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Thermodynamic and Kinetic Study on the Reaction Mechanism of Paracetamol Formation from 4-Aminophenol Using Computational Chemistry Methods

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ABSTRACT

Paracetamol, also known as acetaminophen, is one of the most widely used drugs worldwide and is included in the WHO Essential Medicines List. The synthesis process of paracetamol is carried out through the acetylation reaction of 4-aminophenol with acetic anhydride, producing paracetamol and acetic acid as a by-product. This study aims to analyze the thermodynamic and kinetic aspects of the paracetamol formation reaction from 4-aminophenol using a computational chemistry approach. Calculations were performed using the Restricted Hartree-Fock (RHF) method with a 3-21G basis set implemented in the NWChem software, while molecular structure visualization was conducted using Jmol and Avogadro. The results show that the energy change (ΔE) is –25.0107 kJ/mol (exothermic). In addition, the activation energy (Ea) required to reach the transition state is recorded at 623.13 kJ/mol.

Keywords: Paracetamol, 4-aminophenol, thermodynamics, kinetics, computational chemistry.

1. INTRODUCTION

Paracetamol, Paracetamol, commonly known as Acetaminophen, is one of the most widely used drugs globally and is available over-the-counter in most countries. This medication is listed on the World Health Organization's (WHO) Essential Medicines List (Chidiac et al., 2023). Its primary function is as an analgesic and antipyretic, and it has long been a cornerstone in medical treatments worldwide (Ayoub, 2021). In general, the synthesis of paracetamol is carried out through the acetylation reaction of 4-aminophenol using an acetylating agent, such as acetic anhydride, which produces paracetamol with acetic acid as a by-product (Parveen et al., 2023). Within the realm of chemistry, the reaction's progress is chiefly governed by two aspects: thermodynamics and kinetics. Both play crucial roles in determining not only whether a reaction can occur but also how rapidly the process will proceed (Sandrina and Ahmad, 2023). The formation of paracetamol from 4-aminophenol and acetic anhydride can be analyzed from thermodynamic and kinetic

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perspectives. Thermodynamically, a reaction tends to proceed spontaneously if the change in Gibbs free energy (ΔG) is negative. In addition, a negative reaction enthalpy (ΔH) indicates that the reaction is exothermic, while a positive change in entropy (ΔS) reflects an increase in the system's disorder (Mekky, 2024). On the kinetic side, research focuses on the activation energy (Ea), which determines the reaction rate; a lower Ea implies that the reaction can proceed faster since the energy required to reach the transition state is relatively low. A thorough understanding of both these aspects is essential to optimize the synthesis conditions of paracetamol for greater efficiency (Putri et al., 2022; Chang, 2003). Along with technological advancements, research in the field of chemistry has evolved beyond traditional laboratory experiments. This progress is evident from the increasing number of researchers who now employ theoretical approaches via computational experiments—an area known as computational chemistry—which has been developing since the 1950s, initiated by the pioneering work of John Pople (Paramita et al., 2020). Computational chemistry is a branch of chemistry that utilizes experimental data to be analyzed using computer programs, enabling the calculation of various molecular properties and changes, including their differences (Agustina and Kasmui, 2021).

