000 M
C-C_3	11.202012850000	-11.625131120000	10.934679110000 M
O-O_R	12.882211260000	-13.248751170000	10.660151960000 M H-H_ 27
O-O_R	13.743740870000	-16.646291520000	13.848766360000 M
O-O_R	14.990976770000	-16.930684600000	11.978686030000 M H-H_ 15
C-C_3	11.130579790000	-10.469273230000	9.925545240000 M
H-H_	10.846298470000	-11.291481640000	11.933016450000 M
H-H_	10.539487640000	-12.450906710000	10.592531100000 M
H-H_	14.313103150000	-17.642367940000	11.840910080000 M
C-C_3	9.684995930000	-9.967920440000	9.716958230000 M
H-H_	11.774308150000	-9.628257280000	10.265753930000 M
H-H_	11.529966050000	-10.827381500000	8.950714390000 M
N-N_3	9.622514120000	-8.997725490000	8.622194060000 M
C-C_R	9.137884280000	-9.335903090000	10.971260660000 M
H-H_	9.045237990000	-10.837673890000	9.442312120000 M
H-H_	10.327031180000	-8.240966620000	8.784975230000 M
H-H_	9.885229880000	-9.479865550000	7.731696070000 M
O-O_R	8.148865020000	-9.816167320000	11.509995540000 M
O-O_R	9.757664290000	-8.221948420000	11.500485750000 M
H-H_	9.259382420000	-7.957992320000	12.317258450000 M
H-H_	20.016034830000	-13.873408660000	5.581121740000 H
H-H_	17.385223890000	-18.842596920000	5.241949590000 H
O-O_R	22.975778060000	-15.525504530000	10.621562450000 M
H-H_	23.844091770000	-15.883892790000	10.942102310000 M
O-O_R	25.748865070000	-8.180084890000	15.121512050000 M
H-H_	25.612869430000	-7.413143700000	15.736633980000 M

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112 111 1.000

Table S3 : QM/MM transition state for the reaction between zinc-bound Trx (active site) and GSSG in gas phase

