Computational Study towards Schiff Base Derivatives Length as a Potential Recognition Layer in Electrochemical DNA Sensor

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Abstract. Electrochemical sensing of DNA has been known to be the easiest and sensitive way reported so far. This study focuses on the effect of recognition layer’s length in E-DNA sensor, a theoretical approach has been carried out to four different length of Schiff bases derivatives which involved four different length of R group attached (3, 6, 9 and 12 alkane chain). This study has been carried out using density functional theory (DFT) by using Gaussian09 software package 6-31G (d,p) basis set for all the calculations involved. Structure drawing was performed with GaussView 5.0. After optimization, energy, dipole moment, HOMO, LUMO, hardness (η), softness (σ) and energy gap. Dipole moment value is an important value to determine the optimum length of recognition layer. Preliminary result showed that the length does not play an important role in E-DNA sensor.

1. Introduction
Schiff base compound is known for its low-cost preparation and normally formed by the condensation reaction of ketones or aldehydes with primary amines [1,2,3]. Schiff base compound has been extensively applied in pharmaceutical and biological studies [4]. This has sparked our interest to apply Schiff base compound as linker in electrochemical DNA (E-DNA) sensor with four different alkyl chain as the R group. To date there is no study involving Schiff base molecules in E-DNA sensor.

There are many methods to detect DNA. Electrochemical DNA sensor is the easiest, sensitive and selective method reported so far [5]. However, a suitable linker also known as recognition layer is needed to be attached to a suitable substrate such as gold, platinum, silver or indium tin oxide (ITO). Furthermore, DNA probe must be sufficiently immobilised [6]. All molecular based biosensor relies on highly specific recognition events which typically involve probe sequence immobilised within the recognition layer. The length of linker may also affect DNA immobilisation.

Reaction scheme for Schiff bases molecules derivatives can be seen in Figure 1. COOH group will bind with gold surface substrate while the other R group will bind directly with phosphate group from DNA part. Phosphate group involved, normally taking consideration all four nucleotides which are adenosine, cytidine, guanosine and thymidine. Since this is a preliminary study, this article only reported on the adenosine part. There are many computational chemistry methods and also theoretical studies about the determination of biological and chemical activity [7]. GaussView 5.0 has been used to do all
the structure drawing. Calculations were performed with Gaussian 09 software package program [8]. In this study, quantum-chemical descriptors are suitable to determine the ranking of physical descriptors. Figure 2 shows the complete Schiff base derivate attached to adenosine nucleotide via the oxygen atom using GaussView 5.0. One side of R group attached to a substrate while the other R group is attached to adenosine nucleotide. This side of R group has been varied the length which involves alkane chain which contain (CH$_2$)$_n$ where $n$ = 3, 6, 9 and 12 carbon chains to see the effect of recognition length towards the effectiveness of DNA detection.

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**Figure 1.** Reaction scheme to synthesise Schiff base derivatives with various R group which involve (CH$_2$)$_n$ where $n$ = 3, 6, 9 and 12 carbon chain

**Figure 2.** The overall molecule of Schiff base derivatives bind with adenosine with two R groups, COOH (fixed) and alkane chain length and this image represent R group with (CH$_2$)$_3$ chain
2 Computational Method

The structure drawings were done using GaussView 5.0 and all calculations were performed with Gaussian 09 software package program [7]. There are many computational chemistry methods as well as theoretical studies about the determination of biological activity and chemical activity [8,9]. Quantum-chemical descriptors are very suitable to determine the ranking biological activity. Quantum-chemical descriptors are very suitable to determine the ranking biological activity. These parameters are the highest occupied orbitals (HOMOs) and the lowest unoccupied molecular (LUMOs), the energy gap between LUMO and HOMO (\(\Delta E_{\text{GAP}}\)), dipole moment (\(\mu\)), hardness (\(\eta\)) and softness (\(\sigma\)). Hardness and softness descriptors can be related with biological activity ranking and can determine the stability of chemical system [10]. To analyse these biological activity ranking one of the density functional theory (DFT) methods, named Becke, 3-parameter, Lee-Yang-Parr (B3LYP) was selected and the rest of the atoms were selected as basis sets. The calculation to determine the biological activity were calculated by using Eqs 1-4.

\[
\Delta E_{\text{GAP}} = E_{\text{LUMO}} - E_{\text{HOMO}}
\]

\[
\mu = (E_{\text{HOMO}} - E_{\text{LUMO}}) / 2
\]

\[
\eta = (E_{\text{LUMO}} - E_{\text{HOMO}}) / 2
\]

\[
\sigma = 1 / \eta
\]