Computational chemistry is understood as a discipline that employs theoretical chemical data translated into computer programs to compute molecular properties (Marwan and Nugraha, 2022). Several previous studies have demonstrated the successful application of computational chemistry methods in analyzing chemical reactions. Computational approaches have been applied to predict the structures and molecular formulas of Fe(II)-Htrz complexes using HF and DFT methods with basis sets such as B3LYP/6-31G(d), TPSSh/TZVP, and MO6-2x/6-31G(d). The results showed that complexes with deprotonated ligands (trz^-) had shorter Fe–Fe distances, shorter Fe–N bond lengths, and lower formation energies compared to those with protonated ligands (Htrz), indicating greater stability. The most stable molecular formula obtained was $([Fe(Htrz)_2(trz)]^+)_n$ (Nugraha et al., 2019). Computational studies using HF and DFT methods have also been conducted to investigate the stability of β-carotene interactions with various solvents. The results revealed that β-carotene was most stable when interacting with ethanol and methanol, as indicated by the most negative ΔE values. Polar solvents with –OH groups exhibited stronger interactions than non-polar solvents like n-hexane. Structural visualization supported the presence of specific interactions between the polar solvent groups and the carbon chain of β-carotene (Nugraha et al., 2021). Another computational chemistry study utilizing the DFT B3LYP/6-31G(d) method was carried out to analyze the HOMO and LUMO structures of bis(β-diketonate) Zr(IV) complexes as catalysts in the polymerization of ε-caprolactone (ε-CL) and δ-valerolactone (δ-VL). Orbital visualization showed that the HOMO was localized on the ligand, while the LUMO was localized on the metal center, indicating the potential for charge transfer from the ligand to the metal (Yusuf et al., 2023). A further study using the UHF/6-31G(d) method was conducted on the complexes $[Fe_2(Htrz)_6(trz)_3]Cl$, $[Fe_4(Htrz)_{10}(trz)_5]Cl_3$, and $[Fe_6(Htrz)_{14}(trz)_7]Cl_5$. The results showed that these complexes underwent changes in Fe(II)–Fe(II) distances and energy levels during the transition from low spin to high spin states. Although the visual structures did not change significantly, thermodynamic data such as ΔE, ΔH, and ΔG indicated that the complexes containing two and four Fe(II) ions were spontaneous, while the complex with six Fe(II) ions was non-spontaneous (Nugraha et al., 2022). The complexes $[Fe_2(Htrz)_6(trz)_3]Cl$ and $[Fe_4(Htrz)_{10}(trz)_5]Cl_3$ were also studied computationally using the DFT/B3LYP/6-31G(d) method to observe structural and thermodynamic changes due to spin transitions. The results showed variations in Fe–N bond lengths, Fe–Fe distances, and Fe–Cl distances between low-spin and high-spin

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states. The values of ΔE, ΔH, and ΔG confirmed that $[Fe_2(Htrz)_6(trz)_3]Cl$ was more stable energetically, and the structural and thermodynamic data were consistent with experimental results (Nugraha et al., 2020).
A study employing the computational chemistry method DFT/B3LYP/6-31G using the NWChem 6.6 software was conducted to calculate the total energy, energy differences, and intermolecular interaction distances of several organic solvents, namely benzene, ethanol, methanol, and hexane. The results indicated that the benzene–ethanol (1:2) mixture had the lowest interaction energy (–0.00916429 kJ/mol) and intermolecular distances ranging from 2.44 to 2.5 Å, signifying the highest stability among the evaluated systems (Malau and Nugraha, 2021).

The reaction pathway for the synthesis of ellagic acid from gallic acid was also theoretically examined using Molecular Mechanics (MM) and Density Functional Theory (DFT) with the B3LYP/6-31G basis set, employing software tools such as Gabedit, MPQC, and NWChem. Geometry optimizations were performed on the reactants, transition states, and products, followed by enthalpy (ΔH) and activation energy (Ea) calculations at each reaction step. The results showed that all reaction steps had negative ΔH values, indicating the exothermic nature of the process. The transition state structures exhibited higher energy than the reactants and products. Positive Ea values at each step further confirmed that the proposed reaction pathway is theoretically rational and highlights the effectiveness of computational chemistry in elucidating reaction mechanisms (Wanita and I, 2020). These studies collectively demonstrate that computational chemistry methods are effective in elucidating reaction mechanisms, compound stability, and providing an in-depth and accurate understanding of thermodynamic and kinetic properties. One commonly used computational method is the *Restricted Hartree-Fock* (RHF) approach. Hartree-Fock (HF) calculations are among the ab initio methods used to solve the Schrödinger equation. This approach forms the foundation of electronic structure theory and is utilized to approximate the wave functions and energy of quantum systems based on quantum mechanical principles. Its main advantages lie in its algorithmic simplicity and relatively accurate results, especially for small to medium-sized molecular systems. Therefore, it is often employed as a preliminary study to determine molecular structure and bond energies (Sugisaki et al., 2019). Based on these previous studies, the present work aims to analyze the energy changes and activation energy of the reaction mechanism for paracetamol formation using computational chemistry methods.

2. RESEARCH METHOD

This study is a theoretical investigation based on quantum mechanics aimed at analyzing the thermodynamic and kinetic properties involved in the formation of paracetamol from 4-aminophenol through molecular modeling. Calculations were performed using NWChem version 6.6 (NWChem User Documentation, 2007) employing the Restricted Hartree-Fock (RHF) method and the 3-21G basis set, with molecular visualization carried out using Jmol (version 14.31.36.3.3) (Jmol, n.d.) and Avogadro (version 1.1.1) (Hanwell et al., 2012). The research was conducted at the Computational Chemistry Laboratory, Department of Chemistry, Faculty of Mathematics and Natural Sciences, Universitas Negeri Medan. All calculations were executed on a single desktop computer equipped with an Intel Core™ i3-6100T CPU @ 3.20GHz processor, 4 GB RAM, and a 64-bit Ubuntu Linux operating system. The molecules analyzed included 4-aminophenol, acetic anhydride, acetic acid, paracetamol, and the intermediate structures formed during the course of the reaction mechanism.

