Indonesian Journal of Chemical Science and Technology (IJCST)

State University of Medan, https://jurnal.unimed.ac.id/2012/index.php/aromatika

IJCST-UNIMED 2025, Vol. 08, No. 2 Page ; 38 – 47
Received : Mar 9th, 2025 Accepted : Jul 5th, 2025 Web Published : Aug 26th, 2025

Thermodynamic and Kinetic Study of the Reaction Mechanism of Acetylsalicylic Acid Formation Using Computational Chemistry Methods

Julina Indah Gewa Sitompul[1*], Roma Sinaga[1], Asep Wahyu Nugraha[1]

[1] Department of Chemistry, Faculty of Mathematics and Natural Sciences, Universitas Negeri Medan, 20221, Indonesia
*Corresponding author : julinasitompul12@gmail.com

ABSTRACT

Acetylsalicylic acid or aspirin is one of the most widely used non-steroidal anti-inflammatory drugs (NSAIDs) in medicine because of its properties as an analgesic, antipyretic, and antiplatelet. This study aims to examine the thermodynamic and kinetic aspects of the reaction mechanism of aspirin formation from salicylic acid and acetic anhydride using a computational chemistry approach. The method used to determine energy is the computational chemistry method, the theory used is metode Restricted Hartree-Fock (RHF) with a basis set of 3-21G. The calculation results show the formation of energy (ΔE) of the reaction of -1.21 kJ/mol. The magnitude of the activation energy (Ea) from the computational chemistry calculation is 7.95 kJ/mol. The structure of the intermediate was also successfully identified and visualized, supporting a two-stage reaction mechanism with the presence of a transition state.

Keywords: Aspirin, acetylsalicylic acid, Reaction energy formation, activation energy, computational chemistry.

1. INTRODUCTION

Acetylsalicylic acid, commonly known as aspirin, is one of the first industrially synthesized drugs and remains among the most widely used pharmaceuticals to date. It was first synthesized by Felix Hoffmann in 1897 at Bayer, Germany, and began to be marketed in 1899. However, the use of salicylate compounds as pain-relieving agents has been known for thousands of years, utilized by the Sumerians and Egyptians through extracts from willow bark (Montinari and De Caterina, 2019). This drug has a broad range of therapeutic functions, including analgesic (pain reliever), antipyretic (fever reducer), anti-inflammatory, and antiplatelet (blood clot inhibitor) effects (Fijałkowski et al., 2022). The synthesis of acetylsalicylic acid (aspirin) is typically carried out through a reaction between salicylic acid and acetic anhydride with the aid of concentrated sulfuric acid as a catalyst. Although this reaction is relatively efficient, the use of strong acid catalysts can raise concerns in terms of safety and environmental impact (Golemac & Kondža, 2023). Therefore, a more

e-ISSN : 2622-4968, p-ISSN : 2622-1349

comprehensive understanding of the reaction mechanism is necessary, particularly from thermodynamic and kinetic perspectives. Thermodynamic analysis focuses on the stability and feasibility of a reaction, indicated by parameters such as the reaction energy (ΔE) and Gibbs free energy (ΔG), which determine whether a reaction can proceed spontaneously. Meanwhile, kinetic analysis involves the reaction rate and the pathway taken by molecules during the reaction, especially through the evaluation of activation energy (Ea) and the existence of a transition state. Understanding both aspects is crucial to map the most likely reaction pathway and to assess the energy efficiency of the synthesis process (Danil de Namor et al., 2022).

Computational chemistry is a branch of science that applies quantum mechanics principles to predict molecular properties and reaction pathways. It enables accurate simulation of chemical systems through computer programs (Ananto et al., 2020; Hulyadi et al., 2024).

