Electronic Supplementary Information (ESI)

Dual Antioxidant / Pro-Oxidant Behavior of the Tryptophan Metabolite 3-Hydroxyanthranilic Acid: A Theoretical Investigation on Reaction Mechanisms and Kinetics†

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Table 1S. Molar fraction of the different acid-base species of 3-hydroxyanthranilic acid at different *p*H.

pH	$3H_2AA^{2-}$	$3H_3AA^{-}$	$3H_4AA$	$3H_5AA^{+}$
0.0	0.000	0.000	0.014	0.986
0.5	0.000	0.000	0.044	0.956
1.0	0.000	0.000	0.128	0.872
1.5	0.000	0.000	0.317	0.682
2.0	0.000	0.001	0.594	0.404
2.5	0.000	0.006	0.818	0.176
3.0	0.000	0.022	0.916	0.062
3.5	0.000	0.069	0.911	0.020
4.0	0.000	0.192	0.802	0.005
4.5	0.000	0.431	0.568	0.001
5.0	0.000	0.706	0.294	0.000
5.5	0.000	0.883	0.116	0.000
6.0	0.000	0.960	0.040	0.000
6.5	0.000	0.987	0.013	0.000
7.0	0.001	0.995	0.004	0.000
7.4	0.002	0.996	0.002	0.000
8.0	0.007	0.992	0.000	0.000
8.5	0.023	0.977	0.000	0.000
9.0	0.069	0.931	0.000	0.000
9.5	0.190	0.810	0.000	0.000
10.0	0.427	0.573	0.000	0.000
10.5	0.702	0.298	0.000	0.000
11.0	0.882	0.118	0.000	0.000
11.5	0.959	0.041	0.000	0.000
12.0	0.987	0.013	0.000	0.000
12.5	0.996	0.004	0.000	0.000
13.0	0.999	0.001	0.000	0.000
13.5	1.000	0.000	0.000	0.000
14.0	1.000	0.000	0.000	0.000

Table 2S. LogK for the reaction between $3H_4AA$ and $^{\bullet}OOH$, at 298.15 K.

	$3H_4AA$ PE	$3H_4AA$ Water	$3H_3AA^-$ Water	$3H_2AA^{2-}$ Water
SET	-48.00	-15.51	-9.89	7.18
HT				
site 3a	6.24	7.04	9.85	
RAF				
site 1	-15.19	-12.55	-8.87	-8.82
site 2	-10.70	-7.78	-7.21	-0.19
site 3	-5.86	-5.34	-4.39	-4.25
site 4	-9.29	-8.14	-8.98	-2.01
site 5	-9.43	-8.16	-6.58	-5.83
site 6	-7.19	-5.17	-6.86	-1.07

Table 3S. Gibbs free energies reaction (ΔG), Gibbs free energies of activation ($\Delta G^{\neq}$) and rate constants (*k*, without including *p*H effects) for the reaction between $CH_3OO^{\bullet}$ and 3-hydroxyanthranilic, at 298.15 K.

	ΔG (kcal/mol)	$\Delta G^{\neq}$ (kcal/mol)	*k* (M^{-1} s^{-1})
$3H_4AA$ (PE), HT	-6.48	11.06	5.17E+05
$3H_4AA$ (W), HT	-7.91	11.08	1.18E+06
$3H_3AA^-$ (W), HT	-11.75	8.48	1.17E+07
$3H_3AA^-$ (W), SET	15.11	15.50	2.68E+01
$3H_2AA^{2-}$ (W), SET	-8.17	1.68	7.48E+09

Table 4S. Gibbs free energies reaction (ΔG), Gibbs free energies of activation ($\Delta G^{\neq}$) and rate constants (*k*, without including *p*H effects) for the SET reaction pathways between $HOO^{\bullet}$ and $3H_2AA^{2-}$ (HX), at 298.15 K, including explicit water molecules.

	ΔG (kcal/mol)	$\Delta G^{\neq}$ (kcal/mol)	*k* (M^{-1} s^{-1})
HX(0a)-R(0a)*	-9.79	0.02	7.80E+09
HX(1a)-R(0a)	-7.28	0.26	7.95E+09
HX(1a)-R(1a)	-9.16	0.12	7.69E+09

*The data without explicit water molecules was included for comparison purposes.

