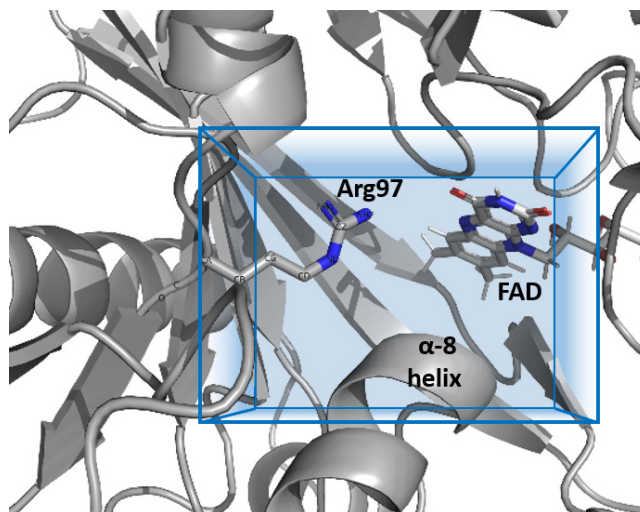
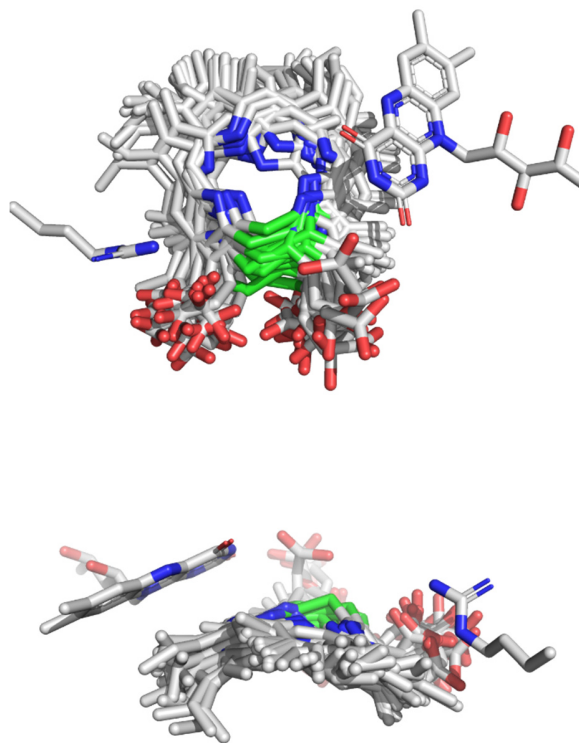


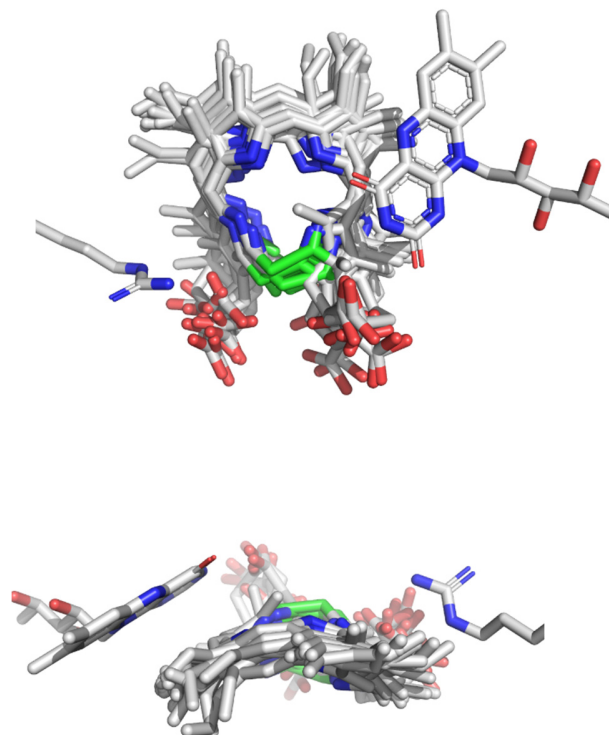
Supplemental Figure S1. Gridbox defining the binding domain of the tetrapyrroles in PPO, including FAD forming the ‘roof’ of the cavity, the top of α -8 helix of PPO upon which the tetrapyrrole rings are centered at the ‘bottom’ of the cavity, and arginine 97 involved in stabilizing the rings on the right side of the cavity.



