

## Thermodynamics Theoretical Investigation for Synthesis of Pyridine from Pyrylium Salt using Density Functional Theory

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### Abstract

Pyridine is a heterocyclic compound that is widely used as an ingredient in medicines, vitamins, food flavors, pesticides, dyes, adhesives, and others. Currently, pyridine synthesis is carried out with coal tar as a raw material, which is a non-renewable natural resource. In this research, a theoretical study was carried out to evaluate the synthesis process of pyridine using pyrylium salt as an alternative raw material to displace coal tar. This study also aims to simulate the pyridine synthesis and the energy required or released in the process. Density Functional Theory (DFT) method was employed to calculate some thermodynamic properties of the species involved in the reaction such as enthalpy, entropy, and Gibbs free energy in a vacuum and solvated model in order to study the progress of the reaction and mechanism. Based on the calculation results, the lowest value of enthalpy, entropy, and free energy Gibbs is obtained when the reaction takes place in a vacuum. The change of entropy and free Gibbs energy of the reaction was not predominantly affected by the degree of polarity of the solvent. Meanwhile, the enthalpy of reaction simulated in water solvent is higher than in the ethanol solvent. The synthesis reaction of pyridine from pyrylium salt is exothermic and exergonic because it has a negative value of enthalpy change and Gibbs free energy at 298.15 K, which is potential to be done at room temperature without extreme condition control.

**Keywords:** *computational chemistry, DFT, pyridine synthesis, pyrylium salts*

### 1 Introduction

Pyridine is a heterocyclic organic compound with the chemical formula  $C_5H_5N$ . The structure of this compound is similar to benzene, but one methine group ( $=CH-$ ) is replaced by one nitrogen atom (N). Pyridine is liquid at room temperature, highly flammable, weakly alkaline, and can be dissolved in the water with a characteristic unpleasant odor like fish. Pyridine are colorless but can turn yellowish if left long enough or contaminated with impurities (not pure) [1].

Pyridine is one of the important precursor in heterocyclic chemistry due to its chemical properties [2]. Pyridine and its derivatives are used as an important ingredient in the manufacture of important commodities such as medicines [3],

vitamins [4], food flavors [1], [5], pesticides [6], paints [7], dyes and pharmacophore [8,9], rubber products [10], adhesives [11], waterproof fabrics, and solvents [12]. The pyridine ring is found in many essential compounds, such as niacin and pyridoxal [13] which are build the structure of vitamin B, isoniazid [14], as well as other compound with antiviral, anti-HIV [15], anticancer, antitumor [2], antibacterial [16], antimalarial [17], anti-inflammatory [18], antidiabetic [19], and antioxidant properties [20]. The worldwide annual production of pyridine reached up to 20,000 tonnes per year [1]. Coal tar is the primary source of pyridine, but the yield is still low [21]. It is also known as non-renewable

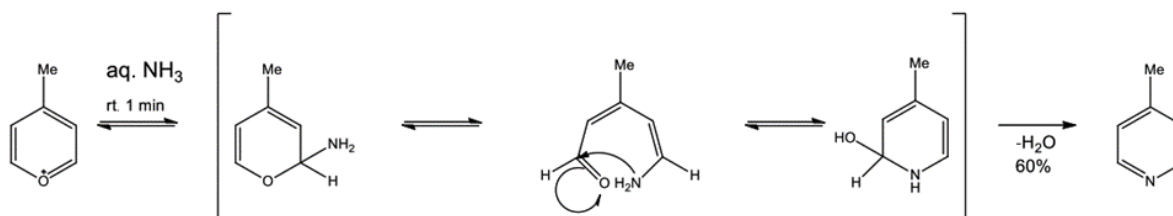


natural resource that is used in various other important sectors such as fuel and industrial products.

Other research invented the laboratory scale pyridine synthesis based on the reaction of acetylene and hydrogen cyanide [22], but its precursor gives some negative effects on health and the environment [23]. Recently, pyridine was produced from aldehydes and ammonia as precursor through gas phase synthesis [24,25] but the problem is the aggregation of aldehydes that increases the cost of production due to gas distribution coking phenomenon [26,27]. Therefore, it is crucial to look for other alternative raw materials in synthesizing pyridine, especially for processes carried out on a small scale.

