

Copper-amyloid- β complex may catalyze peroxynitrite production in brain: evidence from molecular modeling

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Supplementary Information

The 14 amino acids model used for the A β is :

Asp¹-Ala²-Glu³-Phe⁴- Arg⁵-His⁶- Asp⁷- Ser⁸- Gly⁹- Tyr¹⁰- Glu¹¹- Val¹²- His¹³- His¹⁴

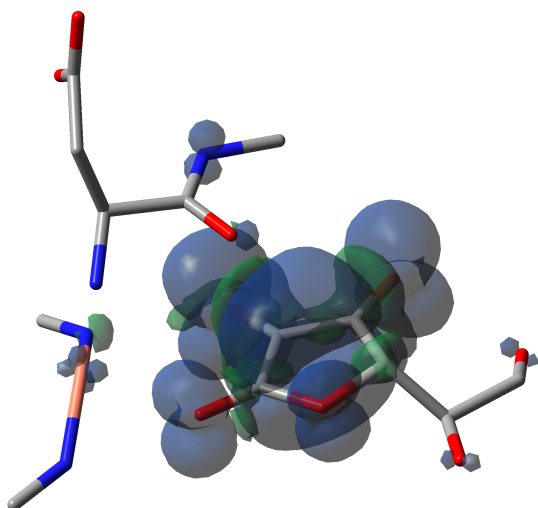


Figure SI.1 Spin density map computed for *R2*

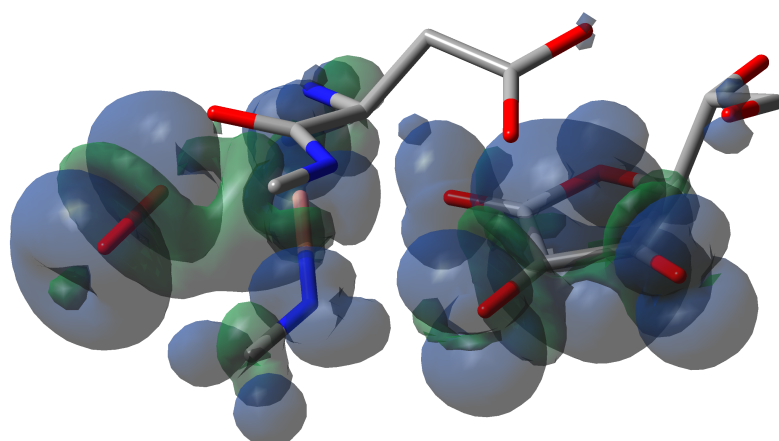


Figure SI.2 Spin density map computed for *R3*

Results based on a small model of the catalytic site

It is worth to notice that the first three steps of the mechanism reported in this contribution, that is ascorbic acid, PCET and molecular oxygen coordination, are similar to those previously proposed for the H_2O_2 formation through Cu/A β catalysis. Indeed, also in this latter case O_2 coordination is computed as an endothermic step, as in our current proposed mechanism (+5.2 kcal/mol).

However, contrary to the results discussed in the present work, the mechanism previously reported in literature was obtained under the hypothesis that copper, within the complex of A β , is coordinated by three histidines and one tyrosine. This last residue was of pivotal importance for the mechanism proposed. Indeed, a more recent experimental study ruled out its presence in the first coordination sphere of copper in the A β complex.

Nonetheless in order to allow a fair comparison between the present mechanism and that previously reported in literature, the reaction mechanism was also investigated using a minimal model of the Cu A β complex that is a model where only the residues and molecules belonging to the copper first coordination shell were considered. In such a case the effect of the different coordination sphere of the Cu atoms can be directly derived by comparison with the data reported in literature.

The small model used for these calculations (where histidines have been modeled by imines) while aspartate and Ascorbate are fully included, is depicted in Figure SI.3 together with the catalytic cycle studied.

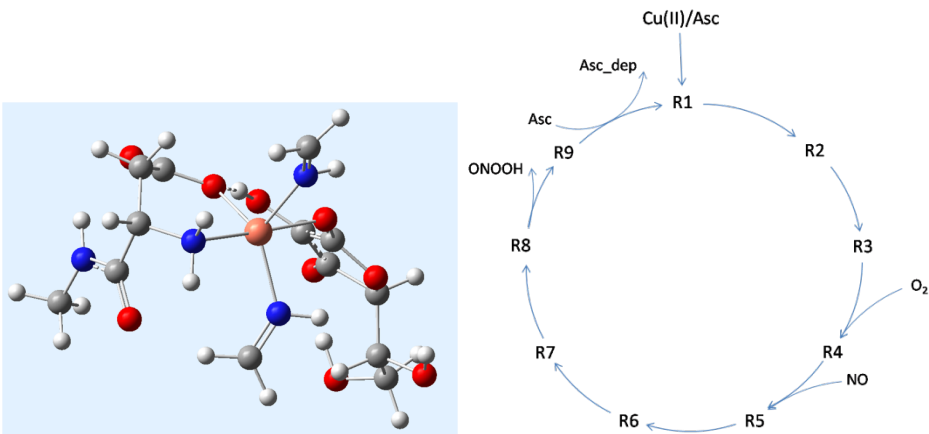


Figure SI.3. “Small model” catalytic cycle (right) and Cu site model used (left).

