

Lowest energy structure determination of Iron/Curcumin/water complexes using computational chemistry.

By Daniel Stubing

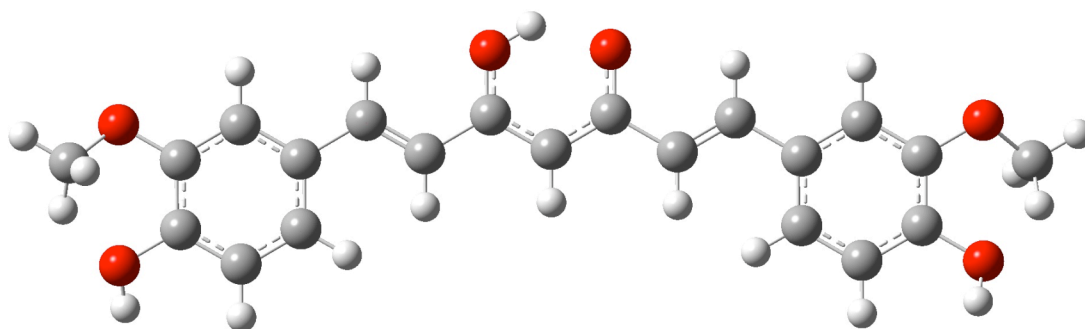
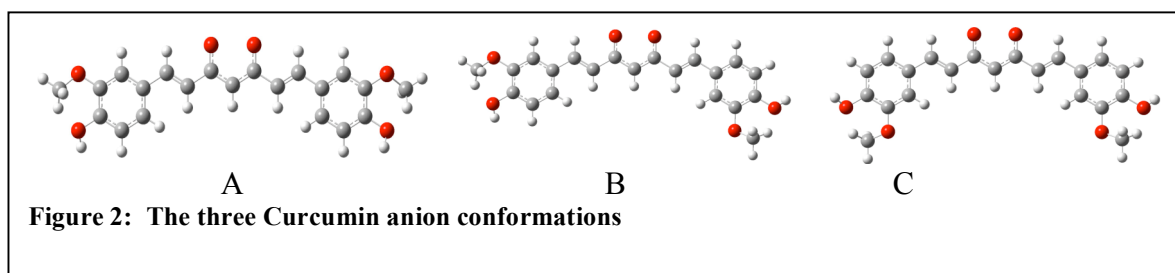


Figure 1: Structure of Curcumin

Introduction

The photosensitive compound Curcumin (Figure 1), found naturally in the plant Turmeric, has been used for generations in the subcontinent for many medicinal purposes. Lately the use of curcumin as a possible anticancer drug has been investigated. Curcumin shows considerable anticancer activity and its use as a potential treatment drug looks promising as it has no toxic, or hazardous effects in healthy cells. There have been many proposed reasons for the activity of curcumin, in actual fact activity would probably be due to a number of these. This group has previously done a computational study on how curcumin could interact with Copper ions. Other theories of its activity involve its binding relationship with Iron.¹ We now aim to work from the results of Copper complexes to find the energies of potential Fe/curcumin complexes to give an idea of which complex will be the most stable and therefore most naturally abundant. Also we have calculated the difference between Fe(II) and Fe(III) to determine if the curcumin anion is likely to reduce Fe(III) and if this would have any effect on natural complex conformation. It has previously been shown that curcumin can have three possible conformations labelled A, B, and C shown below (Figure 2).² Testing the optimised energy of all conformations is important in determining which will be the most likely natural conformation.



In the complexes of Cu(curcumin)(H₂O) it was found that the waters bound in a square planar or a “bridging” arrangement. These possibilities were tested with the Iron, however it is known that usually Iron forms tetrahedral and octahedral conformations depending on the number of ligands bound, and not square planar conformations.

The two oxidation states of Iron (Fe(II) and Fe(III)) were also investigated as well as each of the possible multiplicities, $2S+1$. (where $S = 2, 4$ or 6 for Fe(III) and $1, 3$, or 5

for Fe(II)). Optimisation of the complexes Fe, Fe(H₂O)₄, Fe(H₂O)₆, Fe(curcumin)(H₂O)₂, Fe(curcumin)(H₂O)₄, Fe(curcumin)₂(H₂O)₂ were undertaken with frequency calculations to find the lowest energy conformations.

Experimental

Using the Gaussian 03 program Geometry optimisation and harmonic vibrational frequency calculations were calculated for the Fe-curcumin-water complexes. The B3LYP density functional was used and the Iron was treated with the Stuttgart Relativistic Small Core (srsc) basis set and all other atoms with Dunning's cc-pVDZ basis set. All optimizations were performed with no symmetry constraints, and then were followed by a harmonic frequency calculation to show that there were no imaginary frequencies, meaning that these geometries are the true minimum and not a 'saddle point'.