Pyridine can be synthesized by reacting a pyrylium salt with ammonia [28,29] with the chemical reaction as presented in figure 1. Pyrylium salts can be synthesized using a 1,5-

dicarbonylalkane reagent, which is reacted with acetic anhydride by cyclodehydration reaction [30]. Pentenedial (glutamaldehyde) raw materials could be employed to obtain unsubstituted pyrylium salt products. The use of pyrylium salt involves a more straightforward reaction mechanism, so it is expected that the synthesis of pyridine through this pathway will be more efficient [31]. In synthesizing a compound, many possible reaction pathways will occur with various reagents. Careful study and preparation are necessary before the synthesis process to minimize unnecessary costs and energy expenditures. The reaction pathway of the reaction could be studied through computational chemistry. Modeling using computational chemistry can also minimize the use of chemicals and reduce the release of chemicals that are harmful to the environment from experimental results in the laboratory.



**Figure 1.** Reaction mechanism of pyridine synthesis from pyrylium salt

In this study, the reaction pathway of pyridine synthesis towards pyrylium salts was carefully evaluated thermodynamically using the density functional theory (DFT) [21]. DFT is one of the computational chemistry methods that is widely used for the determination of the electron structure of an atom or molecule using the formalism proposed by Kohn – Sham, that is the electron density outlined into a set of orbitals [32]. Molecular structure, energies, and properties of each species involved in the reaction pathway were analyzed to predict the reaction mechanism of pyridine synthesis through pyrylium salts as precursors. Moreover, the simulation was done in several solvation models to evaluate the effect of solvent on the reaction thermodynamics.

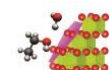
## 2 Method

Avogadro [33] was used to create a molecular input file that will be optimized using DFT on the Orca [34] software. DFT is not affected by the size of the system so the electron density variable is kept constant. Then the input file that has been

created is opened by Gabedit software [9] as the interface for further computations since Orca does not have Graphical User Interface (GUI). All molecular structures including the reactant, intermediate, and product involved in the reaction were optimized using the B3LYP functional hybrid and the 6-31G base set. The B3LYP method has a relatively good and accurate result for measuring a compound, especially organic compounds [35]. In the optimization process, several iterations of calculations were carried out that vary the length and angle to obtain the structure with the minimum energy. Visualization of input and output files was performed using Avogadro software.

## 3 Result and Discussion

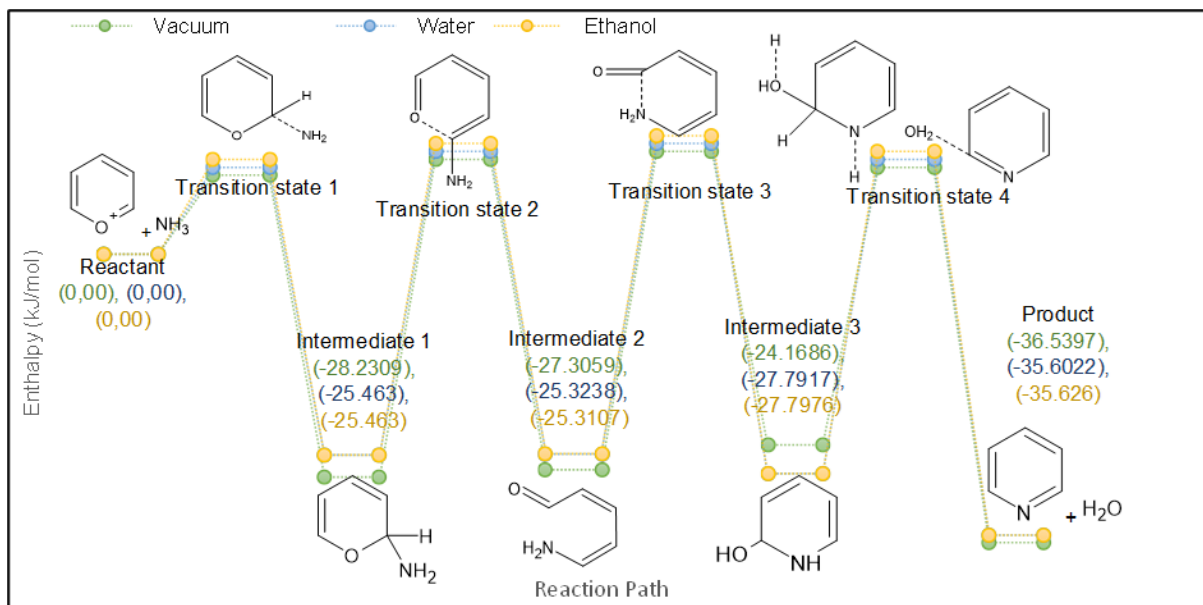
Optimized molecular structures of reactant, intermediate, and product that are involved in Figure 1 with DFT/B3LYP/6-31G are presented in table 1. Some thermodynamic properties of each molecule were obtained, including molecular energy, entropy, and Gibbs free energy.