The energies of the intermediates occurring in such catalytic cycle are reported in Figure SI.4 while all a schematic view of all intermediates characterized are reported in Figure SI.5.

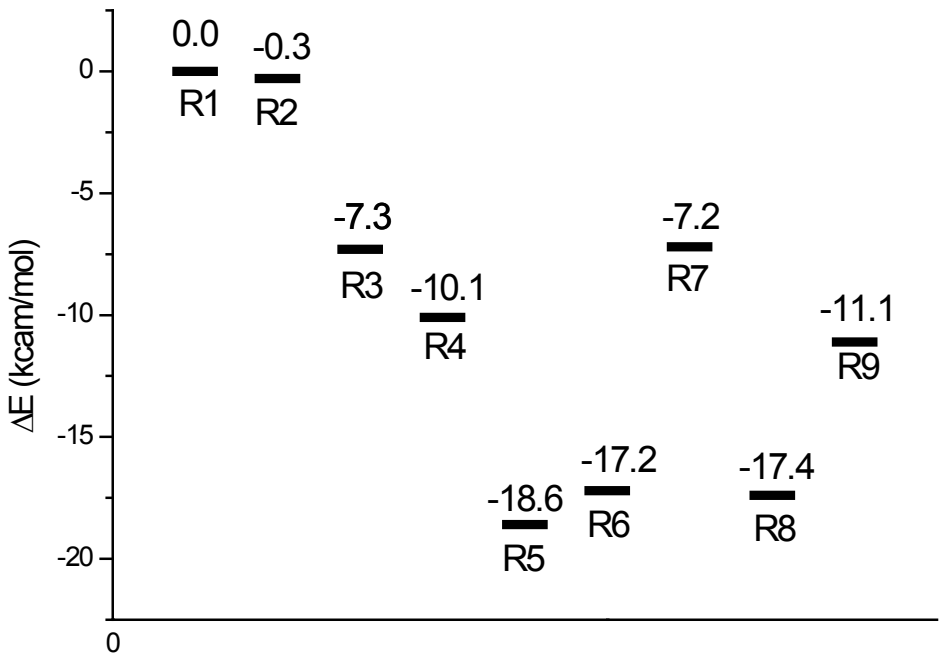


Figure SI.4. “Small model” catalytic cycle. Energies in kcal/mol.

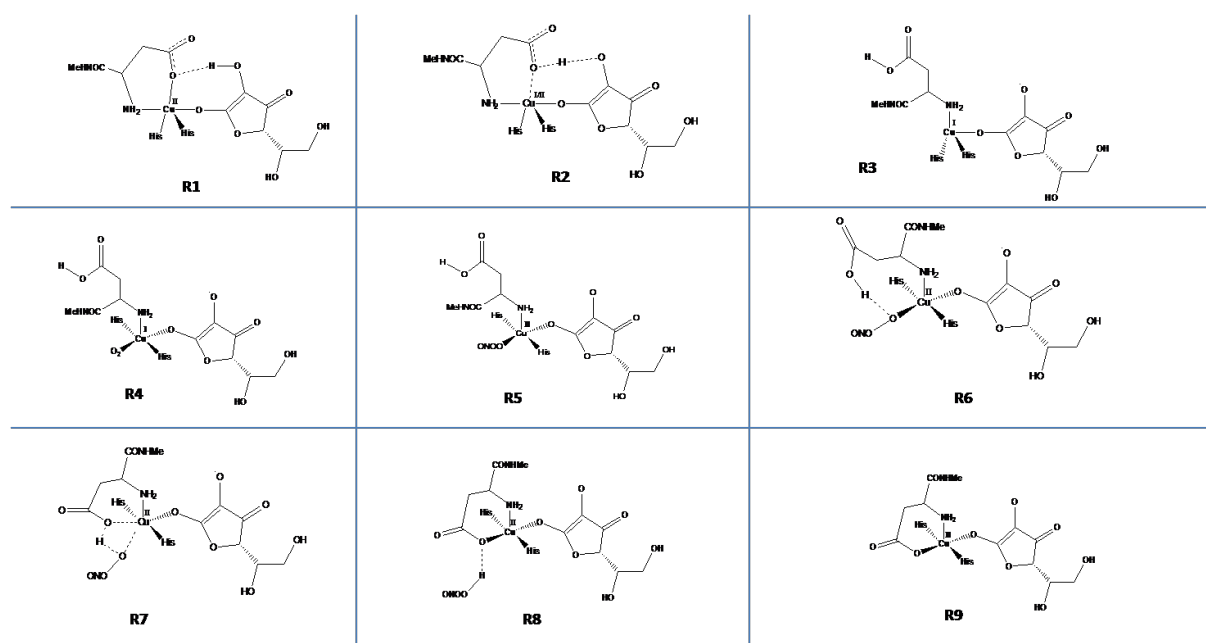


Figure SI.5. Structure of intermediates involved in the “small model” catalytic cycle.

Using such a model, all steps are computed to be exothermic and the whole energetic balance seems to be comparable to that computed, and previously reported in literature, for the H_2O_2 formation. Nonetheless, comparing these results to those obtained for the larger model including the peptide backbone (reported in the present contribution), clearly shows that the backbone plays a non negligible role in modulating the energetic of whole the catalytic cycle.

Complete reference 49

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