Values in parenthesis indicate the number of explicit water molecules interacting with each reactant.

Table 5S. Gibbs free energies reaction (ΔG), Gibbs free energies of activation ($\Delta G^{\neq}$) and rate constants (*k*, without including *p*H effects) for the HT reaction pathways between $HOO^{\bullet}$ (R) and 3-hydroxyanthranilic (HX), at 298.15 K, including explicit water molecules.

	ΔG (kcal/mol)	$\Delta G^{\neq}$ (kcal/mol)	*k* (M^{-1} s^{-1})
$HX = 3H_4AA$			
HX(0a)-R(0a)*	-9.60	11.23	1.30E+06
HX(1a)-R(0a)	-10.49	11.69	2.14E+06
HX(1a)-R(1a)	-8.85	12.46	2.69E+05
$HX = 3H_3AA^{-}$			
HX(0a)-R(0a)*	-13.44	8.84	1.64E+07
HX(1a)-R(0a)	-13.88	8.69	6.59E+07
HX(1a)-R(1a)	-12.24	7.32	2.63E+07

*The data without explicit water molecules was included for comparison purposes.

Values in parenthesis indicate the number of explicit water molecules interacting with each reactant.

Table 6S. LogK for the different Cu^{2+} chelation routes, in aqueous solution, at 298.15 K and pH=7.4.

	(I)	(II)	(III)	(IV)	(V)	(VI)	(VII-b)	(VIII-b)	(IX-b)
O(1a)	0.22	10.26	12.28	9.28			9.07		
O(1b)	-4.39	10.63	12.98	9.65			14.04		
O(3a)	-3.32	-0.33	15.50	6.29	7.07		9.62	7.39	
N(2a)	2.82	9.54	18.09	-3.10	1.21		-5.93	-8.33	
O(1a), O(1b)	-0.42	14.63	17.53	13.65			14.08		
O(1a), N(2a)	4.10	16.36	22.08	15.38	13.43	18.40	11.28	-2.93	-3.68
N(2a), O(3a)	3.32	7.78	24.39	13.06	15.96	16.06	9.74	8.18	-8.33

Table 7S. Gibbs free energies of reaction (ΔG, kcal/mol), reorganization energies (λ, kcal/mol), Gibbs free energies of activation ($\Delta G^{\neq}$, kcal/mol) and rate coefficients (k_{app}, M^{-1} s^{-1}) for the reduction of the most likely Cu(II) chelates by $O_2^{\bullet-}$ and the ascorbate anion (Asc^-). The values were calculated in aqueous solution, at 298.15 K. Free Cu(II) is included for comparison purposes.

	ΔG°	λ	$\Delta G^{\neq}$	k_{app}
		$O_2^{\bullet-}$		
free Cu(II)	-26.19	29.96	0.12	7.46E+09
C1	-20.42	20.29	0.00	7.77E+09
C3	-24.25	25.61	0.02	7.75E+09
C6	-25.99	31.56	0.25	7.67E+09
C7	-27.23	27.23	0.00	7.82E+09
C8	-19.33	30.06	0.96	7.69E+09
C9	-18.92	30.07	1.03	7.68E+09
C10	-20.00	25.47	0.29	7.79E+09
C12	-19.45	27.69	0.61	7.78E+09
C14	-27.53	30.04	0.05	7.69E+09
C15	-19.00	31.23	1.20	7.70E+09
C16	-19.03	31.55	1.24	7.73E+09
C23	-17.76	29.13	1.11	7.65E+09
C24	-11.06	29.27	2.83	6.81E+09
C25	-17.31	32.65	1.80	7.58E+09
C26	-1.73	28.27	6.23	1.64E+08
		Asc^-		
free Cu(II)	-2.24	36.02	7.92	9.69E+06
C1	3.53	26.35	8.47	3.85E+06
C3	-0.30	31.66	7.77	1.26E+07
C6	-2.04	37.62	8.41	4.23E+06
C7	-3.28	33.28	6.76	6.80E+07
C8	4.62	36.11	11.49	2.35E+04
C9	5.02	36.13	11.72	1.59E+04
C10	3.95	31.52	9.98	3.00E+05
C12	4.50	33.74	10.84	7.08E+04
C14	-3.58	36.10	7.32	2.65E+07
C15	4.95	37.28	11.96	1.07E+04
C16	4.92	37.60	12.02	9.55E+03
C23	6.19	35.19	12.16	7.51E+03
C24	12.89	35.32	16.45	5.39E+00
C25	6.64	38.70	13.28	1.15E+03
C26	22.22	34.33	23.29	5.25E-05