C-C_3	14.474130730000	-10.056834540000	6.719557210000 H
C-C_R	13.787462760000	-9.977361910000	5.364389210000 H
O-O_R	12.564765340000	-9.783300230000	5.254474060000 H
C-C_3	13.680898950000	-10.909565210000	7.714384410000 H
H-H_	15.490753140000	-10.447075940000	6.620050940000 H
H-H_	14.176462440000	-10.891638220000	8.689021950000 H
H-H_	12.673592120000	-10.505828530000	7.838946170000 H
N-N_R	14.569338610000	-10.113416980000	4.273567830000 H
C-C_3	14.048104410000	-9.963461960000	2.924408410000 H
C-C_R	13.006297920000	-10.987349340000	2.439700650000 H
O-O_R	12.049819620000	-10.569491200000	1.771408260000 H
H-H_	15.561511340000	-10.261358800000	4.391798950000 H
H-H_	13.562552960000	-8.991121730000	2.815534140000 H
H-H_	14.900480740000	-9.995586300000	2.238824310000 H
N-N_R	13.191508530000	-12.311244770000	2.670175000000 H
C-C_3	12.346145280000	-13.279008570000	1.930130730000 H
C-C_R	10.960560910000	-13.493816170000	2.585483460000 H
O-O_R	10.742746160000	-14.467988990000	3.326703270000 H
C-C_3	13.192697750000	-14.561553770000	1.907849770000 H
C-C_3	14.068950560000	-14.454881320000	3.162681470000 H
C-C_3	14.389908410000	-12.959779590000	3.257536540000 H
H-H_	12.178090390000	-12.883582040000	0.924314840000 H
H-H_	12.572392000000	-15.458913340000	1.895128580000 H
H-H_	13.815685580000	-14.556884680000	1.007222020000 H
H-H_	13.505367630000	-14.770336580000	4.046632720000 H
H-H_	14.974375260000	-15.063583970000	3.098795280000 H
H-H_	14.540115320000	-12.638429620000	4.287929090000 H
H-H_	15.280207280000	-12.702812500000	2.669080190000 H
N-N_R	10.022578470000	-12.598298880000	2.226771230000 H
C-C_3	8.590860630000	-12.777740130000	2.435877420000 H
C-C_3	7.846068790000	-11.473591800000	2.715828180000 H
S-S_3+2	8.091420340000	-10.743198290000	4.393101530000 H
H-H_	10.351833450000	-11.808584970000	1.675235630000 H
H-H_	8.450826570000	-13.495599810000	3.244479800000 H
H-H_	8.155186300000	-10.692576400000	2.014929790000 H
H-H_	6.774894500000	-11.630431150000	2.573184880000 H
H-H_	7.270750880000	-11.579718560000	5.062245000000 H
S	13.580993570000	-12.662313450000	7.151767070000 H
Cl-Cl	9.887509100000	-13.099886360000	8.900724180000 H
O-O_R	20.639655240000	-8.989998450000	4.603390320000 M
C-C_R	19.480507400000	-9.365998140000	4.928782780000 M
C-C_3	19.090025710000	-9.418884060000	6.382616780000 M
C-C_3	18.740249860000	-10.861844320000	6.787648510000 M
H-H_	19.958209250000	-9.086839420000	6.996073860000 M
N-N_3	17.964941320000	-8.518482630000	6.646511860000 M
C-C_3	18.434203320000	-10.980198680000	8.287663870000 M
H-H_	19.604116590000	-11.520637450000	6.544097910000 M
H-H_	17.865862780000	-11.216160140000	6.200127090000 M
H-H_	18.267318120000	-7.538493400000	6.439780520000 M
H-H_	17.176169080000	-8.742265970000	5.997408710000 M
C-C_R	18.267961600000	-12.418207260000	8.680690530000 M
H-H_	17.501531600000	-10.428736820000	8.534020380000 M
H-H_	19.267600020000	-10.532248280000	8.872433680000 M
N-N_R	17.166339300000	-13.183161610000	8.170966900000 M H-H_ 57
O-O_R	19.110617050000	-12.953183290000	9.451355280000 M
H-H_	16.429340380000	-12.678039540000	7.632141320000 M
C-C_3	17.127437570000	-14.638631350000	8.255958270000 H
H-H_	17.297510380000	-14.915478790000	9.305313370000 H
C-C_3	15.743463430000	-15.209662290000	7.873597750000 H
C-C_R	18.226179780000	-15.243526140000	7.423244740000 M H-H_ 57