In various studies, computational chemistry methods have been widely used to investigate thermodynamic properties, molecular structures, and electronic parameters of chemical compounds. Nugraha et al. (2023) applied the Density Functional Theory (DFT) method with the B3LYP/6-31G(d) basis set to calculate the values of ΔH, ΔS, and ΔG for Fe(II) complexes containing 1,2,4-triazole ligands. Geometry optimization was performed to obtain the minimum energy structures, and the results indicated that the complex with Cl^- anions was thermodynamically more stable compared to the complex containing BF_4^- anions. Another study by Nugraha et al. (2020) also employed the DFT B3LYP/6-31G(d) method to evaluate structural changes and thermodynamic parameters of Fe(II) spin crossover complexes in both low-spin and high-spin states. The calculation results showed that spin state transitions affect bond lengths, interatomic distances, and the values of ΔG and ΔS, which were consistent with experimental data. Malau and Nugraha (2021) also implemented the DFT B3LYP/6-31G method using NWChem software to calculate the total energy of organic solvent mixtures such as benzene, methanol, ethanol, and hexane. The optimized structures were visualized using Jmol, and the results showed that solvent composition influenced the system's energy values, although not directly correlated with intermolecular distances.The DFT method with the B3LYP/3-21G basis set was also used by Sinaga and Nugraha (2021) to determine the most stable structure among five benzamide derivatives. Structural optimization was carried out for each compound, and the total energy was calculated to identify the most stable one. The results showed that compounds containing amino groups had the lowest total energy, and were therefore considered the most thermodynamically stable. Meanwhile, Yusuf et al. (2023) used the semi-empirical PM3 method through the HyperChem 8.0 software to analyze the highest occupied molecular orbital (HOMO) and the lowest unoccupied molecular orbital (LUMO) of bis(β-diketonate)Zr complexes. These calculations aimed to evaluate the electron density at the Zr metal center and relate it to the Lewis acidity and catalytic potential of the complex. Orbital distribution visualizations were performed to observe electron concentration on the ligands and the metal center. In a subsequent study, Yusuf et al. (2024) also employed the semi-empirical PM3 method to perform geometry optimization on different Zr(IV) complexes and calculated Mulliken charges to assess the electron density at the central atom. The purpose of these calculations was to compare the effects of ligand substituents on Lewis acidity, which directly correlates with the complex's reactivity in polymerization reactions. The results showed that electron-withdrawing groups such as phenyl and trifluoromethyl increased Lewis acidity; however, steric factors also contributed to reducing coordination efficiency with monomers.

While many previous studies have employed DFT and semi-empirical methods such as PM3 to evaluate the thermodynamic and electronic parameters of compounds, ab initio methods such as Restricted Hartree–Fock (RHF) remain relevant, particularly for small molecular systems. According to Johansson et al. (2013), the RHF method can provide numerically stable solutions to the Schrödinger equation within a limited basis set space such as 3-21G, and it is frequently used as an initial approach in molecular structure and energy studies. The use of both HF and DFT methods was also implemented by Nugraha, Onggo, and Martoprawiro

e-ISSN : 2622-4968, p-ISSN : 2622-1349

(2019) in a study of Fe(II)-triazole complexes, demonstrating that this approach can accurately predict linear polymeric structures with octahedral geometry and distinguish ligand stability based on protonated and deprotonated forms. This reinforces the relevance of ab initio methods in modeling the structure and stability of metal coordination systems. Additionally, Nugraha et al. (2020) used the RHF method to evaluate energy changes in Fe(II) spin crossover complexes, showing that this method can describe thermodynamic tendencies with good computational efficiency. Based on the successful application of the RHF method in these studies, the present research adopts the RHF approach with the 3-21G basis set, which is considered appropriate for small molecular systems such as acetylsalicylic acid. This approach enables the analysis of activation energy and reaction energy formation during the synthesis of the compound.

2. METHODS

This research was conducted at the Computational Chemistry Laboratory, Faculty of Mathematics and Natural Sciences, State University of Medan. The tools used in this study consisted of hardware and software components. The hardware included a computer equipped with an Intel Core™ i3-6100T CPU @ 3.20GHz, 4.00 GB of RAM, 64-bit system architecture, and the Linux Ubuntu operating system. The software used in the study included Avogadro version 1.1.1 for molecular modeling (Hanwell et al., 2012), NWChem version 6.6 for geometry optimization and molecular calculations using the Restricted Hartree-Fock (RHF) method with the 3-21G basis set (Molecular Sciences Software Group, 2007; Valiev et al., 2010), and Jmol version 14.31.36.3.3 for visualizing the computed structures (Jmol Development Team, 2020; Scalfani et al., 2016).

The computational procedure involved the installation of software, the preparation of input files in z-Matrix format, the configuration of parameters such as molecular charge, multiplicity, and basis set, followed by execution of the calculations using NWChem via the Linux terminal. The results were verified through the log file to ensure that the optimization process ran correctly, as indicated by the appearance of the message “Optimization Converged.” The optimized structures were then visualized using Jmol, and each successfully calculated molecular structure was saved in image format. This procedure was repeated for each compound observed in the study

3. RESULT AND DISCUSSION

3.1. Computational Result

Based on the computational chemistry calculations using the RHF method with a 3-21G basis set, the total energy of each compound involved in the formation reaction of acetylsalicylic acid was obtained. The energy values were initially calculated in Hartree (Ht) units and then converted into kilojoules per mole (kJ/mol). The intermediate compound showed the highest total energy at –2,290,381.2242 kJ/mol, while the lowest energy was observed in acetic acid, at –597,794.3151 kJ/mol. A summary of the calculated energies is presented in Table 1.