3. RESULTS AND DISCUSSION

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3.1 Computational Data Results

Based on computational chemistry calculations using the RHF method with the 3-21G basis set, the total energy values of the compounds involved in the paracetamol formation reaction were obtained. The energy values were calculated in Hartree (Ht) units and then converted to kJ/mol. The results show that the intermediate compound has the highest total energy, amounting to –1743013.6248 kJ/mol, while the compound with the lowest total energy is acetic acid at –597794.3175 kJ/mol. The total energy values obtained from these computational chemistry calculations are presented in Table 1.

Table 1. Energy Data Calculated Using the RHF Method and 3-21G Basis Set

No	Compound Name	Total Energy (Ht)	Total Energy (KJ/mol)
1.	Oxygen	-149.20412837	-391735.4390
2.	Nitrogen	-108.86800503	-285832.9472
3.	Hydrogen	-1.12682783	-2958.4865
4.	Carbon	-37.58820402	-98687.8297
5.	4-Aminophenol	-360.45148722	-946365.3797
6.	Acetic Anhydride	-379.39348047	-996097.5830
7.	Intermediate	-663.87873731	-1743013.6248
8.	Paracetamol	-512.16669429	-1344693.6559
9.	Acetic Acid	-227.68779947	-597794.3175

The computational chemistry data were used to calculate the energy change (ΔE) for 4-aminophenol, acetic anhydride, the intermediate compound, paracetamol, and acetic acid. The energy change values were obtained by subtracting the total energy of the system in the final state from the total energy in the initial state (Nurhadi, 2021). The calculated energy change (ΔE) data are presented in Table 2.

Table 2. Calculated Energy Change (ΔE) Data

Compound Name	Energy (KJ/mol)
4-Aminophenol	-5099.5060
Acetic Anhydride	-4867.6464
Intermediate	-9344.0205
Paracetamol	-7225.9169
Acetic Acid	-2766.2462

Based on the computational results, all energy change values (ΔE) for each compound—including 4-aminophenol, acetic anhydride, intermediate, paracetamol, and acetic acid—are negative. The formation energy is defined as the difference between the total energy of the products and the total energy of the reactants. The energy change in the paracetamol formation reaction calculated using the RHF/3-21G method is –25.0107 kJ/mol. The negative value indicates that the reaction releases heat to the surroundings and is therefore exothermic. Additionally, the negative Gibbs free energy suggests that the formation stage of paracetamol occurs spontaneously (Rahayu et al., 2023).

Based on the obtained calculations, all energy change values (ΔE) for each compound—including 4-aminophenol, acetic anhydride, intermediate, paracetamol, and acetic acid—are negative. This indicates that each step of the reaction is exothermic, as evidenced by ΔE values below zero. The negative values also suggest that the reaction can proceed spontaneously.

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After obtaining the total energy values of each compound, the next step is to analyze the energy change that occurs during the reaction process of paracetamol formation. 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 –25.0107 kJ/mol. The negative result indicates that the reaction releases a certain amount of heat into the surroundings, making it exothermic. In addition, the negative value of Gibbs free energy indicates that the paracetamol formation step occurs spontaneously (Rahayu et al., 2023).

3.2 Reaction Energy Diagram of the Compounds

The calculated energy data for each compound has been obtained and is subsequently presented in a simplified energy diagram. This diagram illustrates the energy levels of 4-aminophenol, acetic anhydride, intermediate, paracetamol, and acetic acid, as shown in Figure 1.

