

Supporting Information

Joint Use of Bonding Evolution Theory and QM/MM Hybrid Method for Understanding the Hydrogen Abstraction Mechanisms via Cytochrome P450 Aromatase

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Table S1. Relative potential energies (ΔE , kcal/mol) for the hydrogen abstraction process of substrate ASD via Aromatase enzyme calculated at the UB3LYP/6-31G(d) level. The values correspond to the single energy point calculations in gas phase for both doublet and quartet spin state surfaces. The origin of energies has been set at the lowest energy reactant (doublet).

ΔE (kcal/mol)			
Spin	Reactant	TS	Intermediate
doublet	0.0	28.7	24.0
quartet	0.2	29.0	23.5

Table S2. Atomic spin densities for atoms or fragments included in the QM model, obtained from single energy point calculations for both doublet and quartet spin states surfaces.

fragment	spin	R	TS	I
SCH ₃ ⁻	doublet	-0.30	-0.29	-0.24
	quartet	0.25	0.19	0.21
Fe	doublet	1.41	1.22	1.02
	quartet	1.39	1.20	0.99
O	doublet	0.71	0.48	0.13
	quartet	0.71	0.48	0.11
Fe=O	doublet	2.12	1.70	1.15
	quartet	2.09	1.68	1.10
C ₁₉	doublet	0.00	0.51	1.01
	quartet	0.00	0.51	1.02
H ₁₉	doublet	0.00	-0.08	-0.01
	quartet	0.00	-0.08	-0.01
Porphyrin	doublet	-0.83	-0.83	-0.84
	quartet	0.65	0.72	0.74
Substrate*	doublet	0.00	-0.02	-0.06
	quartet	0.00	-0.02	-0.06

* Does not include the C₁₉ and H₁₉ atoms.

Table S3. Population of the most significant basins involved in the hydrogen abstraction reaction in the single energy point calculations from the doublet spin state surface in gas-phase. The anterior and posterior points to the turning points as well as the stationary points are also included.

BASIN	SSD I		SSD II		SSD III			SSD IV		SSD V	
	Reactant	last point	1st point	last point	1st point	TS	last point	1st point	last point	1st point	Product
V(C ₁₈ ,C ₁₉)	1.86	1.85	1.85	1.85	1.85	1.81	1.77	1.77	1.76	1.75	1.65
V(C ₁₉ ,H ₁₇)	2.01	2.03	2.03	2.04	2.04	2.06	2.05	2.04	2.03	1.98	1.82
V(C ₁₉ ,H ₁₈)	2.00	2.02	2.02	2.02	2.03	2.05	2.12	2.13	2.17	2.00	1.79
V(C ₁₉ ,H ₁₉)	2.01	2.06	2.06	2.06							
V ₁ (C ₁₉)					1.32	1.70	1.76	1.76	1.69	1.75	1.42
V ₂ (C ₁₉)										0.24	1.12
V(H ₁₉)					0.75	0.49	0.57				
V _u (O)	7.27	7.16	6.48	6.37	6.37	5.76	5.56	5.56	5.61	5.50	5.40
V _x (O)			0.68	0.76	0.76	1.11	1.03				
V(O,H ₁₉)								1.60	1.56	1.61	1.57
Rx (amu ^{1/2} bohr)	-9.845	-0.489	-0.452	-0.379	-0.360	0.000	0.245	0.262	0.745	0.759	6.947
Energy (kcal/mol)	0.00	18.38	19.01	20.85	21.14	28.75	28.64	28.64	28.43	28.42	24.04

Table S4. Population of the most significant basins involved in the hydrogen abstraction reaction in the single energy point calculations from the quartet spin state surface in gas-phase. The anterior and posterior points to the turning points as well as the stationary points are also included.