Results/discussion

Optimisation of Fe(H₂O)₆ complexes show that an octahedral arrangement is preferred. The optimal energy of Fe(III)(H₂O)₆³⁺ is -581.49 Hartrees and for Fe(II)(H₂O)₆²⁺ is -582.10 Hartrees.

The energy calculations of the naked Iron metal showed that the lowest energy multiplicity of Fe(III) is a sextet with an energy of -121.81 Hartrees and the lowest energy conformation of Fe(II) is a quintet with an energy of -122.97 Hartrees. These multiplicities were expected according to the NIST Atomic Spectra Database³.

Adding two water molecules and a curcumin anion to the metal ion can give two binding arrangements similar to what is seen with the Copper. The first is a four coordinate metal centre where both the water molecules are around the metal. For these structures the waters are not in the plane of the curcumin, like with copper, but are slightly skewed off the plane, but not to the point of being tetrahedral. The other arrangement is 3 coordinate, where one water is on the metal and the second is bridging the coordinated water and the curcumin (Figure 3). The most stable Fe(II) structure is the tetrahedral like arrangement with Curcumin C (Figure 4a), and for Fe(III) it is the tetrahedral like with Curcumin B (Figure 4b).

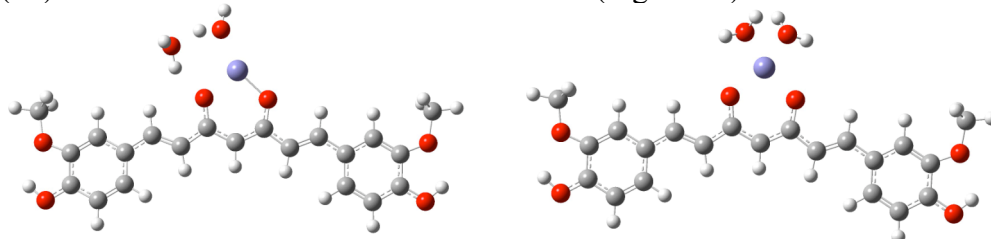


Figure 3: Bridging and tetrahedral like arrangements of [Fe(curcuminA)(H₂O)₂]

Adding another two more waters interestingly gives two arrangements, where we expected only an octahedral arrangement the system also minimised to a five coordinate system with the extra water bridging a water bound to the metal and the Curcumin. The calculations indicate that for a Fe(II) metal centre the most stable arrangement is this five coordinate system with the extra water bridging to Curcumin B on the methoxy side (Figure 4c). This has an energy of -1692.68 Hartree with a binding energy of -25.50 eV. The most stable Fe(III) complex however is octahedral with curcumin B with an energy of -1692.37 HF and a binding energy of -48.67 eV

(Figure 4d). The Fe(III) complexes have a greater binding energy than the Fe(II) complexes however the Fe(II) complexes are lower in energy.