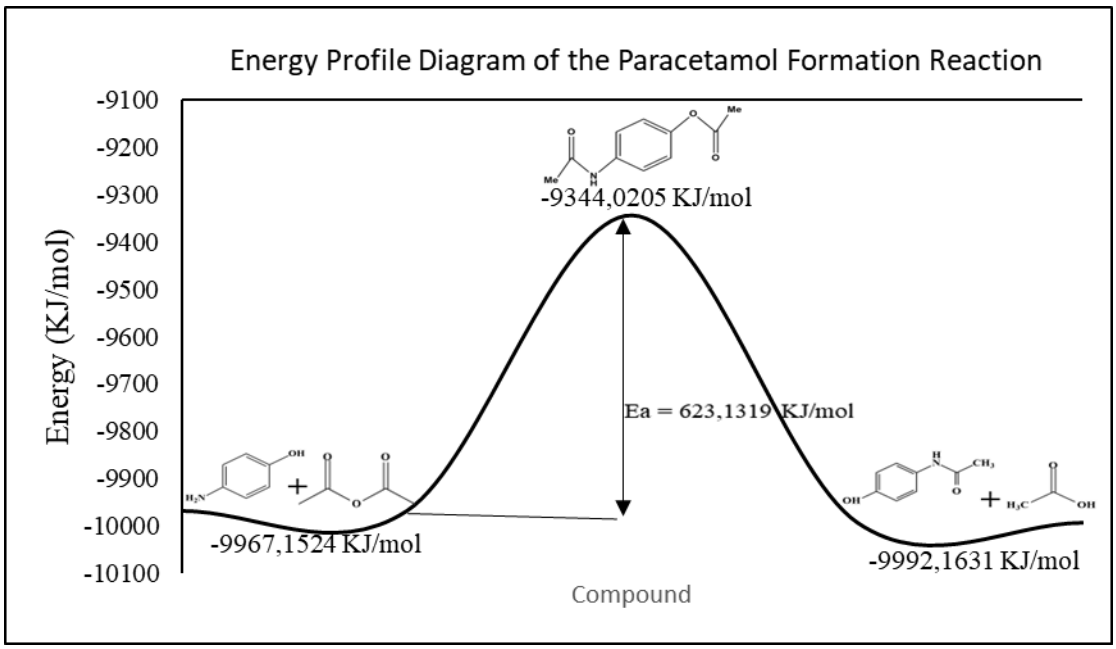

Figure 1. Energy level diagram of 4-aminophenol, acetic anhydride, intermediate, paracetamol, and acetic acid compounds.

The compound located at the peak of the curve in the energy diagram represents the *intermediate*, which is a transient structure formed temporarily before yielding the final product. The identification of this compound as an intermediate is based on geometry optimization and energy calculations using computational chemistry methods, which indicate that at this point the system is at the highest energy state along the reaction pathway. This structure shows that partial bonding between the reactants has occurred but the product has not yet been fully formed, thus representing a transition state during the acylation process between the amino group of 4-aminophenol and the acetyl group of acetic anhydride. This is further supported by its higher energy value compared to both the reactants and products, as well as the indication of newly forming bonds that are not yet fully stabilized. In addition to paracetamol as the main product, acetic acid is also formed at the final stage of the reaction as a by-product. The formation of this by-product is consistent with the acylation mechanism, where an acetyl group is transferred to the amino group and the

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remaining anhydride moiety forms acetic acid. This by-product is shown together with paracetamol at the end of the energy diagram, with the total system energy being lower than that of the reactants, indicating that the reaction is exothermic and produces thermodynamically more stable products.

The diagram above illustrates the energy profile of the reaction for the formation of paracetamol from 4-aminophenol and acetic anhydride, based on computational calculation results. In this diagram, the vertical axis represents energy in units of kJ/mol, while the horizontal axis depicts the progression of the reaction from reactants to products. The reactants, namely 4-aminophenol and acetic anhydride, have a total energy of –9967.1524 kJ/mol. This energy increases to the peak of the curve, representing the transition state, with a total energy of –9344.0205 kJ/mol. The energy peak indicates the point at which the reactants reach their highest energy before converting into products. The difference between the energy of the reactants and the transition state gives the activation energy (*Ea*), which is 623.1319 kJ/mol.

After passing through the transition state, the system's energy decreases to a product energy level of –9992.1631 kJ/mol, indicating that the products possess lower energy than the reactants. This implies that the formation of paracetamol via this reaction pathway is thermodynamically spontaneous, as it releases energy, resulting in more stable products. Thus, the diagram demonstrates that although the reaction requires a relatively high activation energy, the final products have lower energy, supporting the feasibility and continuation of the paracetamol formation reaction.

3.3 Visualization of Computational Results Using Jmol Software

The main output of this calculation is the total energy value of the optimized structures. These computational data are then utilized to visualize the three-dimensional molecular structures using the Jmol software. The molecular structures of each compound, which have undergone the computational optimization process, are shown in the figures below.

The 3D structure of 4-aminophenol, obtained from geometry optimization, is visualized using Jmol software and presented in Figure 2.

