

# New insights on Glutathione's Supramolecular Arrangement and Its In Silico Analysis as an Angiotensin-Converting Enzyme Inhibitor

Antônio S. N. Aguiar <sup>1,\*</sup>, Igor D. Borges <sup>1,2</sup>, Leonardo L. Borges <sup>1,3</sup>, Lucas D. Dias <sup>1,4</sup>, Ademir J. Camargo <sup>1</sup>, Pál Perjesi <sup>4</sup> and Hamilton B. Napolitano <sup>1,4,\*</sup>

<sup>1</sup> Grupo de Química Teórica e Estrutural de Anápolis, Universidade Estadual de Goiás, Anápolis, GO, Brazil

<sup>2</sup> Centro de Pesquisa e Eficiência Energética, CAO A Montadora de Veículos LTDA, Anápolis, GO, Brazil

<sup>3</sup> Escola de Ciências Médicas e da Vida, Pontifícia Universidade Católica de Goiás, Goiânia, GO, Brazil

<sup>4</sup> Laboratório de Novos Materiais, Universidade Evangélica de Goiás, Anápolis 75083-515, GO, Brazil

\* Correspondence: toninho.quimica@gmail.com (A.S.N.A.); hbnapolitano@gmail.com (H.B.N.)

## SUPPLEMENTARY MATERIAL

**Table S1.** Second-order perturbation theory analysis in NBO basis obtained at M06-2X/6-311++G(d,p) level of theory for the GSHA polymorph.

Interaction	Occupancy	Donor NBO ( <i>i</i> )	Hybrids	Occupancy	Acceptor NBO ( <i>j</i> )	Hybrids	$E^{(2)}$ (kcal/mol)	$\epsilon_{(j)} - \epsilon_{(i)}$ (a.u.)	$F(i, j)$ (a.u.)
S–H...O <sub>2</sub>	1.99199	$\eta_1(\text{S})$	S: $sp^{0.66}$	0.06022	$\sigma^*(\text{C}_5\text{-O}_2)$	C <sub>5</sub> : $sp^{2.04}$ O <sub>2</sub> : $sp^{1.80}$	0.07	1.27	0.009
	1.99341	$\sigma(\text{C}_5\text{-O}_2)$	C <sub>5</sub> : $sp^{2.04}$ O <sub>2</sub> : $sp^{1.80}$	0.01311	$\sigma^*(\text{S-H})$	S: $sp^{3.34}$ H: $s$	0.08	1.47	0.01
	1.98348	$\pi(\text{C}_5\text{-O}_2)$	C <sub>5</sub> : $p$ O <sub>2</sub> : $p$	0.01311	$\sigma^*(\text{S-H})$	S: $sp^{3.34}$ H: $s$	0.98	0.84	0.026
	1.88395	$\eta_2(\text{O}_1)$	O <sub>1</sub> : $p$	0.01311	$\sigma^*(\text{S-H})$	S: $sp^{3.34}$ H: $s$	0.10	0.74	0.008
	1.9791	$\eta_1(\text{O}_2)$	O <sub>2</sub> : $sp^{0.58}$	0.01311	$\sigma^*(\text{S-H})$	S: $sp^{3.34}$ H: $s$	0.24	1.2	0.015
	1.88406	$\eta_2(\text{O}_2)$	O <sub>2</sub> : $p$	0.01311	$\sigma^*(\text{S-H})$	S: $sp^{3.34}$ H: $s$	1.53	0.72	0.03
N <sub>2</sub> –H...O <sub>2</sub>	1.71526	$\eta_1(\text{N}_2)$	N <sub>2</sub> : $p$	0.05091	$\sigma^*(\text{C}_5\text{-O}_5)$	C <sub>5</sub> : $sp^{1.94}$ O <sub>2</sub> : $sp^{1.68}$	0.24	0.91	0.014
	1.97429	$\eta_1(\text{O}_2)$	O <sub>2</sub> : $sp^{0.60}$	0.0208	$\sigma^*(\text{N}_2\text{-H})$	N <sub>2</sub> : $sp^{1.95}$ H: $sp^{1.68}$	2.01	1.69	0.052
	1.89151	$\eta_2(\text{O}_2)$	O <sub>2</sub> : $p$	0.0208	$\sigma^*(\text{N}_2\text{-H})$	N <sub>2</sub> : $sp^{1.95}$ H: $sp^{1.68}$	2.93	1.21	0.054
O <sub>6</sub> –H...O <sub>3</sub>	1.98034	$\sigma(\text{O}_6\text{-H})$	O <sub>6</sub> : $sp^{2.01}$ H: $sp^{2.01}$	0.02804	$\sigma^*(\text{C}_4\text{-O}_3)$	C <sub>4</sub> : $sp^{2.20}$ O <sub>3</sub> : $sp^{1.49}$	0.13	1.59	0.013
	1.98034	$\sigma(\text{O}_6\text{-H})$	O <sub>6</sub> : $sp^{2.01}$ H: $sp^{2.01}$	0.29654	$\pi^*(\text{C}_4\text{-O}_3)$	C <sub>4</sub> : $p$ O <sub>3</sub> : $p$	0.20	1.01	0.014
	1.95731	$\eta_1(\text{O}_6)$	O <sub>6</sub> : $sp^{2.89}$	0.02804	$\sigma^*(\text{C}_4\text{-O}_3)$	C <sub>4</sub> : $sp^{2.20}$ O <sub>3</sub> : $sp^{1.49}$	0.13	1.17	0.011
	1.95731	$\eta_1(\text{O}_6)$	O <sub>6</sub> : $sp^{2.89}$	0.07635	$\pi^*(\text{C}_8\text{-O}_4)$	C <sub>8</sub> : $sp^{2.80}$ O <sub>4</sub> : $sp^{2.26}$	1.83	0.75	0.035
	1.96552	$\eta_1(\text{O}_3)$	O <sub>3</sub> : $sp^{0.73}$	0.03126	$\sigma^*(\text{O}_6\text{-H})$	O <sub>6</sub> : $sp^{2.01}$ H: $s$	8.52	1.71	0.108