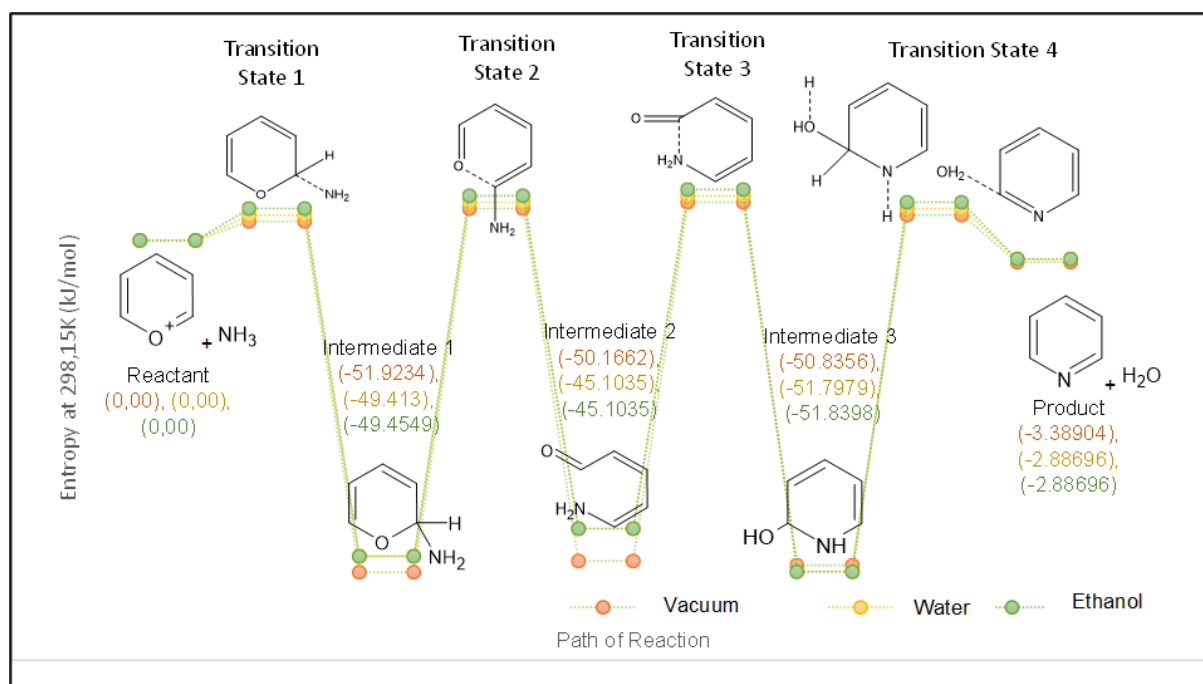


The reaction starts with the attack of the  $\text{NH}_2^-$  group from ammonia ( $\text{NH}_3$ ) as a reagent on the carbon atom of the pyrylium salt as starting material that is adjacent to the positively charged oxygen atom. This position can cause a nucleophilic attack due to the induction effect from the oxygen atom. The resonance of the pi electrons on the double bond to the oxygen induces the carbon in that position to be relatively positively charged, leading to the formation of intermediate 1. This structure undergoes the

