Comparison analysis between experiment and computational chemistry data on citronellal and tyrosine conjugation

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Abstract. Combination of functional group between hydroxyl-aromatic and prenyl in certain compounds or materials, according to literature research analysis, would have antibacterial property. Conjugation of tyrosine and citronellal to produce new compound which has antibacterial activity has been done. The result was embedded chemically onto neutral material surface so that the combined materials have antibacterial activity. However, the product of conjugation has low antibacterial activity. Therefore, computational chemistry analysis was deployed to investigate the effectiveness of reaction. Computational analysis was done by electronic quantum and application of time dependent density functional theory (infra-red spectra analysis). This analysis was applied to the reactant and product. The analytical results were compared to the infra-red spectral experiment data. The findings show that there was the relevant result between computational analysis result and experimental data in particular to the both wave lengths and vibrational frequencies were still in range of the determinant functional groups range. In addition, the imine bond formation to the product which indicates that the conjugation has happened.

1. Introduction
Antibacterial substances needs tend to increase year by year which correlated to increasing of human population and infection diseases caused by bacteria. In addition, the antibiotic resistance also another factor caused to boost the discovery and development of new antibiotics [1]. The antibacterial substance resources are generally extracted from nature such as part of plant like leaves, roots, and trunks. It is common knowledge that beside having antibacterial property, they also have biocompatibility to the host and mammalian cell. Unlike the natural product, the synthetic substances have been known that they have poor benefit to the host. However, the synthetic substances are excellent in terms of cost and production which are economically profitable [2].

Some investigations of antibacterial compounds such as novobiocin, serrulatane, xanthorhizol dan tertiary amination [3–8], showed that the functional groups of the investigated compounds contained prenyl and hydroxyl-aromatic. These functional groups strongly assumed to have a key role of the antibacterial activity. Conjugation of two compounds which have prenyl and hydroxyl aromatic such as 2,4-Dimethyl-2,6-heptadien-1-ol and 5-Amino-2-methylphenol produced conjugated compound that has antibacterial activity to gram positive bacteria, Staphylococcus epidermidis [2].
Conjugation of citronellal (3,7-dimethyl-6-octenal) and L-tyrosine by using Schiff Base method produced a compound that has low antibacterial activity. This paper analyses and discusses the quality conjugation result by comparing the vibrational frequency between the infrared spectra of experimental data and spectra generated by computational approach.

2. Experiments
The research was done through laboratory experiment and was well documented [9]. The conjugation method [10], can be briefly explained that in the methanol as solvent and availability of sodium hydroxide, citronellal and L-tyrosine was mixed and refluxed at 60°C for 8 (eight) hours. The residue was then extracted and fractionated by diethyl ether, then the solid product was analysed using IR spectrophotometer.

Computational chemistry analysis was performed by using two software, Orca ver. 3 and Avogadro ver. 1.2.0. both software can be accessed via open source. Approximation of vibrational frequency through Orca software was run by the Hessian calculation using basis set Hess2ElFlags (i1, i2, i3, i4), where ik (ik=0 to 2) which referred to RI dan COSX approximation [11], (1,2,2,1). The input of configuration molecule matrix for basis set and conversion to graphical display of vibrational frequency output used the Avogadro software ver 1.2.0.

3. Results and Discussions
The vibrational frequency of conjugation of citronellal and tyrosine to experimental data, FTIR (Fig.1) and to Hessian calculation result (Fig.2) indicated that some spectra shift between reactant (citronellal and L-tyrosine) and product ((E)-2-((3,7-dimethyloct-6-en-1-ylidene)amino)-3-(4-hydroxyphenyl)propanoic acid).

3.1. FTIR analysis as the experimental data
As can be seen at Fig. 1A that a stretch vibration at wave length 2917 cm⁻¹, 1727 cm⁻¹ respectively correspond to functional group of C-H, C=O [12–14]. These two identifications would be enough to represent the citronellal. the Fig. 1B showed the stretch vibration at 1589 cm⁻¹, 3363 cm⁻¹ and 1242 cm⁻¹ which referred to the functional groups of C=C aromatic, N-H, dan C-N [12–14].

The result product of the reaction spectra (Fig. 1C) beside some spectra which related with the original substances or reactants (see Fig 1A and 1B) such as C=C aromatic, C-H, and C-N, there also new spectrum at 1689 cm⁻¹ emerged which corresponds to imine functional group [12,15].