BASIN	SSD I		SSD II		SSD III			SSD IV		SSD V	
	Reactant	last point	1st point	last point	1st point	TS	last point	1st point	last point	1st point	Product
V(C ₁₈ ,C ₁₉)	1.85	1.86	1.86	1.86	1.86	1.82	1.78	1.78	1.75	1.75	1.65
V(C ₁₉ ,H ₁₇)	2.01	2.03	2.03	2.04	2.04	2.06	2.06	2.06	1.99	1.99	1.83
V(C ₁₉ ,H ₁₈)	2.01	2.02	2.02	2.02	2.03	2.05	2.10	2.10	2.23	2.00	1.78
V(C ₁₉ ,H ₁₉)	2.00	2.02	2.02	2.02							
V ₁ (C ₁₉)					1.30	1.62	1.72	1.72	1.72	1.72	1.34
V ₂ (C ₁₉)										0.24	1.19
V(H ₁₉)					0.71	0.50	0.58				
V _u (O)	7.17	7.17	6.69	6.70	6.69	5.88	5.61	5.61	5.52	5.51	5.39
V _x (O)			0.46	0.41	0.42	0.98	1.01				
V(O,H ₁₉)								1.59	1.61	1.61	1.59
Rx (amu ^{1/2} bohr)	-10.787	-0.473	-0.454	-0.321	-0.302	0.000	0.208	0.227	0.507	0.540	8.935
Energy (kcal/mol)	0.19	19.28	19.66	22.66	23.14	29.01	29.85	29.84	29.41	29.44	23.47

Figure S1. The MEP of the hydrogen abstraction reaction obtained from single energy point calculations in gas phase for doublet (a) and quartet (b) spin states. The different SSDs obtained from BET analysis are also depicted.