Table 8S. Gibbs energy cost (ΔG) associated with the semi-reaction corresponding to the Cu(II) reduction to Cu(I).

	ΔG		**ΔG**
free Cu	118.46	C16	111.30
C1	112.70	C17	106.50
C3	116.52	C18	108.71
C6	118.26	C19	109.08
C7	119.50	C20	105.00
C8	111.60	C21	102.71
C9	111.20	C23	110.03
C10	112.27	C24	103.33
C12	111.72	C25	109.58
C13	108.29	C26	94.00
C14	119.80	C27	82.95
C15	111.28	C28	88.92

Table 9S. Comparison of the results obtained, with and without including explicit water molecules, for the reduction reactions of free copper:

$$Cu^{2+}_{free} + O_2^{\bullet -}\left(nH_2O\right) \rightarrow Cu^{+}_{free} + {}^3O_2\left(mH_2O\right)$$

$$Cu^{2+}_{free} + Asc^{-}\left(nH_2O\right) \rightarrow Cu^{+}_{free} + Asc^{\bullet}\left(mH_2O\right)$$

	n	*m*	ΔG (kcal/mol)	k, T=298.15 K ($M^{-1}s^{-1}$)
Reductant = $O_2^{\bullet -}$	0	0	-26.19	7.46×10^9
	1	0	-26.10	7.41×10^9
	1	1	-23.26	6.90×10^9
Reductant = Asc^-	0	0	-2.24	9.69×10^6
	1	0	-4.22	5.06×10^6
	1	1	-0.38	8.42×10^5

Table 10S. Comparison of the results obtained, with and without including explicit water molecules, for the reduction reactions of C27:

$$Cu^{2+}_{C27} + O_2^{\bullet -}\left(nH_2O\right) \rightarrow Cu^{+}_{C27} + {}^3O_2\left(mH_2O\right)$$

$$Cu^{2+}_{C27} + Asc^{-}\left(nH_2O\right) \rightarrow Cu^{+}_{C27} + Asc^{\bullet}\left(mH_2O\right)$$

	n	*m*	ΔG (kcal/mol)	k, T=298.15 K ($M^{-1}s^{-1}$)
Reductant = $O_2^{\bullet -}$	0	0	9.33	8.90×10^5
	1	0	9.42	6.12×10^5
Reductant = Asc^-	0	0	33.28	1.58×10^{-16}
	1	1	35.89	1.06×10^{-17}

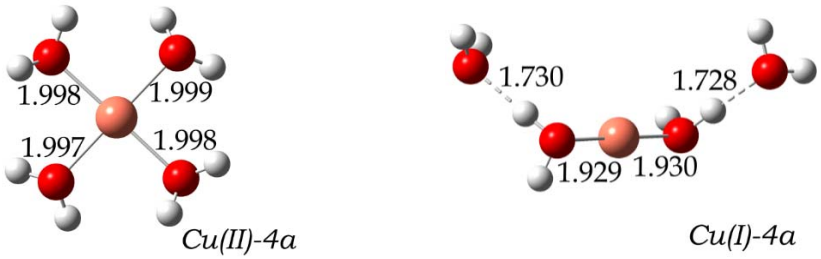

Figure 1S. Structures of Cu(II) and Cu(I), including 4 explicit water molecules.