H-H_	15.416527570000	-14.950548050000	6.865687770000 H
H-H_	15.758351410000	-16.303616020000	7.938525000000 H
S-S_3+4	14.387052070000	-14.660408580000	8.990728870000 H
O-O_R	19.049941110000	-16.007754920000	7.994987150000 M
N-N_R	18.481105680000	-14.860626600000	6.058679390000 M
S	12.368807250000	-15.812738290000	7.305692670000 H
H-H_	19.353254290000	-15.251218840000	5.632807170000 M
C-C_3	11.332094830000	-16.666153180000	8.577421590000 H
C-C_3	10.627660690000	-17.923789690000	8.020104760000 H
H-H_	10.627020440000	-15.934295280000	8.980151890000 H
H-H_	12.014924510000	-16.947469630000	9.386294310000 H
N-N_R	9.734436640000	-17.570631560000	6.923299770000 M H-H_ 69
H-H_	11.404566710000	-18.608516530000	7.659231330000 H
C-C_R	9.844907420000	-18.611204220000	9.095690540000 M H-H_ 69
H-H_	9.081747460000	-16.765757570000	7.056394620000 M
C-C_R	9.737335420000	-18.249847550000	5.657389360000 M
O-O_R	10.168987520000	-19.780305520000	9.440157780000 M
N-N_R	8.739609230000	-17.948271390000	9.731547860000 M
C-C_3	8.915132460000	-17.726429070000	4.515958840000 M
O-O_R	10.456754270000	-19.270474140000	5.482163640000 M
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H-H_	18.949615610000	-9.659660450000	3.013302340000 M
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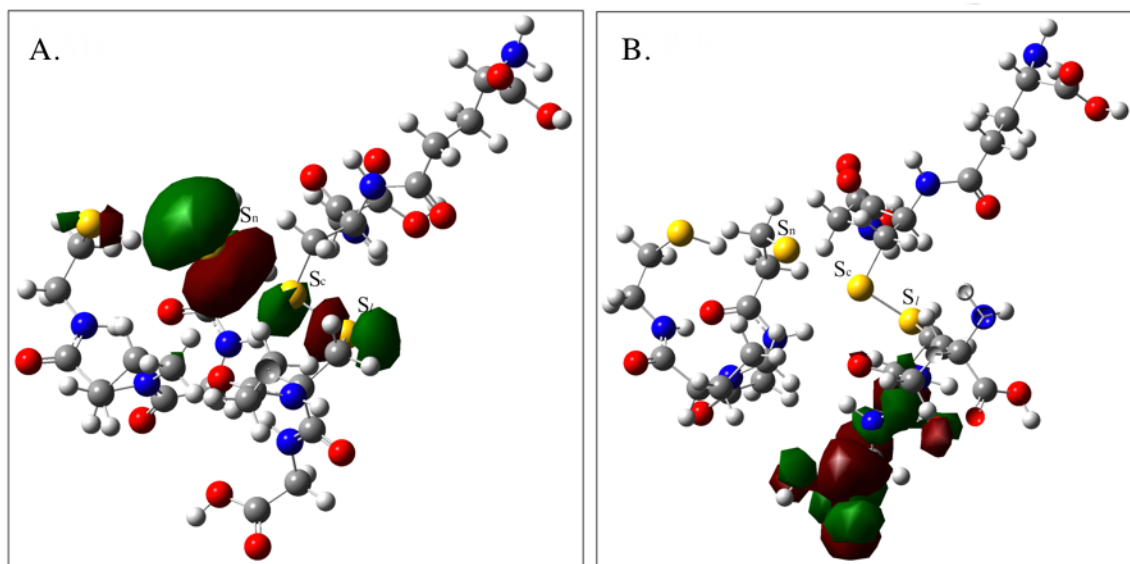