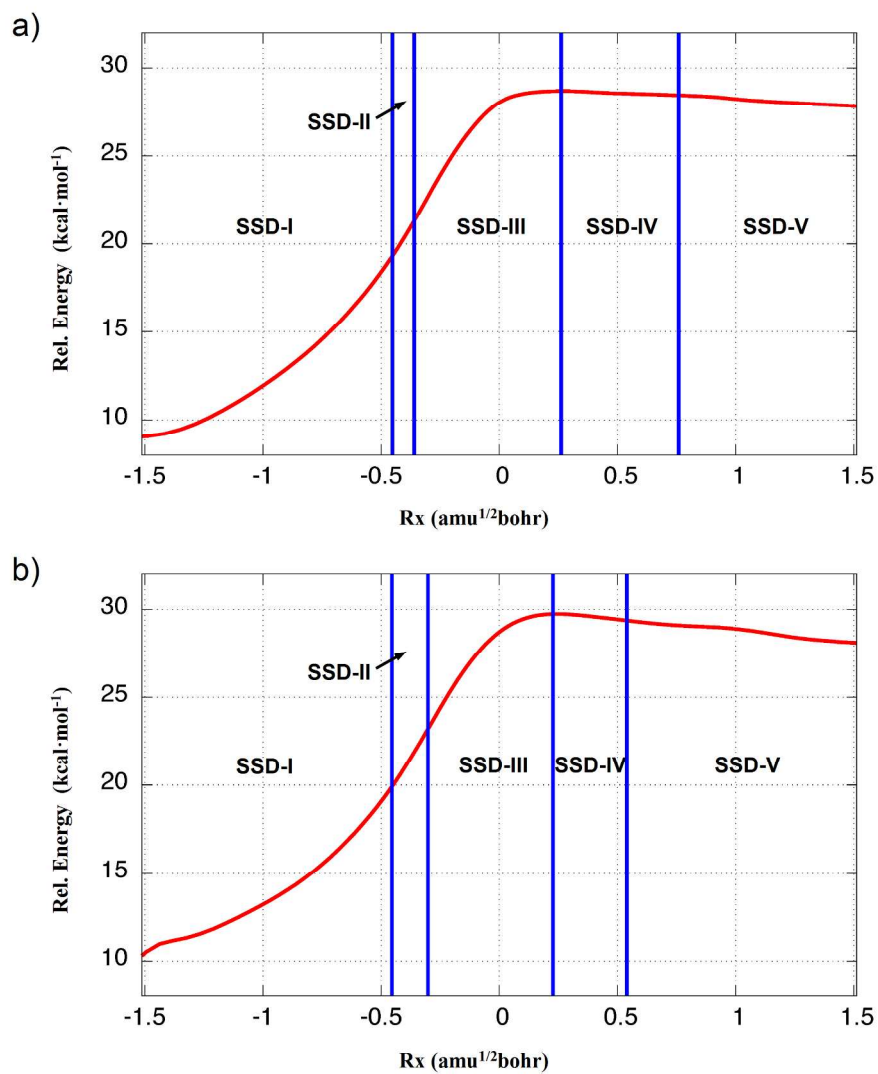


Figure S2. Comparison between the MEP obtained for the doublet spin state catalyzed by the enzyme and the corresponding obtained from single point energy calculations in gas phase. The different SSDs obtained from the BET analysis are also depicted.

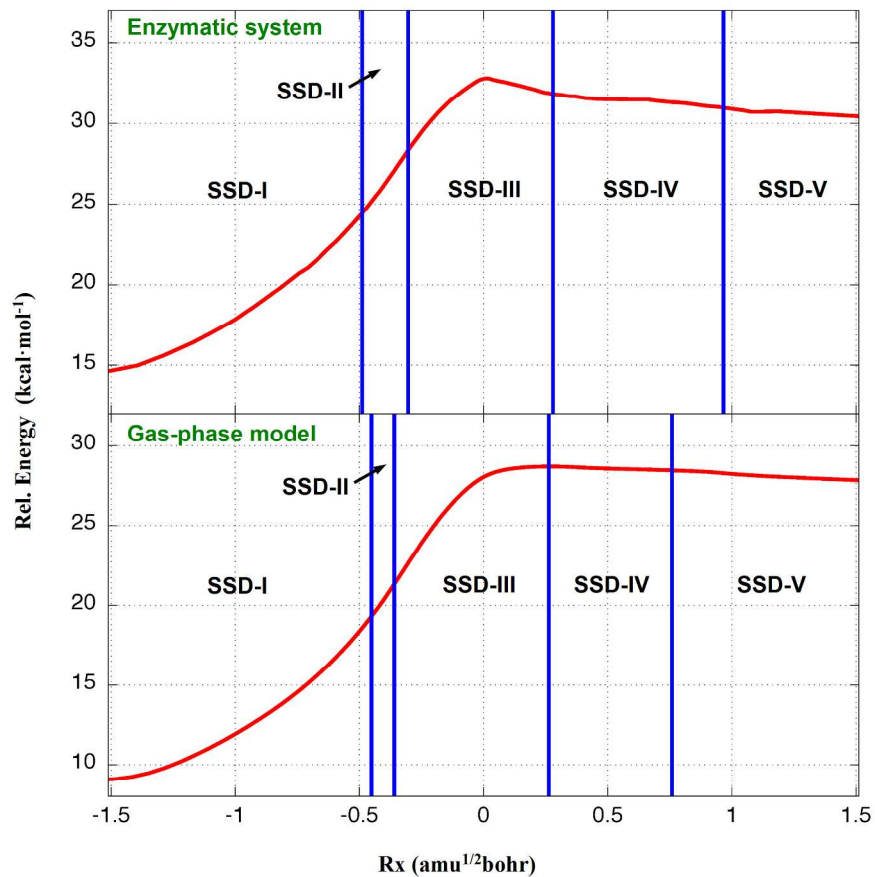


Figure S3. Comparison between the MEP for the doublet spin state catalyzed by the enzyme and the corresponding obtained from single energy point calculations in gas phase. The different SSDs obtained from the BET analysis are also depicted. Blue dashed lines corresponds to SSDs for the ${}^4\text{Fe}^{\text{IV}}\text{Por}$ electromer.