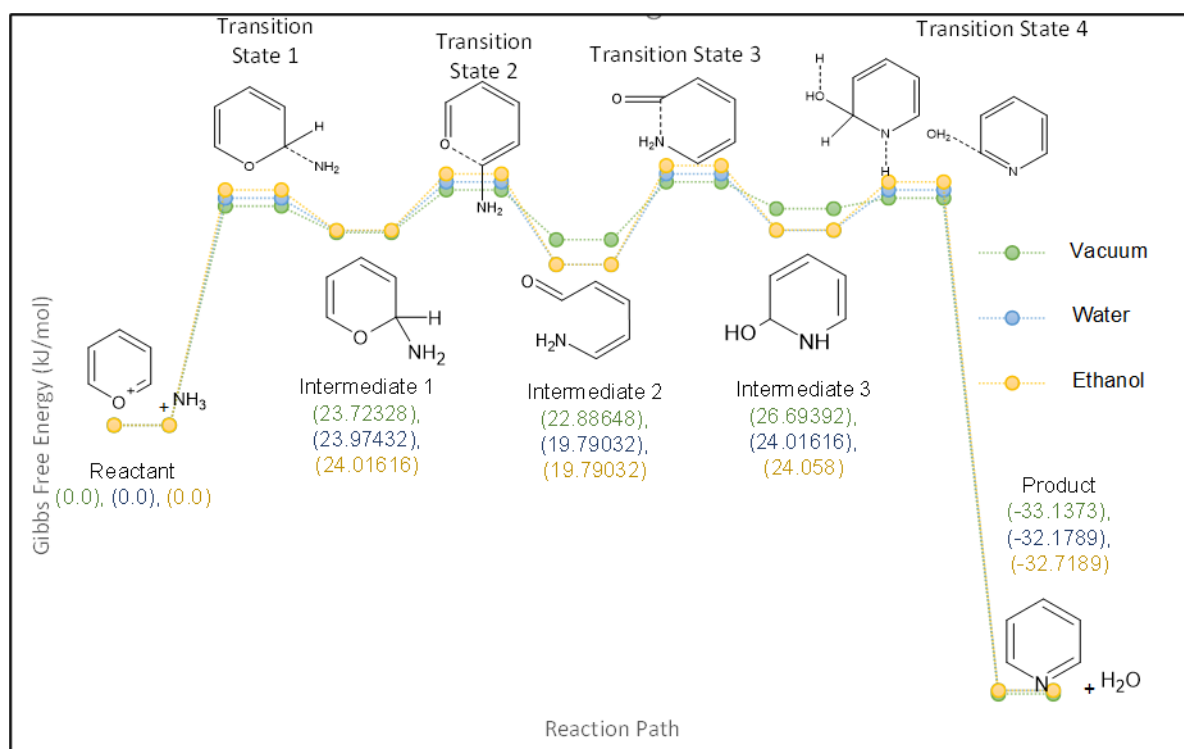
opening of the pyran ring and forms an open chain compound containing amine and aldehyde groups (intermediate 2). The amine's free electrons can attack the carbonyl aldehyde's carbon to form a heterocyclic compound with nitrogen as a heteroatom and an alcohol group, resulting in intermediate 3. The hydroxyl group can be dehydrated (released as water), forming a double bond to produce pyridine compounds. The process of the reaction can be depicted in a diagram in **Figures 2-4**.



**Figure 2.** Enthalpy change diagram for the reaction of pyridine synthesis from pyrylium salt



**Figure 3.** Entropy change diagram for pyridine synthesis reaction from pyrylium salt



**Figure 4.** Gibbs free energy change diagram for pyridine reaction from pyrylium salt.

At the beginning of the reaction,  $\text{NH}_3$  releases  $\text{H}^+$  to form the nucleophilic substance  $\text{NH}_2^-$ . The  $\text{H}^+$  is not included in the reaction diagram because the electronic structure of  $\text{H}^+$  is a substance with no electrons, but DFT calculation is executed based on electron density. In the second transition state, there is a cleavage between oxygen and carbon that bonded to the  $\text{NH}_2$  and opens the pyran heterocyclic ring to form the second intermediate compound. Furthermore, in the third transition state, the nitrogen atom reacts with the carbon atom in the carbonyl group, which causes the formation of a six-ring nitrogen heterocyclic compound. Meanwhile, the aldehyde turns into alcohol due to proton binding. In the fourth transition state, the alcohol group attached to the six-ring heterocyclic undergoes a dehydration reaction to form a pyridine compound.

