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Cysteine sulfonic acid formation catalyzed by a functional model of Cysteine Dioxygenase: a theoretical exploration of Trispyrazolylborato Iron Cysteinato complex reaction mechanism

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-Computational Details-

All the computations reported in the manuscript were carried out using the Gaussian 09 code¹ at DFT level of theory. The unrestricted hybrid UB3LYP functional, composed by Becke's three-parameter hybrid exchange functional (B3)² and the correlation functional of Lee, Yang, and Parr (LYP)³ was adopted to perform geometry optimizations in combination with 6-31G* basis set for all atoms, except for iron(II) ion which was described by means of SDD⁴ pseudopotential. In order to confirm proper convergence to equilibrium and transition state geometries, vibrational frequency analysis was carried out on the basis of analytical second derivatives of the Hamiltonian at this level of theory. Intrinsic reaction coordinate (IRC)⁵ calculations were performed to confirm that the transition states properly connected reactants and products.

More accurate energy values were obtained in solvent using the larger basis set 6-311+G(2d,2p). The effect of the environment were introduced in the framework of the Self-Consistent Reaction Field, by means of the PCM⁶ approach and by using the dielectric constant of dichloromethane ($\epsilon = 8.93$) to reproduce the experimental conditions.⁷

Since the X-Ray structure of **-1-** is available in The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk, the initial model of the reactant was constructed on the basis of its crystallographic coordinates (CCDC-846736).

All calculations were done for the lowest singlet, triplet and quintet spin states. Moreover, in order to confirm the obtained spin state ordering and the relative energies of the various spin states for the reactant molecule, we performed a series of calculations adopting the pure BP86⁸ functional and the dispersion-corrected density functional theory B3LYP-D.⁹ No spin contamination was found for the open-shell systems, being the $\langle S^2 \rangle$ values after annihilation for all the stationary points, those expected for the considered multiplicities ($\langle S^2 \rangle$ equal to: 0.0, 2.0 and 6.0 for singlet, triplet and quintet spin states, respectively). NBO charge analysis has been carried out on the structures of some important intercepted stationary points.¹⁰ The analysis of charge distribution, orbital occupation and spin densities mainly on Iron metal ion, sulphur and oxygens atoms, allowed the electronic characterization of the stationary points located along the three spin state surfaces.

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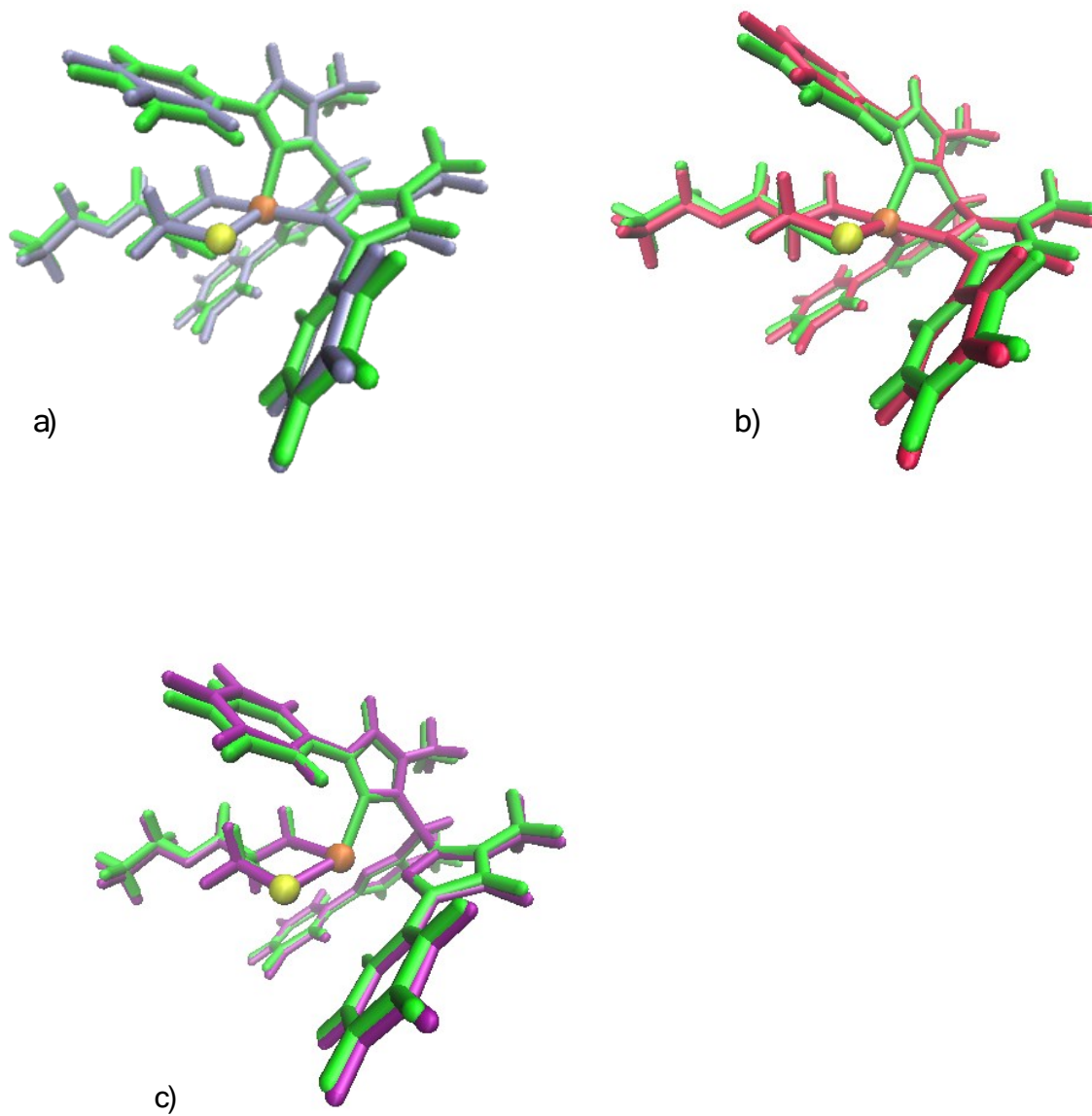
-Table S1-