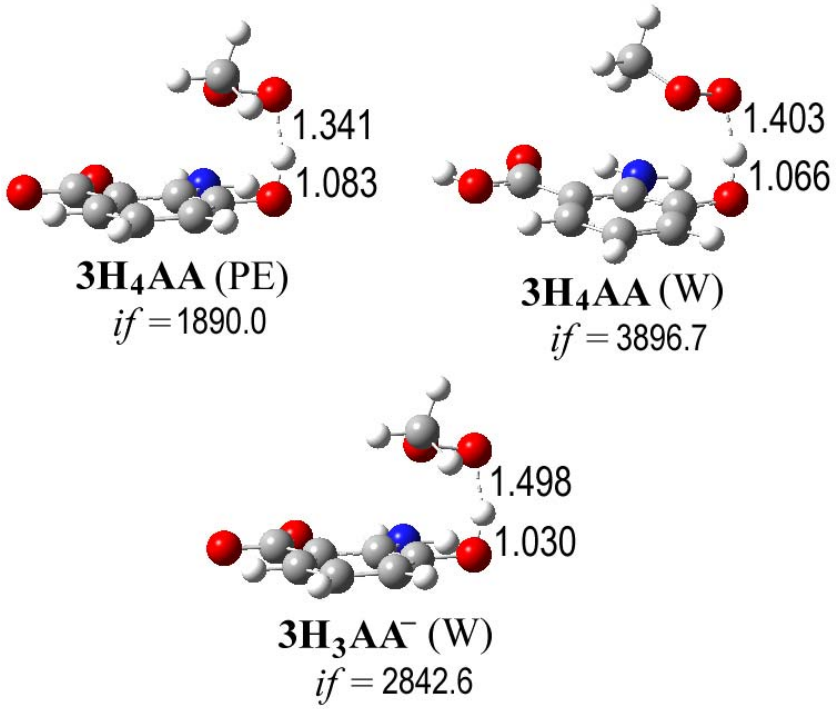

Figure 2S. Transition states of the HT reactions between 3-hydroxyanthranilic acid and $CH_3OO^{\bullet}$. PE = pentyl ethanoate, W = water, *if* = imaginary frequency.

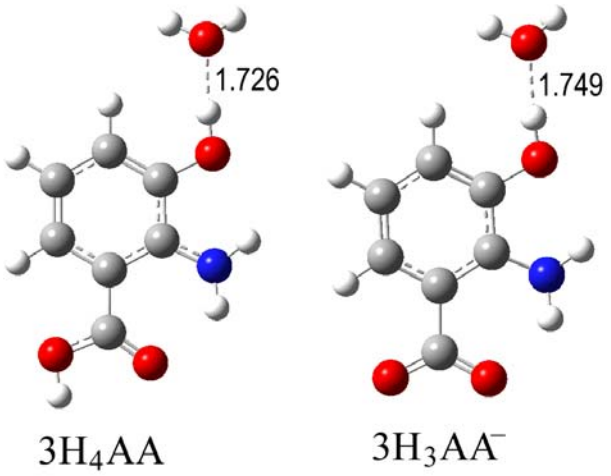

Figure 3S. Structures of S···HBD complexes involving the neutral and mono-anionic species of 3-hydroxyanthranilic acid.

