Computational Prediction of the Reactivity Sites of Alzheimer Amyloid b-Peptides A*b*40 and A*b*42

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Abstract

Alzheimer's illness is an advanced nervous syndrome that is connected to the existence of extracellular senile plaques. The extracellular senile plaques are predominantly composed of 40-42 residues of amino acid comprising polypeptides identified as b-peptides. The Theory of Chemical Reactivity together with MEDT (Molecular Electron Density Theory) and Conceptual DFT have been used to determine descriptors that permitted the forecast of the sites of reactivity of the Alzheimer amyloidb-Peptides Ab40 and Ab42 through QM:MM calculations with the ONIOM methodology.

Keywords: Alzheimer; Amyloid b-peptides; Ab40; Ab42; Computational chemistry; Molecular modeling; Conceptual DFT; Chemical Reactivity theory

Introduction

The non-enzymatic reaction between the amino groups of amino acids, peptides and proteins and reducing carbohydrates is referred to as glycation. A series of several reactions causes the AGEs (Advanced Glycation End products) formation. These molecules have been linked to certain illnesses such as diabetes, Parkinson and Alzheimer. The non-enzymatic glycation of proteins has been connected to the significant cause of the Alzheimer and diabetes ailment complications. It is recognized that glycation comprises of the reaction of the *e*-amino groups of the lysines present in the proteins.

The amino group immediate chemical environment controls the reaction of glycation. Some years ago, [1,2] studied several peptides of the A*b*40 and A*b*42 kind. The primary structure of these peptides is DAEFRHDSGYEVHHQKLVF-

FAEDVGSNKGAIILGLMVGGVVIA. The major difference between these two peptides is the absence or presence of the C-terminal dipeptide (e.g. two hydrophobic residues Ile41-Ala42). The dipeptide has been described to make a significant effect on Ab(1-40) and Ab(1-42) oligomerization rates and mechanisms. Thus, it is critical to understand the molecular details of each species in early Ab combination for a coherent design of therapeutics to inhibit Alzheimer's illness.

Therefore, it is considered necessary to develop a computational and theoretic tool that can be helpful in a forecast of the ideal sites of glycation for the diverse Ab peptides since they can assist in AGE inhibitors development [3]. The goal of this effort is studying the sites of glycation of the peptides through calculation of various Conceptual DFT descriptors such as the Fukui function indices, nucleophilic and electrophilic Parr functions and the condensed dual descriptor Df(r) [4]. As the preferred glycation sites, will be equivalent to the ones for the protonation reaction, the results of the calculations will permit us to qualitatively forecast the pKa variation of the lysine residues between the two peptides.

Theoretical Framework

As this work is part of an ongoing project, the theoretical background is similar to that presented in previous research [5-11] and will be shown here for the sake of completeness. The chemical potential m in the theoretical background of DFT is well defined as: $m = (\partial E/\partial N)_{v(\sim r)} = c$ where c represents the electronegativity [12,13]. On the other hand, the global hardness h is: $h = \partial^2 E/\partial N^2{}_{v(\sim r)}$. Through finite difference approximation, the two expressions may be written as: $c=0.5$ (I+A) and h=(I-A). I and A represents the ionization potential and electron affinity, respectively. The electrophilicity index w has been defined as [14]: $w=m^2/2h = (I+A)^2/4(I\ A)$.

The electroaccepting (w^+) and electrodonating (w) powers are stated as: [15] $w^+=(I+3A)^2/16(I\ A)$ and $w=(3I+A)^2/16(I\ A)$. The larger value of w^+ value corresponds to enhanced ability to accept charge, while a smaller value of w makes it an improved electron donor. The following net electrophilicity definition has been recommended [16] to make a comparison between w+ and w: Dw=w+ (w)=w++w, that is, a relation between the electro donating and electro accepting powers.

Settings and Computational Methods

Following the lines of our previous work, [5-11] the molecular structures of the amyloid b-peptides were optimized by starting with the readily available PDB structures), [17] and finding the most stable conformers by means of the Avogadro 1.2.0 program [18,19] through a random sampling technique with molecular mechanics and a consideration of all the torsional angles through the general AMBER force field [20].

The energies of the neutral, positive and negative peptides were obtained within the framework of QM:MM calculations performed through the ONIOM method [21] in the presence of water as a solvent, by doing IEF-PCM computations according to the SMD solvation model [22]. For the QM region, the MN12SX density functional [23] was selected in association with the Def2TZVP basis set [24,25]. All the ONIOM calculations were done and executed with the Gaussian 09 [26] series of programs.

Results and Discussion

TABLE 1 shows the ionization potentials I and electron affinities A (in eV), and global electronegativity c, total chemical hardness h, global electrophilicity w, electrodonating power, (w), electro accepting power (w^+), and net electrophilicity Dw of the optimized conformers of the amyloid b-peptides Ab40 and Ab42 calculated with the ONIOM method (MN12SX/Def2TZVP:Amber) using water as solvent simulated with the SMD parameterization of the IEF-PCM model.