Relative Energy of the reactant **-1-** in singlet, triplet and quintet spin states, as calculated with 3 different XC functional methods combined with a 6-31G* basis set, in gas phase.

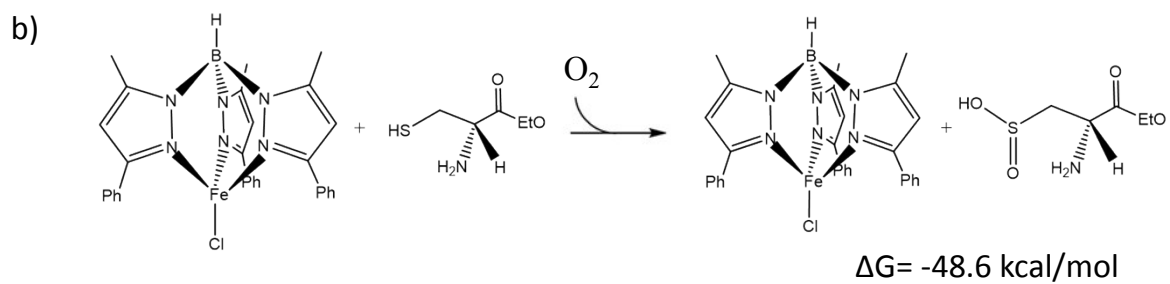
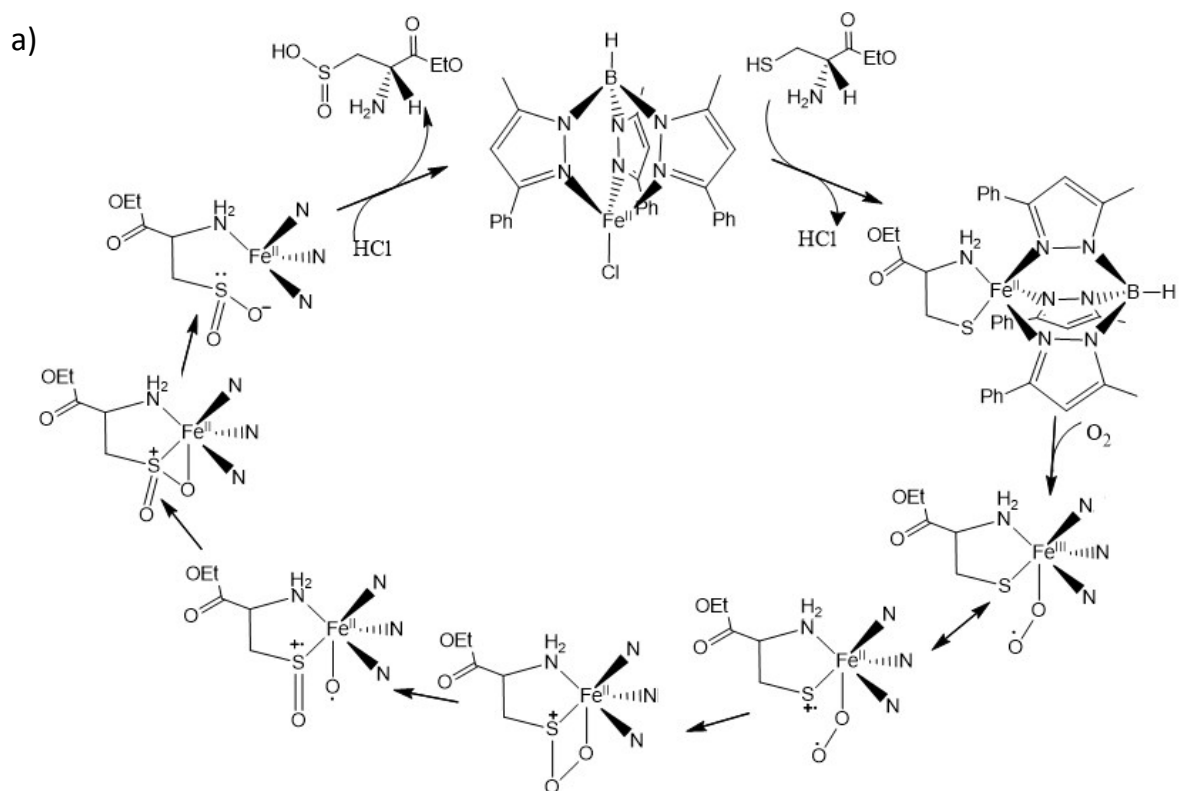
<i>(2S+1)</i>	ΔE (kcal/mol)		
	<i>B3LYP</i>	<i>BP86</i>	<i>B3LYP-D</i>
1	24.3	7.9	21.5
3	13.1	1.5	11.8
5	0	0	0

