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Jumlah Penulis : 3 orang (Indah Pratiwi, **Bambang Cahyono**, Parsaoran Siahaan)

Status Pengusul : penulis ke-2

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# Ab-initio computational study: The activation energy and steric effects in peptide synthesis of ac-aa-nh<sub>2</sub> and ac-ap-nh<sub>2</sub>

Pratiwi, Indah; [Cahyono, Bambang](#); [Siahaan, Parsaoran](#)

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<sup>a</sup> Department of Chemistry, Faculty of Sciences and Mathematics, Diponegoro University, Semarang, Indonesia[View PDF](#) [Full text options](#) [Export](#)[Abstract](#)[Author keywords](#)[SciVal Topics](#)[Funding details](#)**Abstract**

Ab-Initio computational method can be used for simulating reaction mechanisms, such as concerted reaction mechanism on peptide synthesis. The concerted reaction is one of many possible pathways on how peptide can be synthesized. The purpose of this study are probing the concerted reaction mechanism and comparing the steric effect to the reaction, given by different side-chain of alanine (A) and proline (P). Two dipeptides formed from alanine and proline were computed at HF-SCF/6-31G\*\* theory level: Ac-AA-NH<sub>2</sub> and Ac-AP-NH<sub>2</sub>. The res.lts show the activation energy of Ac-AA-NH<sub>2</sub> and Ac-AP-NH<sub>2</sub> forming via concerted pathway are 167.541 kJ/mol and 161.044 kJ/mol, respectively. The steric difference in side-chain affects the dihedral angle of the structure, and also gives difference to the entropy value of reaction. © 2021, Universitas Jenderal Soedirman. All rights reserved.

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Yuliani, S.V. , Salimah, S.N.M. , Hudiyan, D. (2019) *Journal of Physics: Conference Series*

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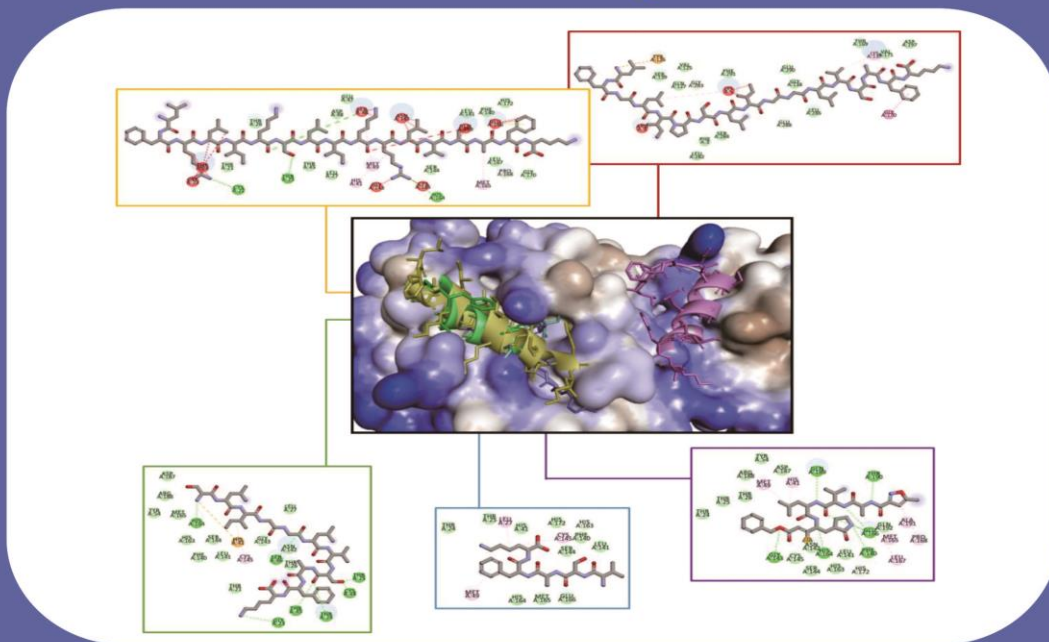
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**Ab-Initio Computational Study : The Activation Energy and Steric Effects in Peptide Synthesis of Ac-AA-NH<sub>2</sub> and Ac-AP-NH<sub>2</sub>**Indah Pratiwi<sup>1</sup>, Bambang Cahyono<sup>1</sup>, Parsaoran Siahaan<sup>1\*</sup><sup>1</sup>Department of Chemistry, Faculty of Sciences and Mathematics, Diponegoro University, Semarang, Indonesia\*Corresponding author email: [siahaan.parsaoran@live.undip.ac.id](mailto:siahaan.parsaoran@live.undip.ac.id)