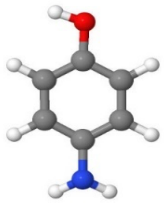

Figure 2. 3D Structure of 4-Aminophenol Compound

The 3D structure of the 4-aminophenol compound shown in Figure 2 is the result of geometry optimization using computational chemistry methods. This visualization illustrates that 4-aminophenol consists of a benzene ring bonded to two major functional groups: a hydroxyl group (–OH) and an amino group (–NH_2). These groups are located opposite each other on the benzene ring, a position chemically known as *para*. The carbon atoms in the benzene ring are visualized in gray, hydrogen atoms in white, oxygen in red, and nitrogen in blue.

The 3D structure of the acetic anhydride compound resulting from geometry optimization is visualized using the Jmol software, as shown in Figure 3.

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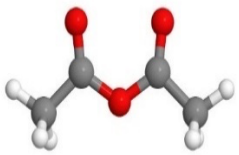

Figure 3. 3D Structure of the Acetic Anhydride Compound

The 3D structure of the acetic anhydride compound shown in Figure 3 is the result of geometry optimization using computational chemistry methods and was visualized using the Jmol software. This compound consists of two acetyl groups (CH_3–CO–) connected by a central oxygen atom, forming the anhydride structure of acetic acid. In the visualization, carbon atoms are shown in gray, hydrogen atoms in white, and oxygen atoms in red. The methyl groups (–CH_3) are attached to carbonyl groups (C=O), and the two carbonyls are bridged by a central oxygen atom.

The 3D structure of the intermediate compound resulting from geometry optimization is visualized using Jmol software and shown in Figure 4.

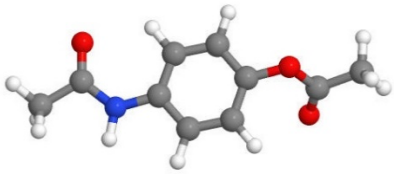

Figure 4. 3D Structure of the Intermediate Compound

The 3D structure of the intermediate compound after geometry optimization is shown in Figure 4. This structure represents a transient species formed during the reaction mechanism of paracetamol synthesis from the reactants 4-aminophenol and acetic anhydride. The visualization was carried out using the Jmol software following computational calculations and geometry optimization. In the figure, it can be observed that the carbonyl group from acetic anhydride has interacted with both the –OH and –NH_2 groups of 4-aminophenol. In the model, carbon atoms are represented in gray, hydrogen atoms in white, oxygen atoms in red, and nitrogen atoms in blue.

The 3D structure of the paracetamol compound, resulting from geometry optimization, is visualized using the Jmol software and presented in Figure 5.

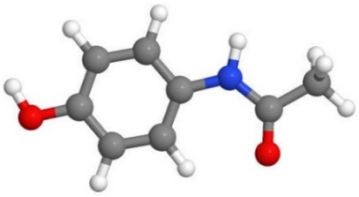

Figure 5. 3D structure of the paracetamol compound

The 3D structure of the paracetamol compound shown in Figure 5 is the result of geometry optimization using computational chemistry methods and visualized with the Jmol software. In this structure, it is clearly visible that the –NH group from 4-aminophenol has bonded with the carbonyl group from acetic anhydride, forming an amide group, which is a characteristic feature of paracetamol. In addition, the –OH group remains attached to the aromatic ring, confirming that no positional changes occurred to this group during the reaction.

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The 3D structure of the acetic acid compound resulting from geometry optimization is visualized using Jmol software, as shown in Figure 6.

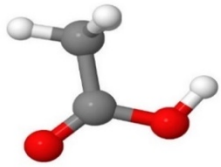

Figure 6. 3D structure of the acetic acid compound

The 3D structure of the acetic acid molecule, obtained from geometry optimization, shows the characteristic arrangement of acetic acid. It consists of a methyl group ($–CH_3$) directly connected to a carboxyl group (–COOH). The oxygen atoms in the carbonyl and hydroxyl groups are bonded to a central carbon atom, forming a stable planar structure.

4. CONCLUSION

Based on the results of computational chemistry calculations, the formation energy of paracetamol from the reactants 4-aminophenol and acetic anhydride was found to be –25.0107 kJ/mol, indicating that the reaction is exothermic. Meanwhile, the activation energy (Ea) required to reach the transition state in the reaction mechanism is 623.13 kJ/mol. These results indicate that although the formation of paracetamol is thermodynamically favorable, the reaction still requires a relatively high activation energy to proceed to the transition state.

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