Figure: S1A (HOMO) & S1B (LUMO) for the reactant complex

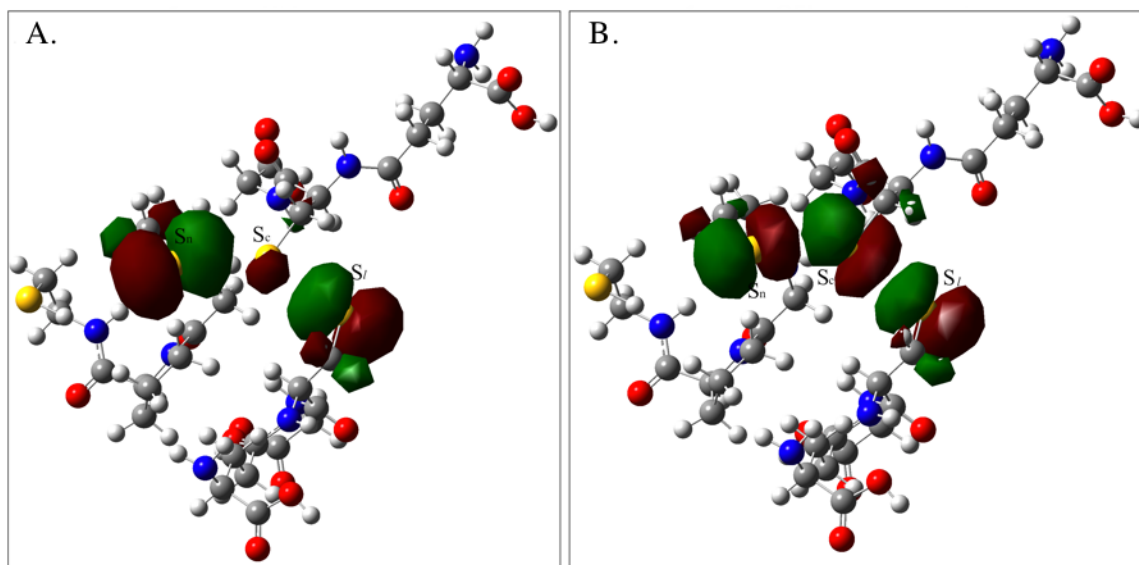


Figure: S2A (HOMO) & S2B (LUMO) for the transition state

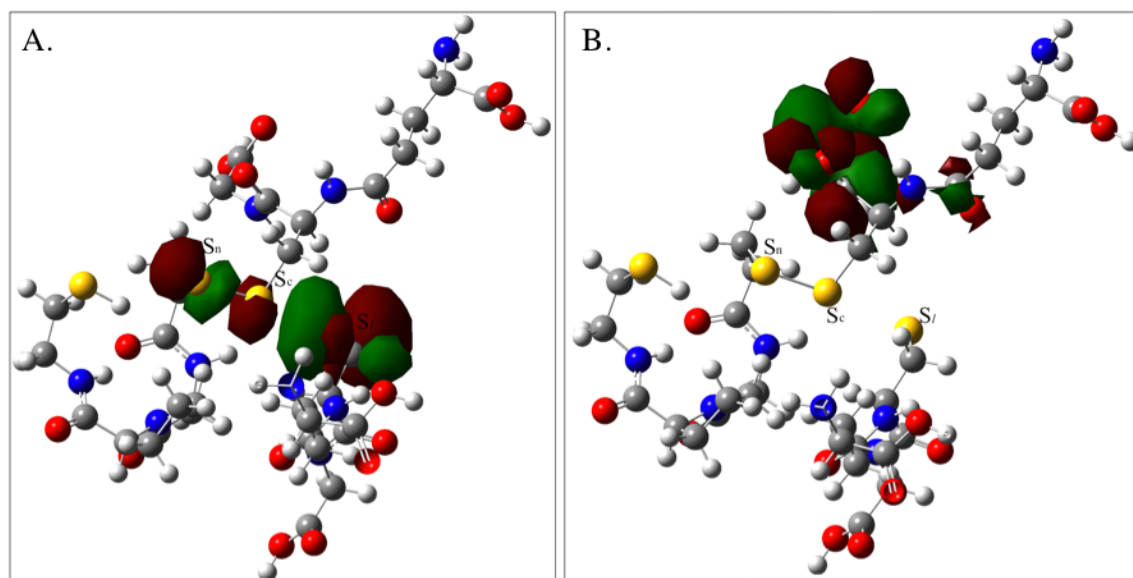


Figure: S3A (HOMO) & S3B (LUMO) for the product complex

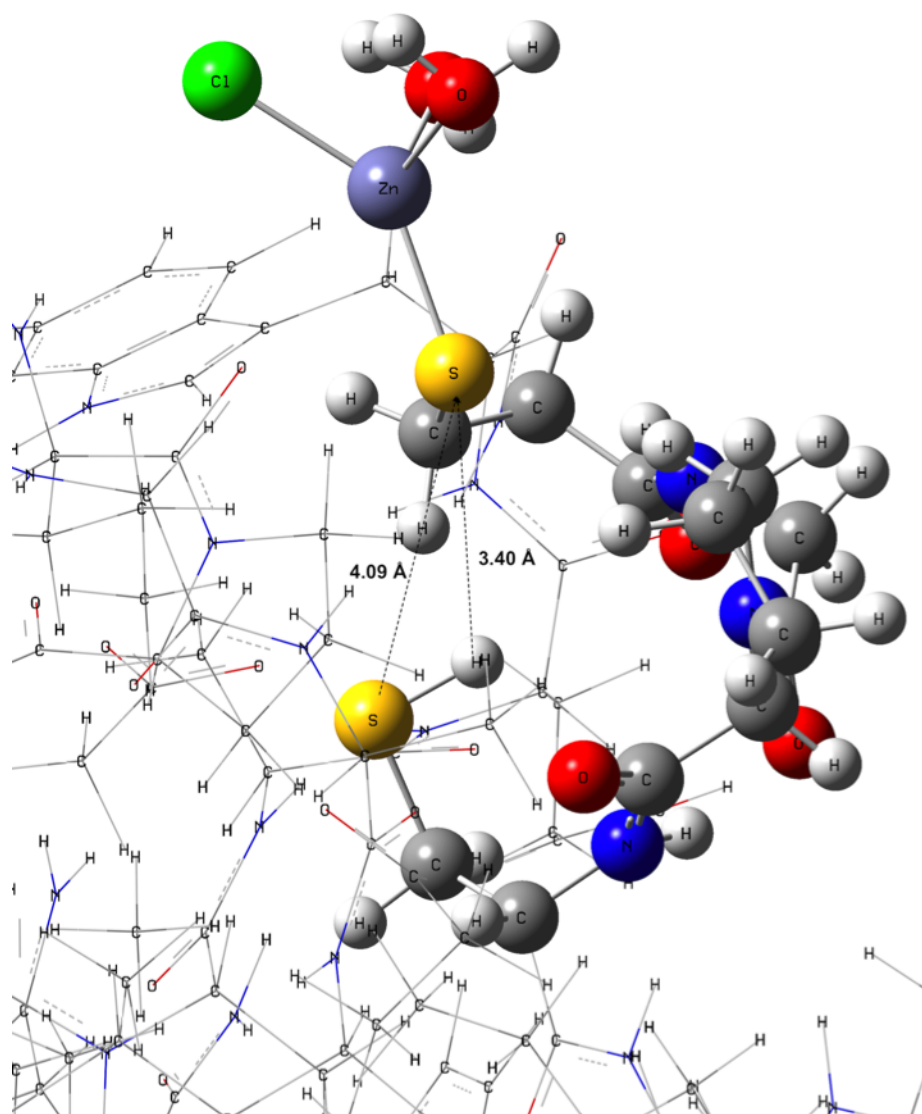