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**ABSTRACT.** Ab-Initio computational method can be used for simulating reaction mechanisms, such as concerted reaction mechanism on peptide synthesis. The concerted reaction is one of many possible pathways on how peptide can be synthesized. The purpose of this study are probing the concerted reaction mechanism and comparing the steric effect to the reaction, given by different side-chain of alanine (A) and proline (P). Two dipeptides formed from alanine and proline were computed at HF-SCF/6-31G\*\* theory level: Ac-AA-NH<sub>2</sub> and Ac-AP-NH<sub>2</sub>. The results show the activation energy of Ac-AA-NH<sub>2</sub> and Ac-AP-NH<sub>2</sub> forming via concerted pathway are 167.541 kJ/mol and 161.044 kJ/mol, respectively. The steric difference in side-chain affects the dihedral angle of the structure, and also gives difference to the entropy value of reaction.

**Keywords:** ab-initio; activation energy; peptides; reaction mechanism

## INTRODUCTION

Condensation of amino acids is a crucial reaction in protein chemistry as it represents a key reaction for all life processes. An essential structural element of all proteins is a peptide bond (C-N), which is formed because of the conjugation between the  $\alpha$ -amino group of one amino acid and the  $\alpha$ -carboxylic group of another amino acid (Santos et al., 2014). The detailed knowledge of the peptide bond formation mechanism is vital for understanding of various biological processes, and it is a subject of intensive investigations as such.

Non-catalyzed reaction of peptide bond formation has been studied by Bhunia et al. (2016) and Monajemi et al. (2012). Concerted reaction mechanism is one of possible mechanism propose. It also has been studied using molecular dynamics approach by Trobro and Aqvist (2005) and further by Wallin and Aqvist (2010), as a process of peptides synthesis occurring at cell level. Ribosome transforms genetic information, expressing genes into proteins (Ramkumar & Ramakrishnan, 2010; Yonath, 2010). Briefly, a peptide formation reaction is a reaction between two active groups: the amine (-NH<sub>2</sub>) group and the carboxylic group (-COOH) from two different amino acids. The reaction mechanism involves the nucleophilic attack of the nitrogen atom from amine group to the carbon of the carboxylic group. Furthermore, a hydrogen atom of the amine group will

be attracted to the oxygen atom (hydroxyl group of carboxylic), out in the molecular form of H<sub>2</sub>O and the dipeptide will be produced (Anslyn & Dougherty, 2006a; Konwar et al., 2016; Solomons et al., 2014). The peptide bond forming reaction according to concerted mechanism shown in **Figure 1**.

The kind of mechanism in term of the topology of the potential energy surface, the nature of the transition states, the presence or absence of intermediates. Reactants progress over transition states on to intermediates, perhaps through multiple intermediates and ending at products. This type of scenario analysis has a long successful story for studying organic reactions (Dai et al., 2018; Gale et al., 2020; Singh et al., 2020; Trinchillo et al., 2016).

Besides of only studying the pathway from thermodynamics and kinetics, the steric effect also studied as well in some previous studies. It can be seen from the bulky steric structure, bond torsions, or the size of atom attached to the particular chain of organic compound (Elias et al., 2020; Ghosh et al., 2007; Mukherjee et al., 2019). Steric effect relates on how electron are occupied in space and reaction mechanism itself tells how electron go through particular reaction pathway which we desired. However, steric can affect the electron, and finally, can affect on how reaction occurs.