	1.88081	$\eta_2(\text{O}_3)$	O <sub>3</sub> :	$p$	0.03126	$\sigma^*(\text{O6-H})$	O <sub>6</sub> : $sp^{2.01}$ H: $s$	9.45	1.27	0.100
	1.9927	$\sigma(\text{C}_4\text{-O}_3)$	C <sub>4</sub> : $sp^{2.20}$ O <sub>3</sub> : $sp^{1.49}$		0.03126	$\sigma^*(\text{O6-H})$	O <sub>6</sub> : $sp^{2.01}$ H: $s$	0.16	2.07	0.016
	1.98922	$\pi(\text{C}_4\text{-O}_3)$	C <sub>4</sub> : $p$ O <sub>3</sub> : $p$		0.03126	$\sigma^*(\text{O6-H})$	O <sub>6</sub> : $sp^{2.01}$ H: $s$	1.50	1.4	0.041
N <sub>3</sub> -H...O <sub>5</sub>	1.68454	$\eta_1(\text{N3})$	N <sub>3</sub> :	$p$	0.02682	$\sigma^*(\text{C}_{10}\text{-O}_5)$	C <sub>10</sub> : $sp^{1.94}$ O <sub>5</sub> : $sp^{1.42}$	0.14	1	0.012
	1.86223	$\eta_2(\text{O}_5)$	O <sub>5</sub> :	$p$	0.01319	$\sigma^*(\text{N3-H})$	N <sub>3</sub> : $sp^{2.12}$ H: $s$	1.63	1.21	0.041
C <sub>2</sub> -H...O <sub>4</sub>	1.97281	$\sigma(\text{C}_2\text{-H})$	C <sub>2</sub> : $sp^{2.74}$ H: $s$		0.0208	$\sigma^*(\text{N2-H})$	N <sub>2</sub> : $sp^{1.95}$ H: $s$	0.27	1.56	0.018

**Table S2.** Second-order perturbation theory analysis in NBO basis obtained at M06-2X/6-311++G(d,p) level of theory for the GSHB polymorph.