Figure S4: Zinc-bound Trx. Cys32, Gly33, Pro34, Cys35 residues and ZnCl(H₂O)₂ are shown as ball & stick model

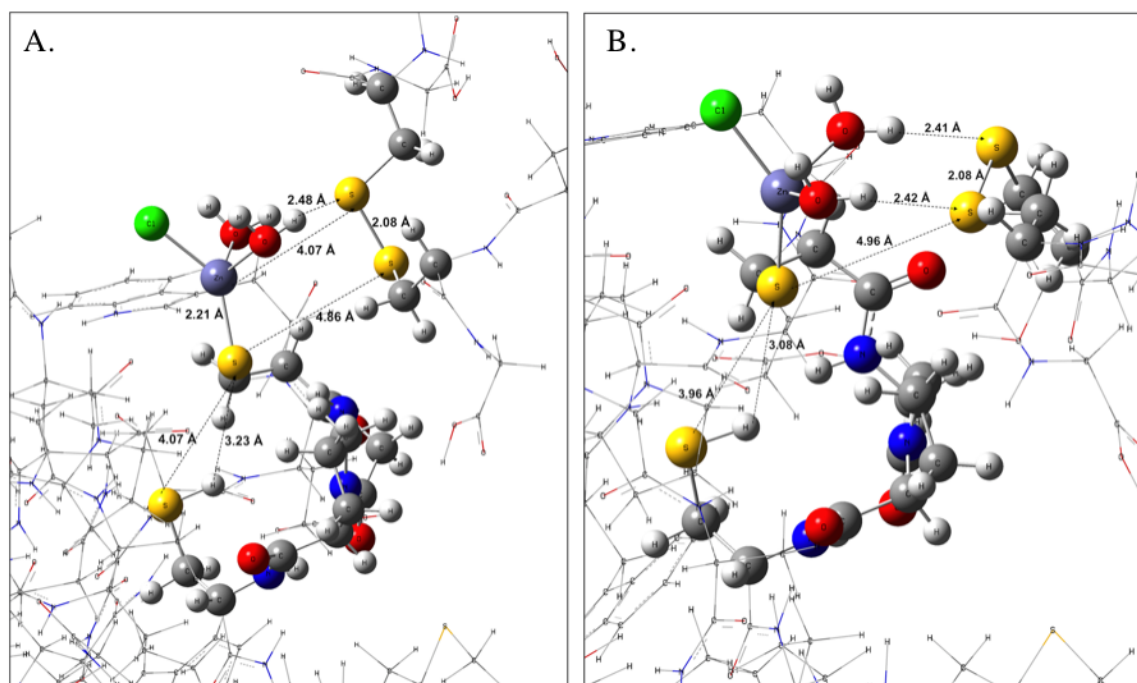


Figure S5: Substrate orientation with zinc-bound Trx. (A) parallel orientation of GSSG, (B) perpendicular orientation.