-Figure S1-

Superposition of the X-ray structure (green) with the optimized a) singlet spin state (iceblue), b) triplet spin state (red), c) quintet spin state (purple) reactant. The big spheres correspond to the iron(II) ion (orange) and sulfur atom of the cysteinato ligand (yellow).



-Scheme S1-



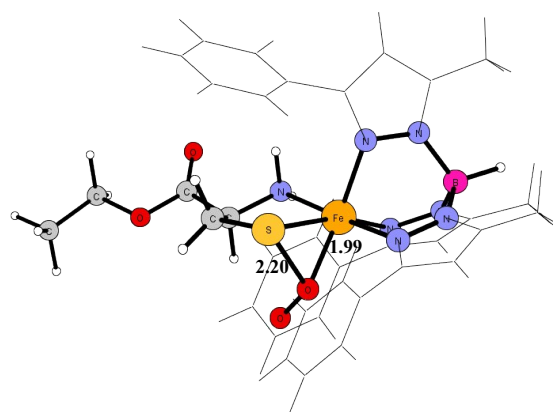
-Table S2-

Most relevant geometrical parameters of the optimized stationary points along the lowest-energy spin states reaction path. Bond lengths and angles are given in Ångstrom and Degrees, respectively.

	⁵ int0	⁵ ts0	⁵ int1	⁵ ts1	¹ int2	⁵ ts2	⁵ int3	⁵ ts3	¹ int4	¹ ts4	⁵ P
Fe-S	2.291	2.262	2.249	2.243	2.243	2.578	2.842	2.896	2.213	2.744	3.122
Fe-O1	5.060	2.627	2.110	2.183	1.871	1.890	1.963	1.778	2.155	2.002	1.962
Fe-O2	-	-	-	-	-	-	-	-	-	-	3.312
S-O1	4.122	3.441	3.297	3.530	3.110	2.894	2.586	2.698	1.561	1.590	1.590
S-O2	3.987	4.444	4.259	3.853	3.510	2.449	1.666	1.594	1.490	1.501	1.516
S-Fe-O1-O2	-	-128.8	-126.0	-35.6	63.9	4.8	-1.56	0.25	-	-	-

-Figure S2-

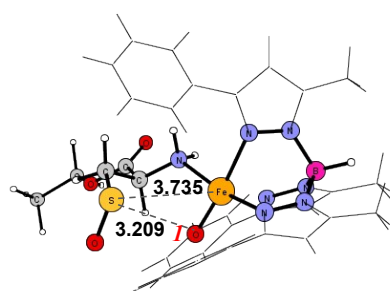
Persulfenate Intermediate formed on the singlet spin-state