Interaction	Occupancy	Donor NBO ( <i>i</i> )	Hybrids	Occupancy	Acceptor NBO ( <i>j</i> )	Hybrids	$E^{(2)}$ (kcal/mol)	$\epsilon_{(j)} - \epsilon_{(i)}$ (a.u.)	$F(i, j)$ (a.u.)
S-H...O <sub>1</sub>	1.96681	$\sigma(\text{C}_9\text{-H})$	C <sub>9</sub> : $sp^{3.03}$ H: $s$	0.01589	$\sigma^*(\text{C}_2\text{-H})$	C <sub>2</sub> : $sp^{3.50}$ H: $s$	0.72	1.04	0.025
	1.99282	$\eta_1(\text{S})$	S: $sp^{0.50}$	0.05303	$\sigma^*(\text{O}_1\text{-C}_5)$	O <sub>1</sub> : $sp^{1.57}$ C <sub>5</sub> : $sp^{1.98}$	0.07	1.37	0.009
	1.97472	$\sigma(\text{C}_2\text{-H})$	C <sub>2</sub> : $sp^{3.50}$ H: $s$	0.01790	$\sigma^*(\text{C}_9\text{-H})$	C <sub>9</sub> : $sp^{3.03}$ H: $s$	0.94	1.05	0.028
	1.97342	$\eta_1(\text{O}_1)$	O <sub>1</sub> : $sp^{0.64}$	0.01938	$\sigma^*(\text{S-H})$	S: $sp^{4.87}$ H: $s$	2.23	1.04	0.043
	1.87540	$\eta_2(\text{O}_1)$	O <sub>1</sub> : $p$	0.01938	$\sigma^*(\text{S-H})$	S: $sp^{4.87}$ H: $s$	0.61	0.57	0.017
	1.62112	$\eta_3(\text{O}_1)$	O <sub>1</sub> : $p$	0.01938	$\sigma^*(\text{S-H})$	S: $sp^{4.87}$ H: $s$	2.56	0.54	0.037
N <sub>1</sub> -H...O <sub>1</sub>	1.98990	$\sigma(\text{N}_1\text{-H})$	N <sub>1</sub> : $sp^{2.87}$	0.05358	$\sigma^*(\text{O}_1\text{-C}_5)$	O <sub>1</sub> : $sp^{1.54}$ C <sub>5</sub> : $sp^{1.97}$	0.10	1.41	0.011
	1.99493	$\sigma(\text{O}_1\text{-C}_5)$	O <sub>1</sub> : $sp^{1.54}$ C <sub>5</sub> : $sp^{1.97}$	0.04675	$\sigma^*(\text{N}_1\text{-H})$	N <sub>1</sub> : $sp^{3.10}$ H: $s$	0.05	1.58	0.008
	1.96840	$\eta_1(\text{O}_1)$	O <sub>1</sub> : $sp^{0.65}$	0.04675	$\sigma^*(\text{N}_1\text{-H})$	N <sub>1</sub> : $sp^{3.10}$ H: $s$	6.25	1.26	0.079
	1.87638	$\eta_2(\text{O}_1)$	O <sub>1</sub> : $p$	0.04675	$\sigma^*(\text{N}_1\text{-H})$	N <sub>1</sub> : $sp^{3.10}$ H: $s$	1.73	0.79	0.034
	1.62453	$\eta_3(\text{O}_1)$	O <sub>1</sub> : $p$	0.04675	$\sigma^*(\text{N}_1\text{-H})$	N <sub>1</sub> : $sp^{3.10}$ H: $s$	0.95	0.76	0.026