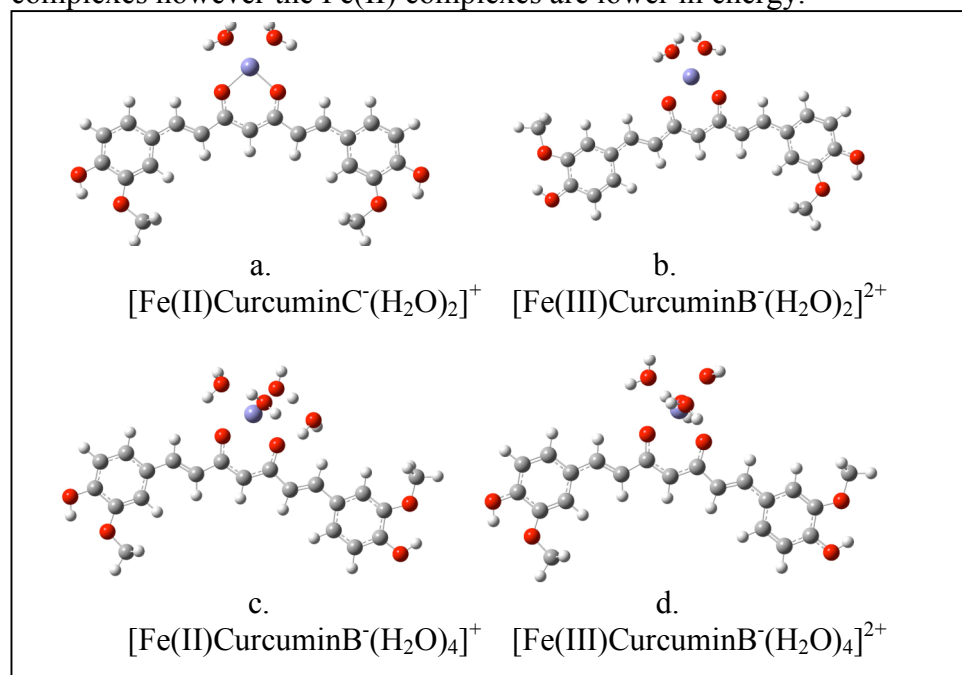


Figure 4: The lowest energy complex arrangements

Using the above results a complexation pathway from the bare metal ion and individual components can be proposed. Figure 5 compares binding energies of each of the Fe(II) complexes investigated. We propose that from the bare metal the $[\text{Fe(II)CurcuminC}^-(\text{H}_2\text{O})_2]^+$ complex will be formed first (this may be done in several steps), then two waters are added to get the $[\text{Fe(II)CurcuminB}^-(\text{H}_2\text{O})_4]^+$ complex. Or another curcumin to form $[\text{Fe(II)(Curcumin)}_2(\text{H}_2\text{O})_2]$ either way the most stable complexes investigated thus far are the $[\text{Fe(II)(Curcumin)}_2(\text{H}_2\text{O})_2]$. Likewise figure 6 shows the relative binding energies of each of the Fe(III) complexes investigated and a similar pathway can be observed.

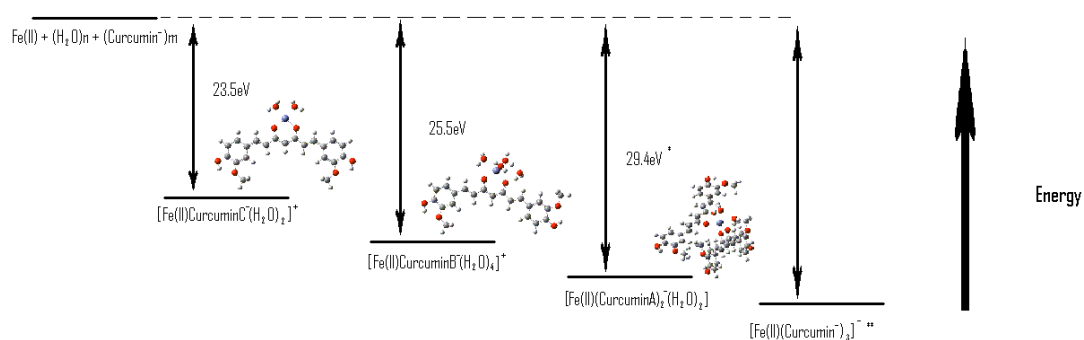


Figure 5: Relative binding energies of the most stable Fe(II) complexes. * preliminary result no frequency calculations performed, and may not be global minima conformation. ** not calculated (see future directions)

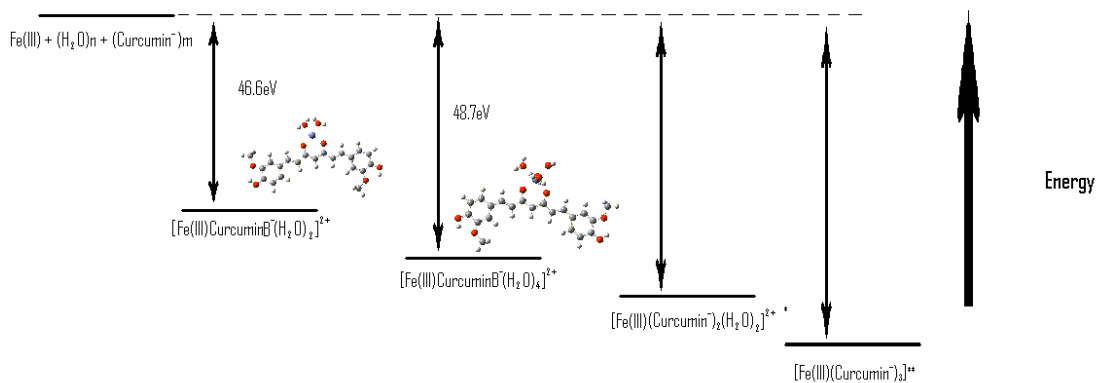


Figure 6: Relative binding energies of the most stable Fe(II) complexes. * not calculated but expect to be similar to Fe(II). ** not calculated (see future directions)

The possibility of the use of GAMESS on the GPU system Tesla and the CPU system corvus was also investigated to test the use of the system as a suitable molecular modelling tool in the future. The speed and the accuracy of the computer was to be tested. But due to system and time problems no calculations were able to be undertaken.

Future directions

This project is still in its early stages, the remaining calculations of $[\text{Fe}(\text{Curcumin}^-)(\text{H}_2\text{O})_2]$ and $[\text{Fe}(\text{Curcumin}^-)(\text{H}_2\text{O})_4]$, need to be completed to get a complete understanding of all the possible conformations. The results for the $[\text{Fe}(\text{curcumin}^-)_2(\text{H}_2\text{O})_2]$ structures will need to be examined. And then $[\text{Fe}(\text{curcumin}^-)_3]$ will be calculated to see if it is likely this exists and is the natural conformation of an Iron Curcumin complex.

Acknowledgments

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References

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