3. Results and Discussion

All calculated parameters are represented in Table 1. In computational chemistry, normally Hartree-Fock (HF) is used as a method of approximation for the determination of the wave function and the energy of a quantum in a stationary state. HF is also known as self-consistent field method (SCF) assuming each particle is subjected to the mean field created by all other particles. \(E_{\text{SCF}}\) in table 1 shows the central starting point for most methods that describe the many-electron system more accurately.

|                  | (CH\(_2\))\(_3\) | (CH\(_2\))\(_6\) | (CH\(_2\))\(_9\) | (CH\(_2\))\(_{12}\) |
|------------------|-------------------|-------------------|-------------------|---------------------|
| \(E_{\text{SCF}}\) (au) | -2664.6088        | -2782.5581        | -2900.5080        | -3018.4574          |
| HOMO (eV)        | -0.19381          | -0.19161          | -0.19174          | -0.19144            |
| LUMO (eV)        | -0.07719          | -0.07655          | -0.07667          | -0.07673            |
| \(E_{\text{GAP}}\) (eV) | 3.1734            | 3.1309            | 3.1312            | 3.1214              |
| \(\mu\) (Debye)  | 1.8296            | 4.1622            | 1.7605            | 3.959               |
| Dipole moment    |                   |                   |                   |                     |
| \(\eta\) (eV)    | 0.05831           | 0.05753           | 0.05754           | 0.05735             |
| Hardness         |                   |                   |                   |                     |
| \(\sigma\) (eV\(^{-1}\)) | 17.1497          | 17.3822           | 17.3807           | 17.4353             |
| Softness         |                   |                   |                   |                     |
HOMO is an important quantum chemical descriptor and mainly associated with electron donating ability of molecule. The higher the value of HOMO, the higher the tendency of electron transfer to acceptor molecule [10]. The ranking of biological activity of the derivatives are as follows:

\[(\text{CH}_2)_3 > (\text{CH}_2)_9 > (\text{CH}_2)_{12} > (\text{CH}_2)_6\]

While the LUMO value indicates that the electron-accepting ability of the molecules is higher. The binding ability of the compounds are:

\[(\text{CH}_2)_3 > (\text{CH}_2)_{12} > (\text{CH}_2)_9 > (\text{CH}_2)_6\]

It can be seen that from the energy gaps \(E_{\text{GAP}}\) between HOMO and LUMO for the compounds are as follows:

\[(\text{CH}_2)_3 > (\text{CH}_2)_9 > (\text{CH}_2)_6 > (\text{CH}_2)_{12}\]

The lower value of \(E_{\text{GAP}}\) explains the eventual charge transfer interaction taking place within the molecules. The lower value of this descriptor shows that the molecule is more active [11].

On the other hand, chemical hardness \((\eta)\) is associated with the stability and reactivity of a chemical system. This descriptor measures the resistance to change in the electron distribution or charge transfer. Hard molecules have a big \(E_{\text{GAP}}\) value and of molecules have small \(E_{\text{GAP}}\) [9-11]. Biological molecules are known as soft molecules. This means that soft molecules can easily interact with biological molecules or human body. Biological activity is proportional to the increase of the softness value and vice versa. Based on the softness values obtained, the sequence of biological activity are:

\[(\text{CH}_2)_3 > (\text{CH}_2)_9 > (\text{CH}_2)_6 > (\text{CH}_2)_{12}\]

Another important descriptor is electronic chemical potential \((\mu)\) also known as dipole moment which is defined as the negative of electronegativity of a molecule. Based on the biological activity obtained the ranking for dipole moment of the molecules are:

\[(\text{CH}_2)_6 > (\text{CH}_2)_{12} > (\text{CH}_2)_3 > (\text{CH}_2)_9\]

From dipole moment descriptor obtained, the optimum recognition layer can be seen at Schiff base molecules with 6 carbon chains attached to adenosine, while other descriptors are almost similar for each chain length. This preliminary result indicates that there is a certain length which is suitable towards the electrochemical DNA system. This indicates dipole moment position and interaction may play a role for recognition layer’s length in E-DNA sensor. However, the future experimental study is much needed and will be carried out to be compared with theoretical results obtained.

4. Conclusion
DFT is a promising tool to study theoretical aspect of recognition layer’s length in electrochemical DNA sensor. From the value of biological activities obtained the length of recognition layers does not play a significant role. The best length obtained was from Schiff base molecules with 6 carbon chain group attached to adenosine. However further study considering other nucleotides which are cytidine, guanosine and thymidine will be further investigated. Furthermore, experimental work will be carried out by synthesizing all the molecules involved to be compared with theoretical results.
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Acknowledgments
Authors wish to thank Universiti Malaysia Terengganu (UMT) and School of Fundamental Science for all the facilities provided also Fundamental Research Grants Scheme (FRGS) vot 59383 for financial support throughout this study. Gratitude to the anonymous reviewers who have spent time and effort, constructive recommendations that enhanced the value of this manuscript.