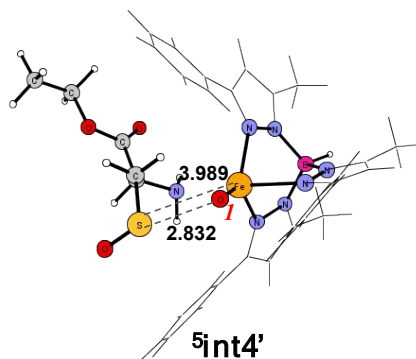
-Figure S3-

Optimized structures of a) **int4'** and b) **ts4'**, lying on the higher triplet and quintet spin surfaces

a)

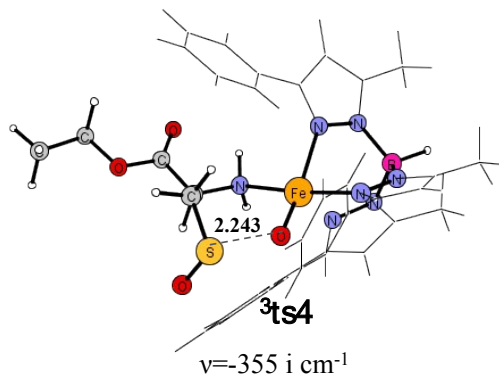


³int4'



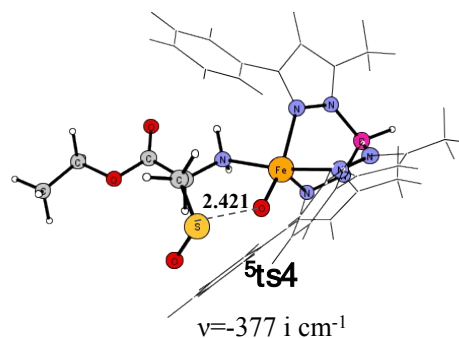
⁵int4'

b)



³ts4

$\nu=-355 \text{ i cm}^{-1}$



⁵ts4

$\nu=-377 \text{ i cm}^{-1}$

-Table S3-

List of SCF Energy values, Entropy and Enthalpy contributions obtained in gas phase and Total free energies in solutions, for all the optimized stationary points along the 3 spin states surfaces

	SCF Energy gas phase	Total free E in solution with all non electrostatic terms	H _{corr} (Hartree)	S _{tot} (Cal/mol K)
¹ Int0	-2587.785221	-2588,418557	0.742126	296.943
³ Int0	-2587.7689221	-2588,40316	0.742046	297.432
⁵ Int0	-2587.7851898	-2588.418544	0.742159	299.555
¹ Ts0	-2587.7518999	-2588,374825	0.741247	281.303
³ Ts0	-2587.7668399	-2588,399241	0.741186	282.782
⁵ Ts0	-2587.7728466	-2588,405261	0.740722	288.398
¹ Int1	-2587.7532671	-2588,390342	0.743432	272.716
³ Int1	-2587.7788252	-2588,419572	0.742846	279.083
⁵ Int1	-2587.7767884	-2588,414979	0.741755	285.711
¹ Ts1	-2587.7486403	-2588,386519	0.742151	269.350
³ Ts1	-2587.7720107	-2588,411068	0.741622	275.552
⁵ Ts1	-2587.7693997	-2588,406798	0.740518	285.273
¹ Int2	-2587.7843471	-2588,422603	0.742937	274.391
³ Int2	-2587.7788252	-2588,417535	0.742846	279.083
⁵ Int2	-2587.7780665	-2588,415823	0.741817	286.036
¹ Ts2	-2587.7525143	-2588,38919	0.742015	269.803
³ Ts2	-2587.7471077	-2588,383584	0.740609	268.062
⁵ Ts2	-2587.7781861	-2588,412871	0.740106	285.093
¹ Int3	-2587.7795944	-2588,41961	0.742676	271.547
³ Int3	-2587.7891926	-2588,42598	0.742083	281.169
⁵ Int3	-2587.8110191	-2588,449862	0.741594	283.020
¹ Ts3	-2587.7529801	-2588,401567	0.741400	271.091
³ Ts3	-2587.786179	-2588,424823	0.740801	278.370
⁵ Ts3	-2587.7993231	-2588,442629	0.740080	282.389
¹ Int4	-2587.8440203	-2588,500948	0.743739	271.169
³ Int4	-2587.8216635	-2588,469156	0.742238	282.192
⁵ Int4	-2587.8269302	-2588,475575	0.741129	294.122
¹ Ts4	-2587.8376164	-2588,494328	0.742568	267.688
³ Ts4	-2587.8156222	-2588,463614	0.741008	280.580
⁵ Ts4	-2587.8165112	-2588,465196	0.740670	284.299
¹ Int5	-2587.8453893	-2588,501384	0.743148	275.520
³ Int5	-2587.865438	-2588,524377	0.742935	278.989
⁵ Int5	-2587.9011758	-2588,549887	0.742091	283.588