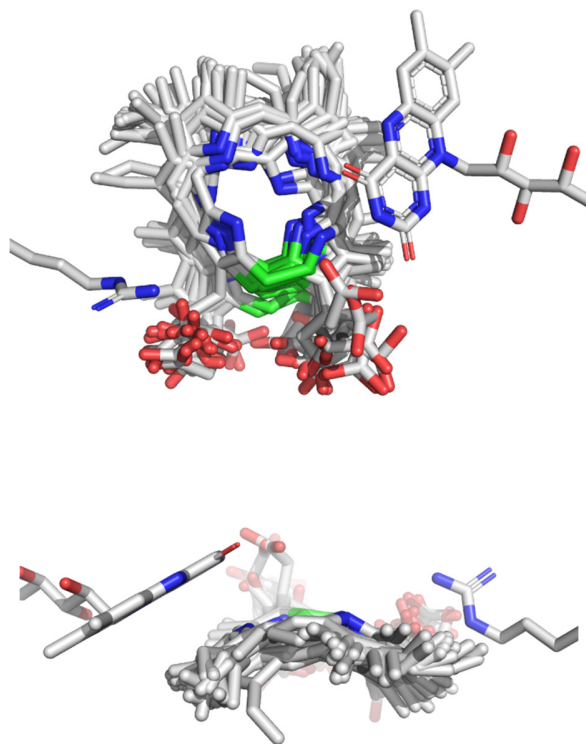
Supplemental Figure S2. Docking poses of the top cluster of intermediate 1a. Top = from above the catalytic domain of PPO and bottom = from inside the catalytic domain of PPO.



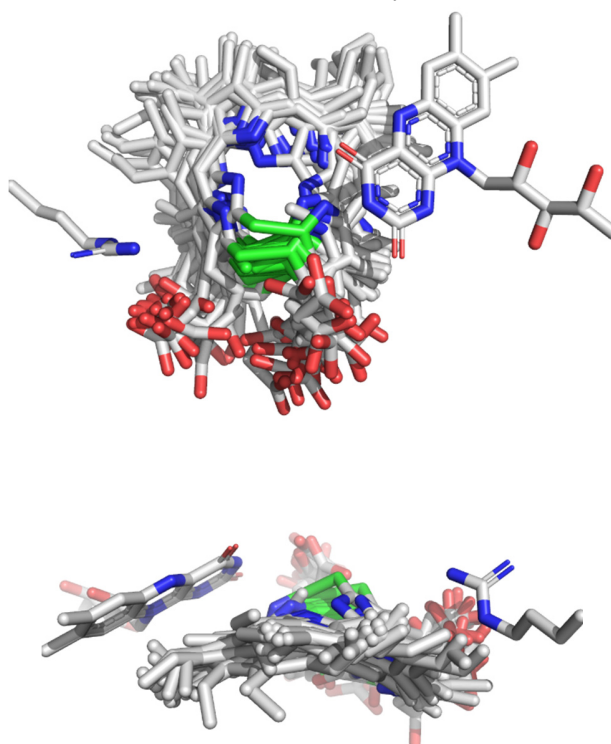
Supplemental Figure S3. Docking poses of the top cluster of intermediate 1c. Top = from above the catalytic domain of PPO and bottom = from inside the catalytic domain of PPO.