TABLE 1. **Ionization potentials I and electron affinities A (in eV), and global electronegativity c, total chemical hardness h, global electrophilicity w, electrodonating power, (w), electro accepting power (w^+), and net electrophilicity Dw of the optimized conformers of the amyloid b-peptides Ab40 and Ab42 calculated with the ONIOM method (MN12SX/Def2TZVP:Amber) using water as solvent simulated with the SMD parameterization of the IEF-PCM model.**

Peptide	I	A	c	h	w	(w)	(w^+)	Dw
Ab40	6.412	0.137	3.275	6.275	0.855	3.739	0.464	4.202
Ab42	6.410	0.238	3.324	6.172	0.895	3.838	0.514	4.352

Within a molecule, the condensed Fukui functions may be used to define the chemical reactivity of each atom. The condensed Fukui functions are as follows: for nucleophilic attack, $f_k^+=q_k(N+1) q_k(N)$, for electrophilic attack, $f_k=q_k(N) q_k(N 1)$, and for radical attack, $f_k^0=[q_k(N+1) q_k(N 1)]/2$, where q_k represents the molecule's gross charge of atom k. The definition of the condensed dual descriptor is D$f_k= f_k^+-f_k$ [27,28]. One can note from the analysis given by the Fukui function that the dual descriptor sign is significant to describe the site of reactivity in a molecule in the direction of an electrophilic or a nucleophilic attack. This means that the ideal reactivity sites for nucleophilic attack will be those associated to to D$f_k>0$, while for the case of electrophilic attack, the direction will be favored by D$f_k<0$ [27-29].

In 2014, Domingo proposed the Parr functions P(r) [30,31] which are given by the following expressions: P (r) = $r^{rc}_s(r)$ (for electrophilic attacks) and $P^+(r)=r^{ra}_s(r)$ (for nucleophilic attacks), which are related to the atomic spin density (ASD) at the r atom of the radical cation or anion of a given molecule, respectively. The ASD over each atom of the radical cation and radical anion of the molecule gives the local nucleophilic P_k and electrophilic P^+_k Parr functions of the neutral molecule [32].

TABLE 2. **The condensed Fukui functions f_k, condensed dual descriptors D f_k and electrophilic Parr functions P_k f over the N atoms of the amino groups of the Lys residues of the amyloid Ab40 and Ab42 peptides calculated with the ONIOM method (MN12SX/Def2TZVP:Amber) using water as solvent simulated with the SMD parameterization of the IEF-PCM model. MPA: Mulliken Population Analysis-HPA: Hirshfeld Population Analysis.**

Peptide	MPA				HPA	
	f_k	D f_k	P_k	f_k	D f_k	P_k

Ab40	0.718	-0.718	0.804	0.633	-0.633	0.776
Ab42	0.717	-0.722	0.804	0.633	-0.640	0.776

TABLE 2 shows the condensed Fukui functions f_k, condensed dual descriptors D f_k and electrophilic Parr functions P_k f over the N atoms of the amino groups of the Lys residues of the amyloid Ab40 and Ab42 peptides calculated with the ONIOM method (MN12SX/Def2TZVP:Amber) using water as solvent simulated with the SMD parameterization of the IEF-PCM model are presented in TABLE 2.

From the examination of the results on TABLES 1 and 2, it can be concluded that there are not significative differences in the chemical reactivity of both peptides. Nevertheless, the sites for glycation will be also the preferred sites for protonation. Therefore, the pKa's of the Lys residues will also be reliant on the peptides conformational structures. Moreover, the trend in the pKa of the different conformers may be predicted in terms of the local hyper softness (LHS), which is a local reactivity descriptor that has been defined so that it permits to measure local reactivities according to the size of the molecule [33,34]. The equation is expressed as LHS D f (r)/h^2 D f (r) S^2 where S represents the global softness [4,35,36].

As the local hyper softness can be condensed over the atomic sites, the condensed local hyper softness is simply computed as LHS ' f_k^+ f_k (I A)^2.

By considering the values for the condensed dual descriptor Df_k from TABLE 2 and the values for the chemical hardness h from TABLE 1, it can be predicted that the pKa of the Lys residue of Ab42 will be slightly higher than the pKa of the corresponding site of Ab40. This difference can be attributed to the presence of the C-terminal dipeptide and may be linked to the mechanisms and the rates of Ab (1-40) and Ab (1-42) oligomerizations.

Conclusions

In this paper, the reactivity sites of Alzheimer's amyloid b peptides Ab40 and Ab42 have been forecasted and determined through the application of the Chemical Reactivity Theory, Conceptual DFT, and molecular electron density theory (MEDT). Amyloid b-peptides are dominant components of the extracellular senile plaques which is an indication of the Alzheimer's illness. Additionally, this paper has looked at the structure and the participation of Ab40 and Ab42 peptides in glycation, their sites of glycation, and the oligomerization rate and mechanisms so as to gain an understanding of their role in Alzheimer's illnesses. Partly, the motivation for the determination of the chemical reactivity sites was to inform about the development of AGE inhibitors.

The determination of the chemical reactivity sites was made possible through the computation of the QM:MM calculations using the ONIOM method with water acting as a solvent. The method was also used to calculate the energies of the positive, negative, and neutral peptides. The MN12SX density functional was selected in the QM region and for the MM region the Amber force field was considered and the calculations were done in accordance with the Gaussian 09 program.

From the whole of the results presented in this work, it can be seen that the sites of interaction of the amyloid *b*-peptides *Ab*40 and *Ab*42 can be predicted by using DFT-based reactivity descriptors such as the electronegativity, global chemical hardness, global electrophilicity, electrodonating and electroaccepting powers, net electrophilicity as well as Fukui functions, condensed dual descriptors, Parr functions and local hyper softness LHS. These descriptors were used in the characterization and successfully description of the preferred reactive sites and provide a firm explanation for the reactivity of those molecules, as well as about the pKa variation of the corresponding Lys residues of the two peptides.

Acknowledgement

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