Table 1. Calculated energy values using RHF/3-21G method

No	Compound	Energy (Hartree)	Energy (kJ/mol)

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	Carbon (C)	-37.58820402	-98687.8297
2	Hydrogen (H_2)	-1.12682783	-2958.4865
3	Oxygen (O_2)	-149.20412837	-391735.4390
4	Salicylic Acid	-492.96956111	-1294291.5827
5	Acetic Anhydride	-379.39348040	-996097.5828
6	Acetylsalicylic Acid	-644.67570608	-1692596.0663
7	Acetic Acid	-227.68779857	-597794.3151
8	Transition State (TS)	-872.36001682	-2290381.2242

These computed energy data were used to determine the energy change (ΔE) for each compound. The energy change was calculated by taking the difference between the total energy of the product (final state) and the total energy of the reactants (initial state). The ΔE values obtained from the calculation are presented in Table 2.

Table 2. Calculated reaction energy changes (ΔE)

Compound	Energy (kJ/mol)
Salicylic Acid	- 6998.15715659
Acetic Anhydride	- 4867.64621601
Transition State (TS)	- 9100.77548092
Acetylsalicylic Acid	- 2766.24386575
Acetic Acid	- 11857.862049

From these results, it is known that all energy changes (ΔE) are negative. The formation energy is defined as the difference between the total energy of the products and the total energy of the reactants. Based on the results of computational chemistry calculations using the RHF method with the 3-21G basis set, the formation energy of acetylsalicylic acid was obtained as -1.21 kJ/mol.

The calculation results show that all energy changes (ΔE) for each compound involved—salicylic acid, acetic anhydride, intermediates, acetylsalicylic acid, and acetic acid—are negative. This condition indicates that each stage of the reaction is exothermic, indicated by a ΔE value less than zero. This negative value also indicates that the reaction is thermodynamically spontaneous.

After obtaining the total energy data for each compound, the next step is to analyze the energy changes that occur during the acetylsalicylic acid formation reaction. The formation energy is calculated by subtracting the total energy of the reactants from the total energy of the products, resulting in a value of -1.21 kJ/mol. This negative value indicates that the complex formation process occurs spontaneously and releases heat to the environment, making it exothermic (Danil de Namor et al., 2022).

3.2. Reaction Energy Diagram of the Compounds

The calculated energy values for each compound have been obtained and presented in a simplified energy diagram. This diagram illustrates the energy levels of the compounds involved, namely salicylic acid, acetic anhydride, intermediate compound, acetylsalicylic acid, and acetic acid, as shown in Figure 1.