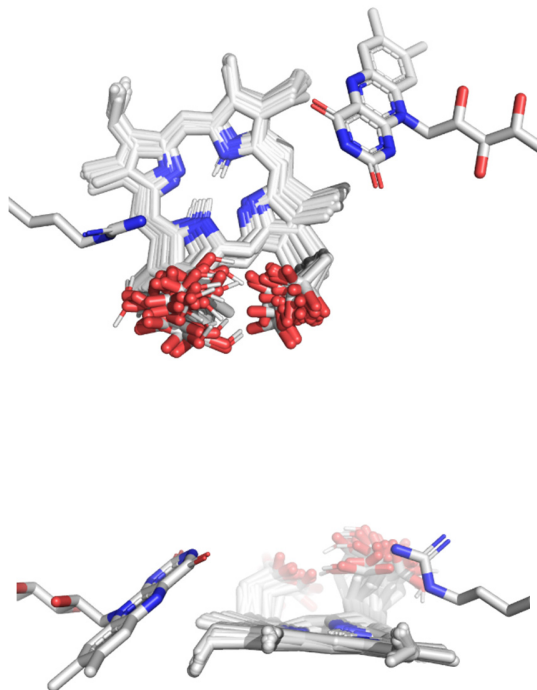
Supplemental Figure S4. Docking poses of the top cluster of intermediate 2a. Top = from above the catalytic domain of PPO and bottom = from inside the catalytic domain of PPO.



Supplemental Figure S5. Docking poses of the top cluster of intermediate 2d. Top = from above the catalytic domain of PPO and bottom = from inside the catalytic domain of PPO.



Supplemental Figure S6. Docking poses of the top cluster of intermediate proto. Top = from above the catalytic domain of PPO and bottom = from inside the catalytic domain of PPO.

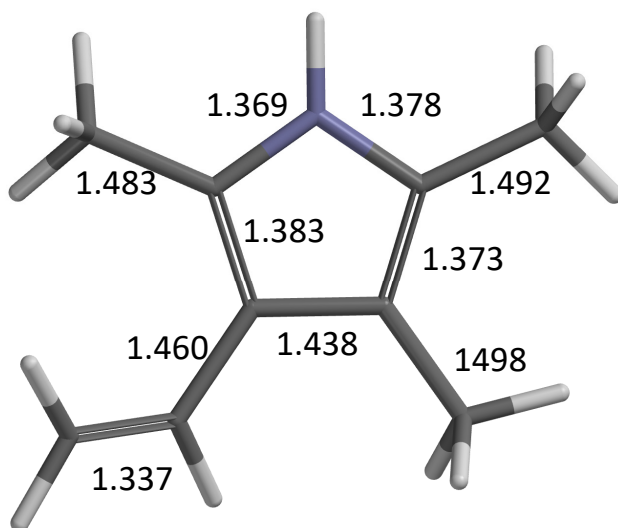


Supplemental Figure S7. DFT calculations on protoporphyrinogen IX pyrroles 1 and 2 in equilibrium geometry with DFT wB97XD 6-31G*.