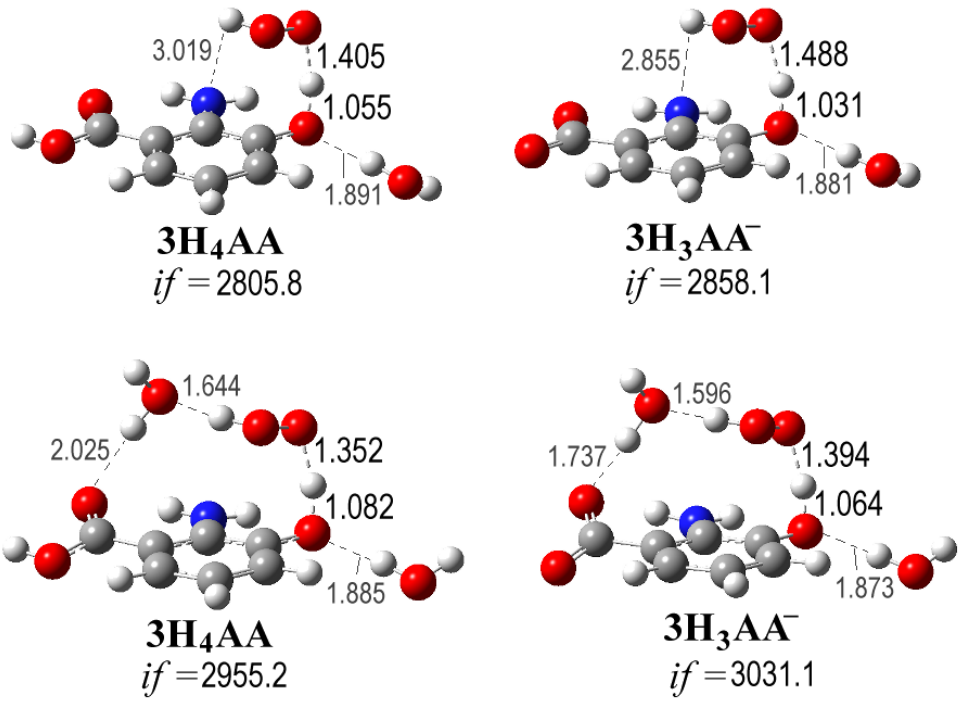

Figure 4S. Transition states of the HT reactions between 3-hydroxyanthranilic acid and HOO•, including explicit water molecules.