e-ISSN : 2622-4968, p-ISSN : 2622-1349

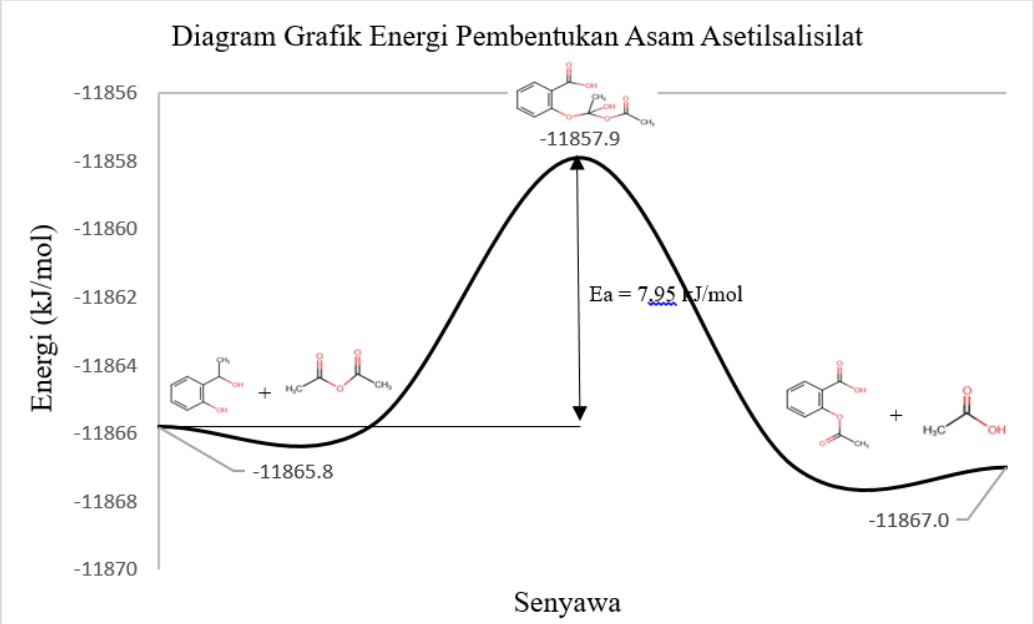

Figure 1. Energy Diagram of Acetylsalicylic Acid Formation

The energy graph above illustrates the reaction pathway for the formation of acetylsalicylic acid (aspirin) from the reactants salicylic acid and acetic anhydride using a catalyst. This graph shows the change in the chemical system's potential energy from the beginning of the reaction (reactants) to the formation of the final products, including the formation of an intermediate compound.

1. Interpretation of the Energy Diagram

In the diagram, the horizontal axis represents the reaction pathway from reactants to products, while the vertical axis shows the change in potential energy of the system in kilojoules per mole (kJ/mol). The reaction begins with the reactants at an energy level of –11,865.8 kJ/mol. The energy then rises to –11,857.9 kJ/mol, marking the peak of the reaction's energy profile. This increase reflects the activation energy (Ea) of 7.95 kJ/mol, which is the minimum energy required for the reaction to proceed. Sulfuric acid acts as a catalyst by lowering the activation energy. It does so by protonating the carbonyl group of acetic anhydride, thereby increasing its reactivity toward nucleophilic attack from salicylic acid. In the acid-catalyzed mechanism, sulfuric acid donates a proton (H^+) to the oxygen atom of the carbonyl group in acetic anhydride. This protonation enhances the electrophilicity of the carbonyl carbon, making it more susceptible to nucleophilic attack (Pearson, 2024). After the energy peak is passed, the system undergoes a decrease in energy, reaching –11,867.0 kJ/mol in the final product state. This energy drop of –1.21 kJ/mol indicates that the reaction is exothermic, where the products are thermodynamically more stable than the reactants.

2. Reaction Mechanism and the Role of the Intermediate

The formation of acetylsalicylic acid proceeds through an esterification mechanism, in which the hydroxyl group (–OH) of salicylic acid attacks the carbonyl group of acetic anhydride that has been activated by sulfuric acid. This attack results in the formation of an intermediate structure known as a tetrahedral intermediate—an intermediate compound where the central carbon is bonded to four groups in a tetrahedral configuration. The phenolic hydroxyl group of salicylic acid acts as a nucleophile, attacking the protonated carbonyl carbon of

e-ISSN : 2622-4968, p-ISSN : 2622-1349

the acetic anhydride. This leads to the formation of the tetrahedral intermediate (Pearson, 2024). This intermediate is crucial as it represents the transition state of the reaction and plays a key role in the formation of the new ester bond. After the intermediate is formed, it undergoes a proton transfer, followed by the departure of the acetate group. This sequence ultimately yields the final product, acetylsalicylic acid, along with a byproduct in the form of acetic acid.

3. Main Product and Byproduct

The main product of this reaction is acetylsalicylic acid (aspirin). Meanwhile, the direct byproduct formed is acetic acid (CH_3COOH), which originates from the separation of the acetyl group from acetic anhydride during the course of the reaction.

4. Alternative Intermediate

Although the tetrahedral intermediate is the most common pathway under acidic conditions, in certain circumstances, alternative intermediates may form. For example, if the reaction is carried out without a catalyst, the ester bond formation process may proceed more slowly and require a higher activation energy. Based on energy calculations and mechanistic studies, the reaction pathway involving the formation of a tetrahedral intermediate catalyzed by sulfuric acid is the most stable and most likely both kinetically and thermodynamically.

3.3. Visualization of Computational Results Using Jmol Software

The calculation results were then used to generate 3D structural visualizations with the help of Jmol software. The 3D structures of each compound that underwent computational analysis are shown in the images below.

The 3D structure of salicylic acid based on the computational results is presented in Figure 2.

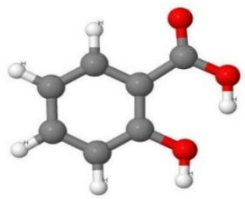

Figure 2. 3D Structure of Salicylic Acid ($C_7H_6O_3$).

