Study of Tyrosine Radical Formation and Di-tyrosine Cross-linking by Cu Ion And H2O2 Using Density Functional Theory.

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Abstract

Alzheimer's disease (AD) is characterized by the deposition of self-assembled Amyloid-β fibrils composed of highly stable and insoluble amyloid plaques in the neuropil. Al-Hilaly et al.[1] investigated the formation of di-tyrosine cross-links in the Amyloid-β (42) peptide by covalent coupling of two tyrosine residues, which has been implied to play a key role in the development of the Alzheimer's disease. These di-tyrosines can be generated by reactive oxygen species catalyzed by Cu²⁺ ions. Using density functional theory, we studied this tyrosine radical formation with Cu ions and H₂O₂ to understand the tyrosine cross-linking mechanism. The TS energy of the reaction catalyzed by Cu(II) was 24.3 kcal/mol, and the TS energy of the reaction catalyzed by Cu(I) was 7.8 kcal/mol. These results suggest that Cu(I) has a higher reactivity than Cu(II), and that the reaction under Cu(II) occurs slowly.

Computational Details

All molecules are optimized with unrestricted-B3LYP/Def2SVP/CPCM(Acetonitrile). Transition states (TS) and minima were verified with frequency calculations. The connections between stationary points were established using IRC calculations. Accurate electronic energies were estimated with single-point calculations with unrestricted-B3LYP/Def2TZVPP/CPCM(Acetonitrile) at TS and minima. The calculations were done with the Gaussian 16 program.

Proposed Mechanism

![Figure 1](image1.png)

**Figure 1.** The reaction mechanism of formation of the tyrosine radical with models of [CuII(H₂O₂)(His)₂(Glu)] at the doublet (S = 1/2) spin state at B3LYP/Def2-SVP//Def2-TZVPP level.

**Figure 2.** The reaction mechanism of formation of the tyrosine radical with models of [CuII(H₂O₂)(His)₂(Glu)] at the singlet (S = 0) spin state at B3LYP/Def2-SVP//Def2-TZVPP level.

![Figure 2](image2.png)

**Table 1.** Mulliken spin density distributions of the tyrosine radical formation reaction mediated by [CuII(His)₂(Glu)].

<table>
<thead>
<tr>
<th></th>
<th>Cu</th>
<th>Qbase</th>
<th>Qsuper</th>
<th>Ligand</th>
<th>Substrate</th>
<th>Sum</th>
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<tbody>
<tr>
<td>RC</td>
<td>0.63</td>
<td>0.04</td>
<td>0.01</td>
<td>0.32</td>
<td>0.00</td>
<td>1.0</td>
</tr>
<tr>
<td>TS</td>
<td>0.62</td>
<td>0.38</td>
<td>0.37</td>
<td>-0.17</td>
<td>0.29</td>
<td>-0.50</td>
</tr>
<tr>
<td>PC</td>
<td>0.62</td>
<td>0.38</td>
<td>0.71</td>
<td>-0.32</td>
<td>0.30</td>
<td>-0.69</td>
</tr>
</tbody>
</table>

**Conclusion**

The results of the reaction calculation in progress so far showed that the rate-limiting transition state reaction energy with Cu(I) was about 16.5 kcal/mol lower than that of Cu(II). Therefore, it may be seen that the reaction occurs predominantly in Cu(I) than in Cu(II). However, so far, the energetic cost of reducing Cu(II) to Cu(I) has not been investigated.

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