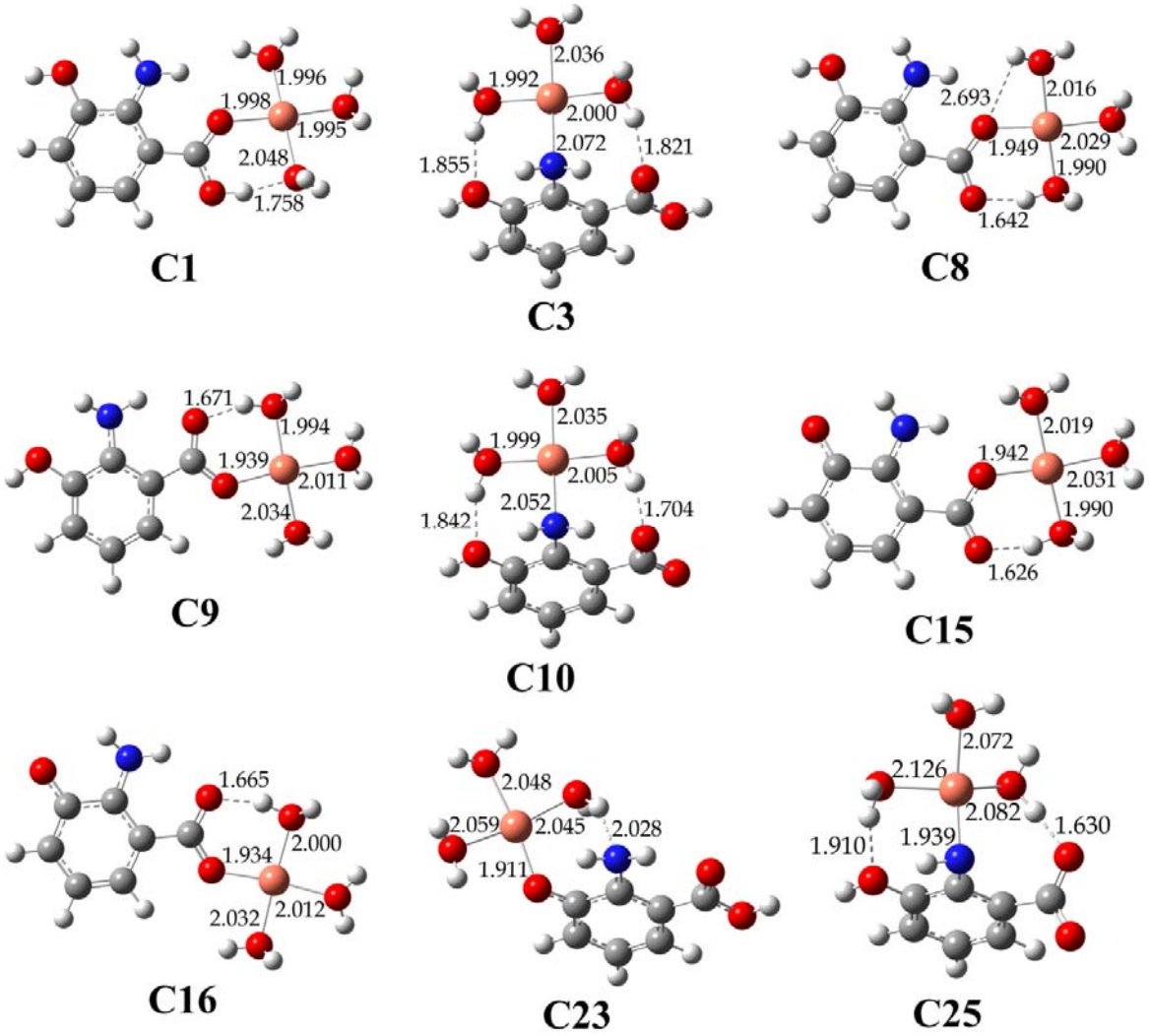

Figure 5S. Structures of monodentate chelates involved in exergonic reaction channels that are not the most exergonic ones.

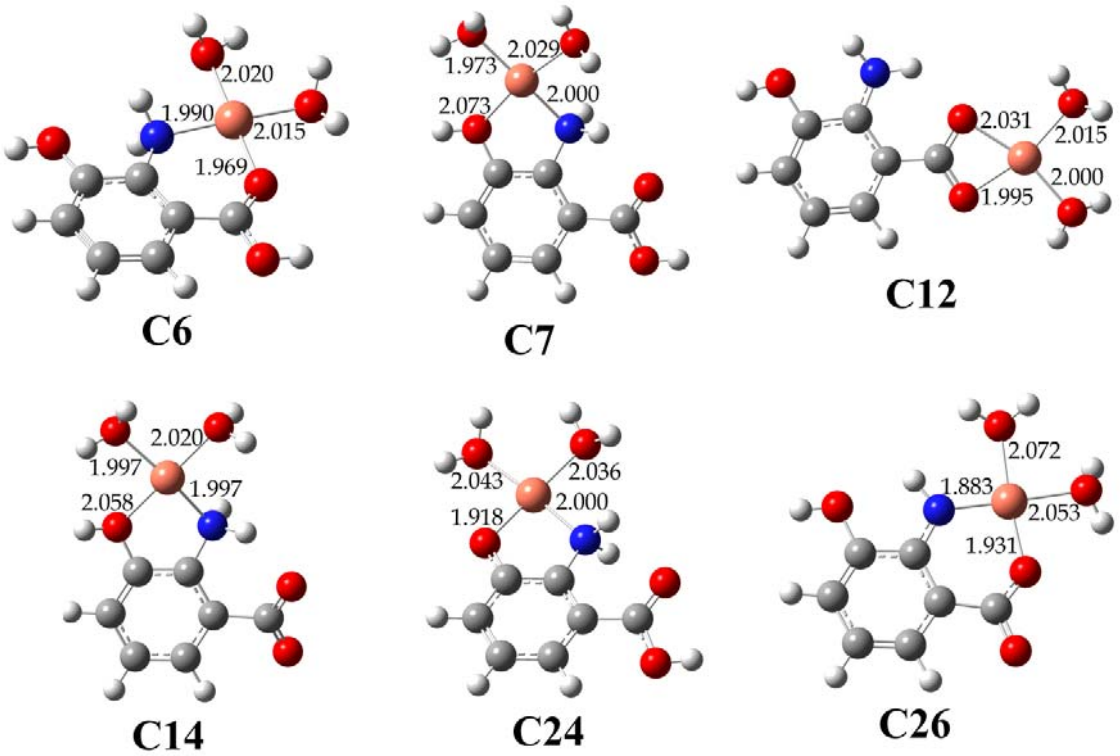

Figure 6S. Structures of bidentate chelates involved in exergonic reaction channels that are not the most exergonic ones.