This molecule consists of 7 carbon atoms (dark gray), 6 hydrogen atoms (white), and 3 oxygen atoms (red). Its core structure is a benzene ring with two substituent groups: a hydroxyl group (–OH) and a carboxyl group (–COOH) attached at the ortho positions. Salicylic acid is a compound known as a precursor in aspirin synthesis and possesses anti-inflammatory properties.

e-ISSN : 2622-4968, p-ISSN : 2622-1349

The 3D structure of acetic anhydride based on the computational results is shown in Figure 3**:**

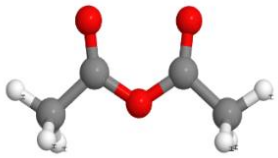

Figure 3. 3D Structure of Acetic Anhydride ($C_4H_6O_3$)

This molecule consists of 4 carbon atoms (gray), 6 hydrogen atoms (white), and 3 oxygen atoms (red). The structure displays two acetyl groups (CH_3–CO) connected by a central oxygen atom, forming an acid anhydride functional group.

The 3D structure of the intermediate compound based on computational results is presented in Figure 4**:**

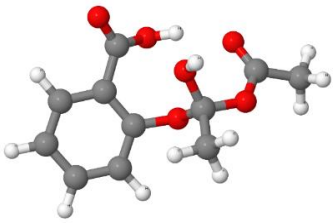

Figure 4. 3D Structure of Intermediate Compound ($C_{11}H_{12}O_6$)

The 3D structure of the intermediate formed during the acetylsalicylic acid (aspirin) reaction, with the molecular formula $C_{11}H_{12}O_6$, is shown in a ball-and-stick representation. The molecule consists of 11 carbon atoms (gray), 12 hydrogen atoms (white), and 6 oxygen atoms (red). This structure represents the intermediate formed when the hydroxyl group (–OH) of salicylic acid reacts with one of the acetyl groups from acetic anhydride, prior to full ester bond formation and acetic acid release.

The 3D structure of acetylsalicylic acid based on computational results is shown in Figure 5**:**

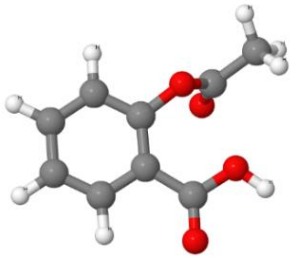

Figure 5. 3D Structure of Acetylsalicylic Acid ($C_9H_8O_4$)

e-ISSN : 2622-4968, p-ISSN : 2622-1349

This molecule consists of a benzene ring with two substituent groups: a carboxyl group (–COOH) and an acetyl ester group (–$OCOCH_3$). Acetylsalicylic acid is the main product of the esterification reaction between salicylic acid and acetic anhydride and is well known as the active ingredient in aspirin. Carbon atoms are shown in gray, hydrogen in white, and oxygen in red.

The 3D structure of acetic acid based on computational results is shown in Figure 6:

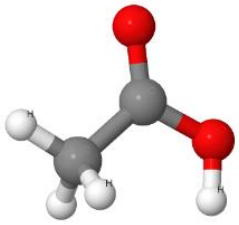

Figure 6. 3D Structure of Acetic Acid ($C_2H_4O_2$)

This compound consists of a methyl group (CH_3–) bonded to a carboxyl group (–COOH). Acetic acid is the byproduct produced in the formation of acetylsalicylic acid. Carbon atoms are represented in gray, hydrogen in white, and oxygen in red.

4. CONCLUSION

Based on the calculation results using the RHF/3-21G method through the NWChem software, the formation reaction of acetylsalicylic acid from salicylic acid and acetic anhydride has a formation energy of –1.21 kJ/mol, indicating that the reaction is thermodynamically spontaneous. The obtained activation energy of 7.95 kJ/mol is considered low, suggesting that the reaction proceeds rapidly and requires minimal energy to initiate. The intermediate structure was successfully modeled based on visual references and its energy was calculated using the same method, reinforcing the understanding of the ongoing reaction mechanism.

5. ACKNOWLEDGEMENTS

The author would like to express sincere gratitude to the Chemistry Laboratory, Faculty of Mathematics and Natural Sciences, Universitas Negeri Medan, for the facilities and technical support provided throughout the research. Special thanks are also extended to Professor Asep Wahyu Nugraha, the academic supervisor, for his invaluable guidance, support, and assistance that greatly contributed to the progress of this research. His insights and expertise played a crucial role throughout the entire process.

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