THE OBJECTIVES OF THIS WORK

1) To determine the global minimum energy conformer of transitional heme-artemisinin complex at the semi-empirical PM3 level, in the presence and absence of water molecules

2) To determine thermodynamical, structural and electronic characteristics of reductive artemisinin decomposition, catalyzed by heme iron via four main routes: Density Functional Theory (B3LYP 6-31G*), chemometric (exploratory analysis) and structural (Cambridge Structural Database - CSD) are applied

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ARTEMISININ: A NEW POTENT ANTIMALARIAL

Artemisinin (in Chinese: qinghaoxu, QHS) is known more than four decades as a natural product from Artemisia annua, effective against human antimalaria, including parasites P. falciparum and Plasmodium strains already resistant against conventional antimalarials. According to the most accepted theory, QHS forms a transitional complex with heme iron, which decomposes into oxygen- or carbon-centered radicals. The radicals follow several decomposition routes in which iron is catalyst. Among species appearing in the decomposition, radicals are species that react with various parasitic molecules. These reactions inhibit parasite defenses and cause its death. Therefore, it is important to have detailed insights into QHS mechanisms of action. Such knowledge can be useful in design of more effective antimalarials from the artemisinin class.

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CONFORMATIONAL STUDY OF THE HEME-ARTEMISININ COMPLEX

Figure 2. The global minimum energy heme-artemisinin complex. Transition angle C-Fe-O1-2 is 46° and 52° in absence and presence of water molecules, respectively.

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FOUR ARTEMISININ DECOMPOSITION ROUTES

Figure 3. Partially hydrated heme-artemisinin complex. Water-water and water-heme hydrogen bonds are visible.

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ROUTES A AND B1

Figure 4. Overlap of hydrated (green) and free (red/blue) heme-artemisinin complexes. A minor change in conformation is due to partial hydration.

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CHEMOMETRIC COMPARISON OF DECOMPOSITION ROUTES

Figure 5. Geometries of QHS and 1/2. Pink ball halves show the radical delocalization between O1 and O2. Interatomic distances before 1,5-hydrogen shift are shown also.

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CHEMOMETRIC COMPARISON OF DECOMPOSITION ROUTES

Table 1. Six electronic* and structural† descriptors of the artemisinin decomposition routes.

<table>
<thead>
<tr>
<th>Species</th>
<th>Erel kcal mol⁻¹</th>
<th>Urel kcal mol⁻¹</th>
<th>ΔHΔG0/22A</th>
<th>ΔGΔG0/22A</th>
<th>ΔEΔG0/22A</th>
<th>ΔHΔG0/22A</th>
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<td></td>
</tr>
</tbody>
</table>

*Electronic descriptors: Erel, Urel – energy and free energy relative to 1/2 (including that of CO₂), respectively
†Structural descriptors: d(O1-O2) – distance between peroxide oxygen atoms O1 and O2, ΔHΔG0/22A = average oxygen-oxygen distance (CO₂ is excluded), ΔEΔG0/22A = natural logarithm of Löwdin bond order of O2 0-0 distances, ΔHΔG0/22A = average of natural logarithms of Löwdin bond orders for the 0-0 distances.

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CONCLUSIONS

1) Stereoelectronic interactions define the global minimum energy conformer of heme-artemisinin complex, whereas water does not affect this conformation significantly.

2) Among studied routes of reductive artemisinin decomposition, there are two clusters: A-B1 and B2-B3. The former is kinetically and latter is thermodynamically favorable.

3) Routes A and B1 are probably interconnected via A/B1 route.

4) Product 4 probably does not belong to the studied decomposition routes.

5) Entropy is the driving force of artemisinin decomposition.

6) Along the decomposition routes, following is observed: formation of branched species and CO₂ release, increase of exothermicity, and weakening of attractive O...O interactions.

ACKNOWLEDGEMENTS