DFT study of advanced glycation endproducts inhibitors.

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Introduction

The Maillard reaction is a spontaneous non-enzymatic reaction between reducing sugars and long-lived proteins and lipids that are a major form of chemical modifications of biomolecules that compromise their functions. This reaction initially involves the reversible condensation of a terminal NH_2 group of a protein or an amine-phospholipid and a C=O group of the sugar to give a Schiff base. The Schiff base is unstable and undergoes a rearrangement to yield a more-stable ketamine compound, the so-called Amadori compound. Subsequently, the Amadori compound can undergo various complex processes to form the ***advanced glycation endproducts*** (AGEs). In some cases the formation of Maillard reaction products ***in vivo*** is also known as the glycation reaction.

Glycation is one of the major sources of reactive oxygen species (ROS), which can induce the deterioration of tissues and organs. It is associated to normal aging and some diabetes diseases, such as diabetes (atherosclerosis and chronic inflammatory diseases) [1,2].

The Amadori product is prone to autoxidation in presence of catalytic metals, like Cu^{2+} and Fe^{3+}. This redox process is a key step in the AGE formation. The Cu^{2+} is now recognized as an essential trace for many biological functions and it serves as a catalytic component in many pathologic oxidative processes. For this reason the biological activity of Cu^{2+} and its complexes with drugs and small molecules have been the subject of a large number of studies [3]

Recently, it has been proposed new aromatic compounds with potent AGE inhibitory effect [4]. One of the most potent AGE-inhibitor is the LR-74 (2-(8-quinolinoxy) propionic acid). The mechanism or mechanisms of action of this compound are still unclear. There are some evidences that chelation of transition metals and/or trapping or indirect inhibition of formation of reactive carbonyl compounds are involved in the mechanism of action of these novel AGE inhibitors. Some of them are potent chelators of Cu^{2+}, cation strongly related to the protein glycation. In this work, we study the formation of different complexes between the Cu^{2+} and the LR-74 inhibitor by theoretical calculations.

Materials and Method.

The DFT calculations were performed using the Gaussian03 program package. All structures were fully optimized at the UB3LYP level of theory. The Stuttgat/Dresden basis set and Effective Core Potential were used in all the non-hydrogen atoms (Dirac-Fock relativistic ECP for Cu^{2+} and Wood-Boring quasi-relativistic ECP for N, C and O). The 6-31G basis set has been used for the hydrogen.

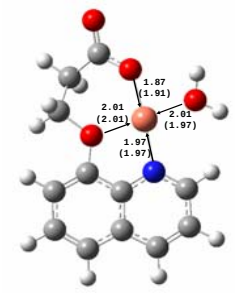
Vibrational analyses were performed on all optimized structures in order to calculate the free energy and characterize them as energetic minima. All structures showed all the force constants positive.

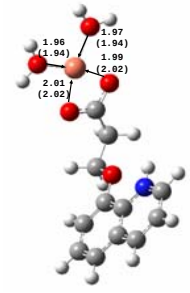
In order to mimic the solvent water effect, we used the Cosmo Polarizable Continuum Method (CPCM).

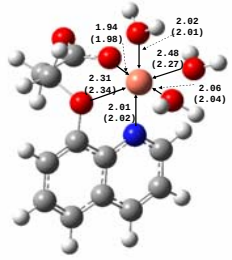
Results and Discusion.

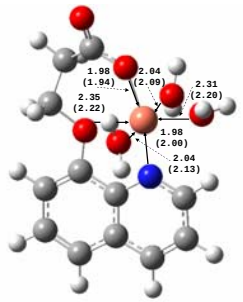
Six different complexes have been investigated. The bond length between Cu atom and the chelator are represented in the figures. Moreover, we obtained of dihedral angle ω_1 that they represent the dihedral angle the four atoms at equatorial positions. Ideally the dihedral angle ω_1 should be 0°.

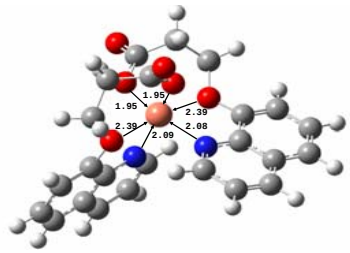
In gas phase the most stable complexes are 5 and 6 ($[Cu(Lr\text{-}74)_2]$), the complexes with only one Lr-74 molecule (complex 1-4), the octahedra complex 3 is the most stable. This fact changes with solvation, being the flat square complex 1 the most stable. In the literature we have found diverse methods to find the relative stability of a complex (differences between absolute energies or differences between Homo - Lumo orbitals), we verify in this work, that is necessary to realize the calculation of the free energy to find the correct scale.

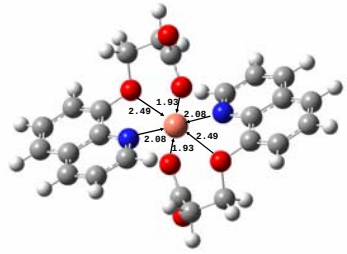












	complex 1	complex 2	complex 3	complex 4	complex 5	complex 6
Formula	$[Cu(Lr\text{-}74)(H_2O)]^+$	$[Cu(Lr\text{-}74)(H_2O)_2]^{2+}$	$[Cu(Lr\text{-}74)(H_2O)_3]^+$	$[Cu(Lr\text{-}74)(H_2O)_3]^+$	$[Cu(Lr\text{-}74)_2]$	$[Cu(Lr\text{-}74)_2]$
	G.P. Sol.	G.P. Sol.	G.P. Sol.	G.P. Sol.	G.P.	G.P.
ω_1	-0.6 (2.4)	0.5 (-0.3)	-15.2 (-11.0)	-2.7 (-8.3)	-23.2	0.1
Δ(ev)	0.147 (0.162)	0.142 (0.145)	0.155 (0.160)	0.158 (0.164)	0.126	0.132
ΔE (Kcal/mol)	-843.6 (-303.1)	-450.4 (-157.3)	-875.0 (-316.3)	-868.9 (-314.8)	-1229.2	-1221.1
ΔG°(Kcal/mol)	-819.9 (-277.9)	-415.4 (-124.8)	-827.3 (-271.7)	-822.4 (-268.4)	-1201.9	-1195.2

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