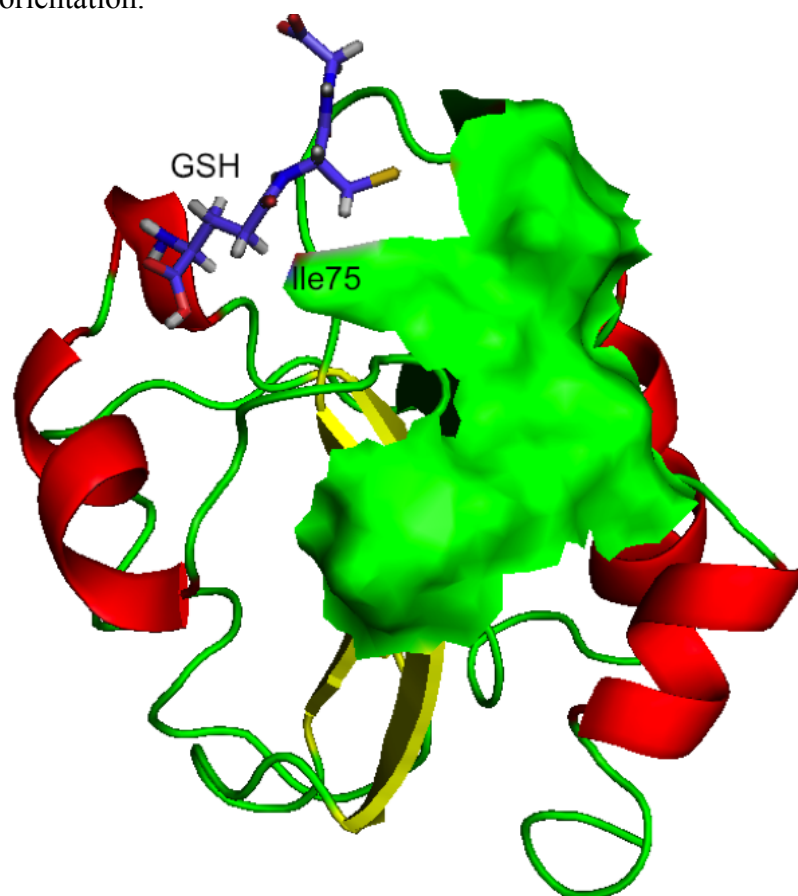


Figure S6: Orientation of GSH away from the hydrophobic patch on the surface of thioredoxin (shown in green). GSH is shown as stick model.