3.2. Computational Result Analysis
According to the vibrational frequencies resulted from experiment data, some determinant functional groups of citronellal also detected with very low shift but still in the range of vibration identity such as 2892 cm⁻¹, 1817 cm⁻¹ and 1463 cm⁻¹ (Fig.2A) which respectively referred to C-H, C=O, and C=C functional group [13,14].

Stretch vibrational frequency which correlated to amino acid, L-tyrosine detected at 1589 cm⁻¹, 3363 cm⁻¹ and 1242 cm⁻¹ (Fig. 2B). Those vibrational frequencies respectively identified as functional group of C=C aromatic, N-H, dan C-N [13–15].

Computational approach to the product as the resulted reaction spectra (Fig. 2C), most of determinant functional groups as stated in the experimental data also detected on hessian calculation such as C=C aromatic, C-H, C-N and R2C=N-R (imine). The vibrational frequencies of functional groups values were not concise to the experimental data but still in the range identification [12–15].
**Figure 1.** Vibrational frequencies result of FTIR as experimental data to the reactant (A and B) and the product (C): A. Citronellal; B. L-Tyrosine; and C. Product.
Figure 2. Vibrational frequencies result of Approximation of Hessian calculation to the reactant (A and B) and the product (C): A. Citronellal; B. L-Tyrosine; and C. Product.
3.3. Comparison of Experimental data and Computational Approach

Vibrational frequencies result of experimental data and computational approach, based on both figures (figure 1 and figure 2) graphically and empirically at a glance looked unidentical. However, further comparison analysis to the functional group classification showed that the key functional groups to the molecule structure obtained from both approach shown at table 1.

| No | Functional Group     | Experimental Data (cm\(^{-1}\))          | Computational Calculation (cm\(^{-1}\)) |
|----|----------------------|------------------------------------------|----------------------------------------|
|    |                      | Citronellal | L-tyrosine | Product | Citronellal | L-tyrosine | Product |
| 1  | NH                   | -           | 3363       | 3394    | -           | 3310       | 3302    |
| 2  | C-H aromatik         | 3016        | Not clear  | 1455    | -           | 1525       | 1463    |
| 3  | CH                   | 2917        | 2924       | 2924    | 1589        | 1512       | 1512    |
| 4  | C=C aromatik         | -           | -          | 1589    | -           | -          | 1589    |
| 5  | C=O                  | 1727        | -          | 1817    | -           | -          | 1589    |
| 6  | C=C                  | 1455(?)     | 1512       | 1512    | 1463(?)     | -          | 1656    |
| 7  | C-N                  | -           | 1242       | 1242    | -           | 1080       | 1327    |
| 8  | OH                   | -           | 3201       | 3209    | -           | 3212       | 3235    |
| 9  | R2C=N-R              | -           | -          | 1689    | -           | -          | 1656    |

Inconsistency was found in functional group of C-H aromatic, whereas the experimental data at reactant detected at 3016. However, according to the graphical spectra, they were not clear due to the small absorption and broaden range peak, so it would be mixed with other functional groups. The same functional group to the computational calculation was detected at 3030 cm\(^{-1}\) (L-tyrosine) and 3035 cm\(^{-1}\) (product) whereas the most references recommended the range of the vibrational frequency of C-H aromatic at 3000-3100 cm\(^{-1}\) [12,14].

Another inconsistency of citronellal frequency vibration also found at wave length 1455 cm\(^{-1}\) (experimental data) and 1463 cm\(^{-1}\) (computational approach) whereas structurally the wave length value would be referred to the C=C aliphatic, but according to references identified as C=C aromatic [12,14]. Surprisingly, the computation result showed that the C=C aromatic of product also detected at the same wavelength of citronellal but the experimental data of C=C aromatic of product have the wave length at 1589 cm\(^{-1}\) which is similar to L-tyrosine.

Vibrational frequency comparison between experimental data and computational approach showed that the analysis results seemed to have some similarities, however the broaden range peaks of experimental data left some questions regarding the possibilities of side product of conjugation. This side product assumed to be able to decrease the antibacterial activity, the additional aliphatic carbon range of product also could minimize the bio activity.

4. Conclusions

Conjugation of two substances that have hydroxyl-aromatic and prenyl by Schiff reaction, according to comparison their vibrational frequency analysis concluded that there are similarity determinant functional groups detected which identified as expected product. However, the range broaden absorption of experimental data would be affected to get the fine analytical comparison. This range broaden absorption also indicated that the side product could be inbound with the expected product that result in low antibacterial activity.
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