	1.99091	$\sigma(\text{N}_1\text{-H})$	N <sub>1</sub> : $sp^{2.73}$	0.05358	$\sigma^*(\text{O}_1\text{-C}_5)$	O <sub>1</sub> : $sp^{1.54}$ C <sub>5</sub> : $sp^{1.97}$	0.09	1.41	0.01
N <sub>1</sub> -H...O <sub>2</sub>	1.99086	$\sigma(\text{N}_1\text{-H})$	N <sub>1</sub> : $sp^{3.10}$	0.04917	$\sigma^*(\text{O}_2\text{-C}_5)$	O <sub>1</sub> : $sp^{1.53}$ C <sub>5</sub> : $sp^{2.01}$	0.11	1.29	0.011
	1.99086	$\sigma(\text{N}_1\text{-H})$	N <sub>1</sub> : $sp^{3.10}$	0.37882	$\pi^*(\text{O}_2\text{-C}_5)$	O <sub>1</sub> : $p$ C <sub>5</sub> : $p$	0.10	0.72	0.008
	1.99255	$\sigma(\text{O}_2\text{-C}_5)$	O <sub>2</sub> : $sp^{1.73}$ C <sub>5</sub> : $sp^{1.95}$	0.03759	$\sigma^*(\text{N}_1\text{-H})$	N <sub>1</sub> : $sp^{2.73}$ H: $s$	0.24	1.61	0.018
	1.87311	$\eta_2(\text{O}_2)$	O <sub>2</sub> : $p$	0.03759	$\sigma^*(\text{N}_1\text{-H})$	N <sub>1</sub> : $sp^{2.73}$ H: $s$	15.51	0.87	0.106
N <sub>2</sub> -H...O <sub>2</sub>	1.98365	$\sigma(\text{N}_2\text{-H})$	N <sub>2</sub> : $sp^{2.34}$ H: $s$	0.37882	$\pi^*(\text{O}_2\text{-C}_5)$	O <sub>2</sub> : $p$ C <sub>5</sub> : $p$	0.18	1.3	0.014
	1.99255	$\sigma(\text{O}_2\text{-C}_5)$	O <sub>2</sub> : $sp^{1.73}$ C <sub>5</sub> : $sp^{1.95}$	0.03353	$\sigma^*(\text{N}_2\text{-H})$	N <sub>2</sub> : $sp^{2.34}$ H: $s$	0.15	1.65	0.014
	1.95852	$\eta_2(\text{O}_2)$	O <sub>2</sub> : $p$	0.03353	$\sigma^*(\text{N}_2\text{-H})$	N <sub>2</sub> : $sp^{2.34}$ H: $s$	6.80	1.36	0.086
C <sub>3</sub> -H...O <sub>2</sub>	1.97934	$\sigma(\text{C}_3\text{-H})$	C <sub>3</sub> : $sp^{3.41}$ H: $s$	0.37882	$\sigma^*(\text{O}_2\text{-C}_5)$	O <sub>2</sub> : $p$ C <sub>5</sub> : $p$	0.12	0.55	0.008
	1.68940	$\eta_1(\text{N}_3)$	N <sub>3</sub> : $p$	0.02517	$\sigma^*(\text{C}_6\text{-H})$	C <sub>6</sub> : $sp^{3.22}$ H: $s$	0.06	0.71	0.006
N <sub>1</sub> -H...O <sub>4</sub>	1.99182	$\sigma(\text{N}_1\text{-H})$	N <sub>1</sub> : $sp^{2.85}$	0.06532	$\sigma^*(\text{O}_4\text{-C}_8)$	O <sub>4</sub> : $sp^{1.94}$	0.17	1.3	0.013