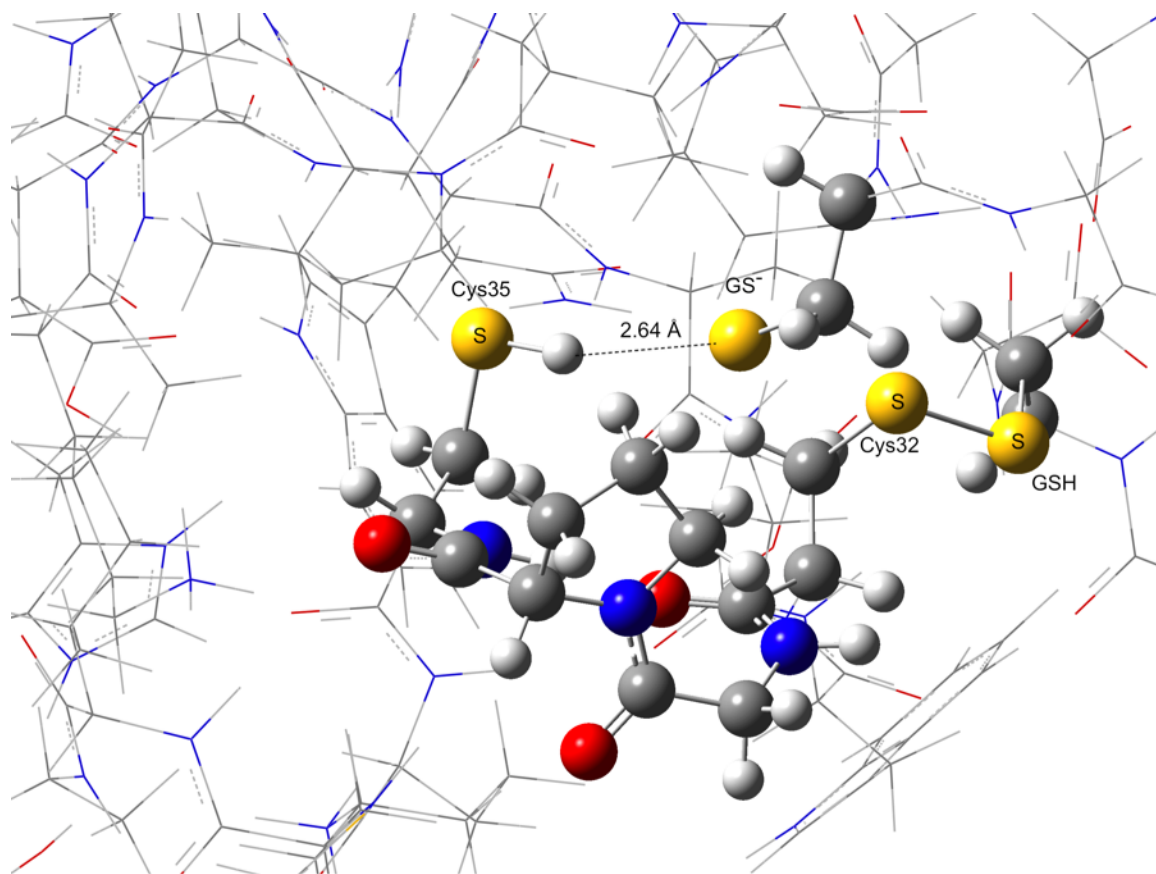


Figure S7: Proton abstraction from Cys35 by GS⁻. S-H-S angle is 158°. Glutathione bound to Cys32 is also shown