**Two Limonoids from The Seeds of *Chisocheton Macrophyllus* and Their Cytotoxic Activity Against MCF-7 Breast Cancer Cells**

Intan Rahmayanti<sup>1</sup>, Nurlelasari<sup>1\*</sup>, Desi Harneti<sup>1</sup>, Rani Maharani<sup>1,2</sup>, Darwati<sup>1</sup>, Yoshihito Shiono<sup>3</sup>, Unang Supratman<sup>1,2</sup>

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**ABSTRACT.** Limonoids (tetranortriterpenoids) are triterpenoid compounds that lose four terminals in their structural framework. These compounds have a wide variety of structures and interesting activities including anti-inflammatory, anti-cancer, anti-tumor and anti-malarial properties. The purpose of this study was to find limonoid compounds from the Indonesian *Chisocheton* plant, and one of which is *Chisocheton macrophyllus*. The dried and powdered seeds of *C. macrophyllus* (4.5 kg) were extracted with methanol and partitioned successively with *n*-hexane, ethyl acetate and *n*-butanol. Evaporation of each extract resulted in the crude extracts of *n*-hexane (346.6 g), ethyl acetate (60.8 g) and *n*-butanol (14.6 g). The *n*-hexane fraction was subjected to a silica gel vacuum-liquid chromatography (VLC) column packed with silica gel 60 using gradient of *n*-hexane, ethyl acetate and methanol (10% stepwise) to afford thirteen fractions (A-M). Fraction F (4.4 g) was subjected to silica gel column chromatography using gradient of *n*-hexane and ethyl acetate (5% stepwise). Subfraction F5 (1.2 g) was chromatographed on a column of silica gel eluted with *n*-hexane: CH<sub>2</sub>Cl<sub>2</sub>: EtOAc (2:7.5:0.5) to give compound **1** (19.7 mg) and fraction H (1.8 g) was subjected to silica gel column chromatography using gradient of *n*-hexane and ethyl acetate (5% stepwise) as eluting solvent to give **2** (12.0 mg). Chemical structures of **1** and **2** were elucidated by spectroscopic methods and determined as 6 $\alpha$ -acetoxyepoxyazadiradione (**1**) and Dysobinin(**2**). Dysobinin (**2**) showed weak cytotoxic activity against MCF-7 breast cancer cells with an IC<sub>50</sub> value of 228.15  $\mu$ M

**Keywords:** 6 $\alpha$ -acetoxyepoxyazadiradione, *C. macrophyllus*, dysobinin, limonoid, MCF-7

## INTRODUCTION

Limonoids are a class of tetranortriterpenoids that are formed through the loss of four terminal carbons of side chain of euphane (20-S) or tirucallane (20-R) skeleton that are followed by a cyclization to form a 17 $\beta$ -furan ring (Tan, & Luo, 2011; Shi et al., 2020). Limonoids are classified into ten classes based on the differences on A, B, C, D, and furan ring of the limonoid skeleton and can be identified by their biosynthetic relationships (Fang, Di, & Hao, 2011; Tan & Luo, 2011; Shi et al., 2020). Ten classes of limonoid include protolimonoids, apoeuphol skeleton, D-ring seco, B, D-ring seco, A-ring seco, A,B-ring seco, C-ring seco, A,D-ring seco and B-ring seco limonoids.

Limonoids occur mainly in the plant order of Rutales and most of them are found in Meliaceae and Rutaceae families (Li, Peng, & Zheng, 2016). Limonoids isolated from species of the family of Meliaceae have been of interest due to their diverse structures and their biological activities, including antifeedant, anticancer, antimicrobial, antimalarial,

and antiviral properties (Tan, & Luo, 2011; Wong et al., 2011; Gualdani, Cavalluzzi, Lentini, & Habtemariam, 2016; Shilpi et al., 2016; Chong et al., 2019; Supratman et al., 2020). Nimbolide is a major limonoid isolated from the leaves of *Azadirachta indica* A. Juss or known as neem tree. Nimbolide as a neem limonoid is widely used for anti-malaria, antibacterial activity against *S. aureus* and *S. coagulase*, anti-feedant and insecticidal activity (Kumar & Navaratnam, 2013; Bodduluru, Kasala, Thota, Barua & Sistla, 2014; Wang et al., 2016; Sophia et al., 2018). Nimbolide was presumed to be a more potent anticancer. Nimbolide shows anticancer activity throughout selective modulation of signaling pathways linked to inflammation, survival, growth, invasion, angiogenesis and metastasis. Nimbolide was reported to induce apoptosis by disruption of Mitochondrial Outer Membrane Potential (MOMP) and inhibits tumor cell proliferation through alterations of cyclins, cdks, PCNA and p53 levels. In addition, nimbolide also reducing the nuclear