			H: $sp^{2.85}$			C <sub>8</sub> : $sp^{2.73}$			
	1.98896	$\pi(\text{O}_4\text{-C}_8)$	O <sub>4</sub> : $p$	0.03821	$\sigma^*(\text{N}_1\text{-H})$	N <sub>1</sub> : $sp^{2.85}$	0.06	1.02	0.007
			C <sub>8</sub> : $p$			H: $s$			
	1.96655	$\eta_1(\text{O}_4)$	O <sub>4</sub> : $sp^{0.72}$	0.03821	$\sigma^*(\text{N}_1\text{-H})$	N <sub>1</sub> : $sp^{2.85}$	6.64	1.25	0.082
						H: $s$			
	1.88004	$\eta_2(\text{O}_4)$	O <sub>4</sub> : $p$	0.03821	$\sigma^*(\text{N}_1\text{-H})$	N <sub>1</sub> : $sp^{2.85}$	9.61	0.82	0.081
						H: $s$			
N <sub>3</sub> -H...O <sub>5</sub>	1.98257	$\sigma(\text{N}_3\text{-H})$	N <sub>3</sub> : $sp^{2.37}$	0.03602	$\sigma^*(\text{O}_5\text{-C}_{10})$	O <sub>5</sub> : $sp^{1.62}$	0.10	1.35	0.011
			H: $s$			C <sub>10</sub> : $sp^{2.13}$			
	1.68499	$\eta_1(\text{N}_3)$	N <sub>3</sub> : $p$	0.03602	$\sigma^*(\text{O}_5\text{-C}_{10})$	O <sub>5</sub> : $sp^{1.62}$	0.05	0.91	0.007
						C <sub>10</sub> : $sp^{2.13}$			
	1.68499	$\eta_1(\text{N}_3)$	N <sub>3</sub> : $p$	0.20915	$\pi^*(\text{O}_5\text{-C}_{10})$	O <sub>5</sub> : $p$	0.05	0.36	0.004
						C <sub>10</sub> : $p$			
	1.96926	$\eta_1(\text{O}_5)$	O <sub>5</sub> : $sp^{0.69}$	0.05430	$\sigma^*(\text{O}_3\text{-C}_4)$	O <sub>3</sub> : $sp^{1.87}$	0.14	1.41	0.013
						C <sub>4</sub> : $sp^{2.51}$			
	1.96926	$\eta_1(\text{O}_5)$	O <sub>5</sub> : $sp^{0.69}$	0.22712	$\pi^*(\text{O}_3\text{-C}_4)$	O <sub>3</sub> : $p$	1.16	0.97	0.032
						C <sub>4</sub> : $p$			
O <sub>6</sub> -H...O <sub>3</sub>	1.96926	$\eta_1(\text{O}_5)$	O <sub>5</sub> : $sp^{0.69}$	0.03034	$\sigma^*(\text{N}_3\text{-H})$	N <sub>3</sub> : $sp^{2.37}$	4.29	1.34	0.068
						H: $s$			
	1.86870	$\eta_2(\text{O}_5)$	O <sub>5</sub> : $p$	0.03034	$\sigma^*(\text{N}_3\text{-H})$	N <sub>3</sub> : $sp^{2.37}$	3.07	0.89	0.048
						H: $s$			
	1.98322	$\sigma(\text{O}_6\text{-H})$	O <sub>6</sub> : $sp^{2.67}$	0.21210	$\pi^*(\text{O}_3\text{-C}_4)$	O <sub>3</sub> : $p$	0.24	1.03	0.015
			H: $s$			C <sub>4</sub> : $p$			
	1.99014	$\sigma(\text{O}_3\text{-C}_4)$	O <sub>3</sub> : $sp^{2.41}$	0.05759	$\sigma^*(\text{O}_6\text{-H})$	O <sub>6</sub> : $sp^{2.67}$	0.46	1.53	0.024
			C <sub>4</sub> : $sp^{3.18}$			H: $s$			
	1.98680	$\pi(\text{O}_3\text{-C}_4)$	O <sub>3</sub> : $p$	0.05759	$\sigma^*(\text{O}_6\text{-H})$	O <sub>6</sub> : $sp^{2.67}$	0.18	1.18	0.013
			C <sub>4</sub> : $p$			H: $s$			
	1.96252	$\eta_1(\text{O}_3)$	O <sub>3</sub> : $sp^{0.74}$	0.05759	$\sigma^*(\text{O}_6\text{-H})$	O <sub>6</sub> : $sp^{2.67}$	7.80	1.33	0.092
						H: $s$			
	1.86499	$\eta_2(\text{O}_3)$	O <sub>3</sub> : $p$	0.05759	$\sigma^*(\text{O}_6\text{-H})$	O <sub>6</sub> : $sp^{2.67}$	22.01	0.93	0.13
						H: $s$			