DFT calculation on protoporphyrinogen pyrrole 1

Equilibrium geometry with DFT wB97XD 6-31G*

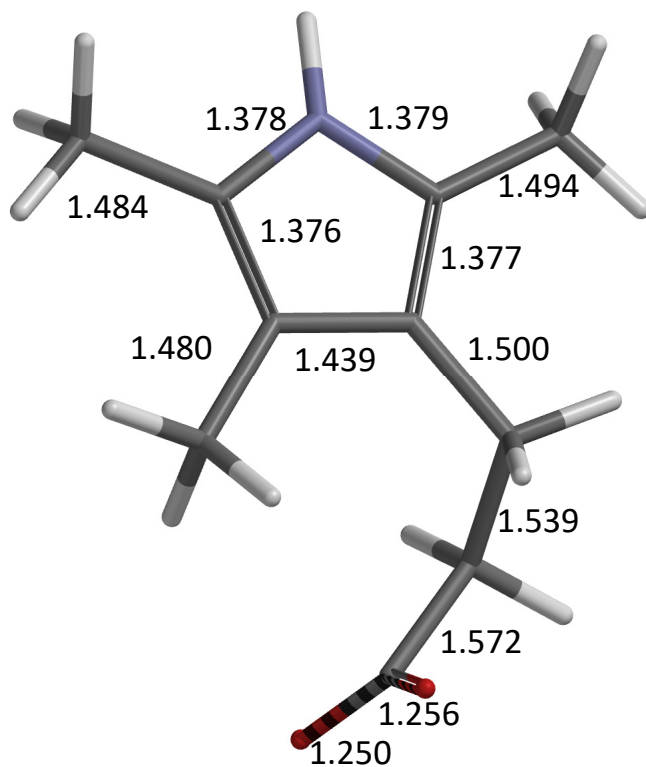
Neutral molecule



DFT calculation on protoporphyrinogen pyrrole 2

Equilibrium geometry with DFT wB97XD 6-31G*

Carrying negative -1 charge



Supplemental table S1. Percent identity matrix of the Clustal Omega alignment made with the file of 16 model organisms protoporphyrinogen oxidase proteins.

	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16
1 PPO <i>C. elegans</i>	100	12.96	12.7	13.19	13.35	14.91	14.95	13.71	13.82	15.25	17.7	10.66	11.85	12.89	13.84	14.29
2 PPO <i>Saccharomyces cerevisiae</i>	12.96	100	27.33	22.88	24.58	26.11	24.09	24.09	19.87	20.73	20.26	21.88	19.26	21.7	21.67	20.35
3 PPO2 <i>Drosophila melanogaster</i>	12.7	27.33	100	36.01	40.43	37.96	38.48	38.04	25.56	25.11	24.72	22.81	29.48	22.37	23.94	22.65
4 PPO <i>Trichoplax</i> sp. H2	13.19	22.88	36.01	100	39.66	40.64	40.17	39.74	27.88	28.32	26.83	27.42	28.76	24.89	25.22	26.55
5 PPO2 <i>Danio Rerio</i>	13.35	24.58	40.43	39.66	100	57.89	52.85	50.74	24.16	25.28	25.11	27.15	31	25.84	23.73	24.72
6 PPO2 <i>Anolis carolinensis</i>	14.91	26.11	37.96	40.64	57.89	100	58.02	57.17	25.28	24.83	26.01	28.73	32.35	24.05	25.5	24.28
7 PPO2 <i>Homo sapiens</i>	14.95	24.09	38.48	40.17	52.85	58.02	100	88.68	24.94	26.06	24.55	25.96	30.86	25.94	27.15	25.5
8 PPO2 <i>Mus musculus</i>	13.71	24.09	38.04	39.74	50.74	57.17	88.68	100	24.94	24.72	25	25.96	31.08	26.39	26.93	25.72
9 PPO2 <i>Oryza sativa japonica</i>	13.82	19.87	25.56	27.88	24.16	25.28	24.94	24.94	100	57.75	57.26	22.3	27.45	26.57	26.85	27.29
10 PPO2 <i>Arabidopsis thaliana</i>	15.25	20.73	25.11	28.32	25.28	24.83	26.06	24.72	57.75	100	66.53	24.12	26.95	27.29	26.57	27
11 PPO2 <i>Nicotiana tabacum</i>	17.7	20.26	24.72	26.83	25.11	26.01	24.55	25	57.26	66.53	100	23.5	26.33	27.94	26.79	27.97
12 PPO <i>Bacillus subtilis</i>	10.66	21.88	22.81	27.42	27.15	28.73	25.96	25.96	22.3	24.12	23.5	100	27.68	27.25	30.33	29.71
13 PPO <i>Myxococcus Xanthus</i>	11.85	19.26	29.48	28.76	31	32.35	30.86	31.08	27.45	26.95	26.33	27.68	100	29.51	29.36	30.04
14 PPO <i>Chlamydomonas reinhardtii</i>	12.89	21.7	22.37	24.89	25.84	24.05	25.94	26.39	26.57	27.29	27.94	27.25	29.51	100	56.32	57.76
15 PPO1 <i>Arabidopsis thaliana</i>	13.84	21.67	23.94	25.22	23.73	25.5	27.15	26.93	26.85	26.57	26.79	30.33	29.36	56.32	100	75.99
16 PPO1 <i>Nicotiana tabacum</i>	14.29	20.35	22.65	26.55	24.72	24.28	25.5	25.72	27.29	27	27.97	29.71	30.04	57.76	75.99	100