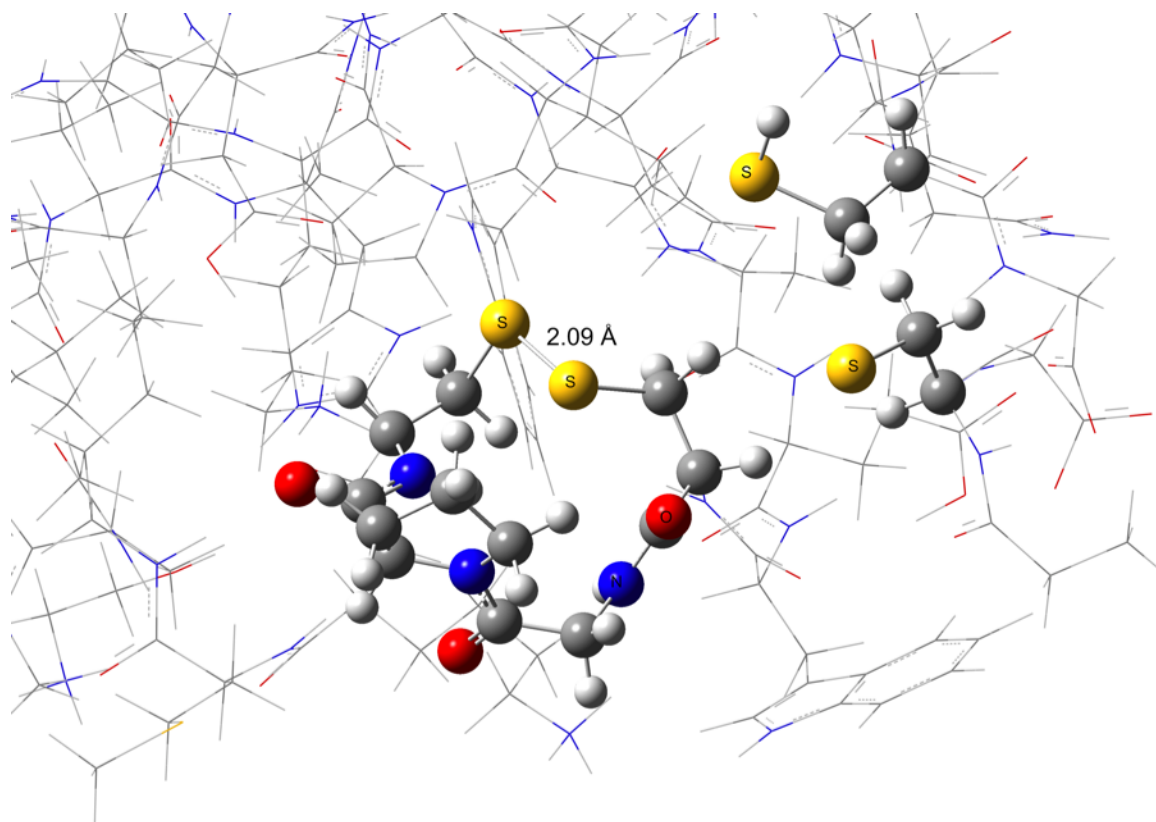


Figure S8: Oxidized thioredoxin. Reduced GS⁻ and GSH are also shown.

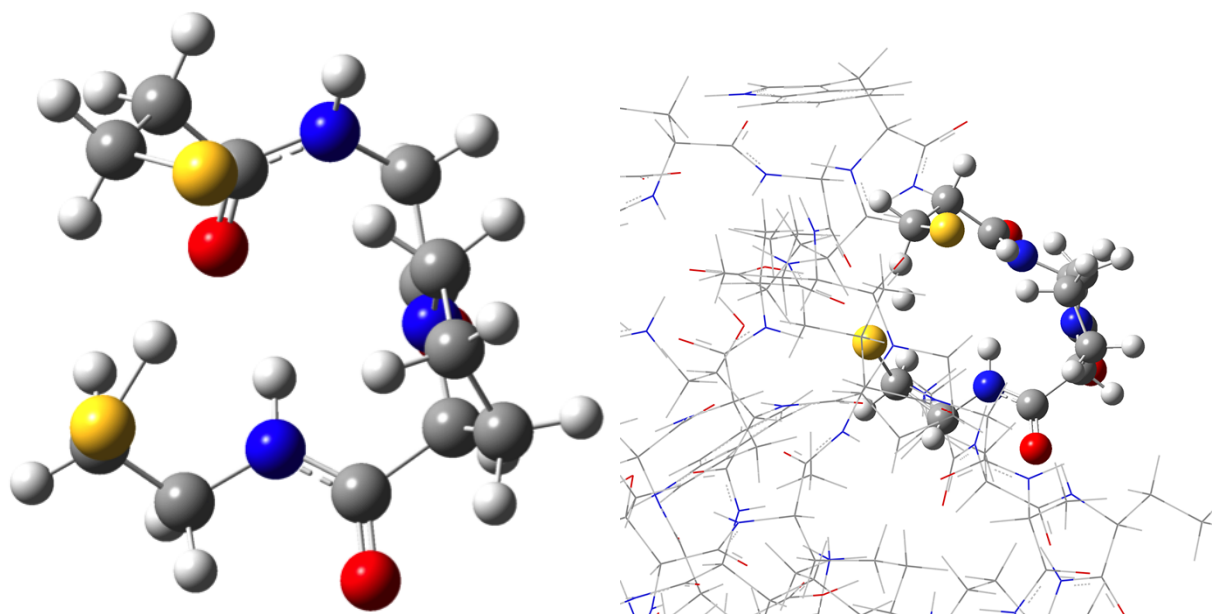


Figure S9: A comparison of active site of thioredoxin when it is clipped out and as part of protein.