The spontaneity of a chemical reaction can be assessed based on the reaction's kinetic and thermodynamic aspects. Kinetic aspect analysis is carried out by comparing the transition state energies of a reaction [36]. Every reaction process will have a transition state or a state when a compound changes the arrangement of atoms from the initial state to the final state. Structures in these transition states could be similar to initial or final state compounds and are relatively high-energy. A reaction that proceeds in several steps will have several transition states and intermediate

compounds. One step that proceeds more slowly is rate-determining. The rate-determining step can be predicted based on structural analysis and the reactivity to undergo a reaction. The reaction of the nucleophilic  $\text{NH}_2^-$  on the carbon atom as in the first reaction step is predicted to have a relatively faster reaction, as well as the ring-opening reactions and alcohol dehydration. In contrast, the cyclization reaction is estimated to be the rate-determining step [37].

Thermodynamics aspect analysis of the reaction is conducted by analyzing the energy of the products and reactants involved in a reaction [38]. Based on the computational chemistry data obtained from this study, the thermodynamic aspect can be evaluated. A reaction will occur spontaneously when the energy of the products is lower than the energy of the reactants. In addition, **Figures 2 and 4** ascertained that the first stage reaction is an exothermic and endergonic reaction. At this stage, the pyrylium salt is attacked by the nucleophilic  $\text{NH}_2^-$  which derived from  $\text{NH}_3$ . The first intermediate compound that has been formed has a lower enthalpy value than the reactants while the Gibbs free energy value is higher.

In the second step reaction, the change of enthalpy value was positive even the difference is not quite significant. Meanwhile, based on the Gibbs free energy point of view, this reaction is classified as an exergonic reaction. This is because

the Gibbs free energy value of the second intermediate is lower than the first intermediate.

In the next step of the reaction, the calculation result reveals that this reaction is classified as an endothermic and endergonic reaction. This means that at this stage of the reaction, energy is needed from the environment so that the reaction can take place because this reaction will not run spontaneously.

In the final step of the reaction where the product is formed, the enthalpy change is negative, indicating that this reaction step is considered an exothermic reaction. Based on Gibbs free energy, this reaction step is classified as an exergonic reaction because there is a fairly high decrease in the value of Gibbs free energy between the third intermediate compound and the final reaction product. This also indicates that the products formed (in this case pyridine and water) have a relatively high level of stability compared to other compounds involved in this reaction.

From the results of the plot diagram of enthalpy, entropy, and Gibbs free energy for the reactants, intermediates, and products of pyridine formation from pyrylium salt, this reaction is categorized as an exothermic reaction which means that the heat from the system goes out to the surroundings due to the higher enthalpy value of the reactant. Based on the calculation of the enthalpy, entropy, and Gibbs free energy, the lowest value was obtained when the reaction was modeled in a vacuum. Based on the solvated model in ethanol and water solvents, the value of the entropy and Gibbs free energy seems not affected by the level of the polarity of the solvent used. This can be seen from the value of the entropy value and Gibbs free energy of the synthesis reaction in ethanol and water solvents that are almost similar. For the enthalpy, the synthesis reaction that was carried out in the water solvent has a higher value than the reaction that was carried out in the ethanol solvent. It suggests that the reaction will be more favorable in less polarity solvent based on the thermodynamic aspect.

#### 4 Conclusion

In this study, a diagram of the energy plots of the reactants, intermediates, and products involved in synthesis of pyridine compounds from pyrylium salts was obtained through DFT calculation. T changes in the Gibbs free energy and entropy values modelled in vacuum condition are -33.1373 kJ/mol and -3.38904 kJ/mol,

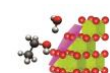
respectively, while in solvated condition (water and ethanol solvents) were similar, with the value of Gibbs free energy and entropy are -32.7189 kJ/mol and - 2.88696 kJ/mol, respectively. Then the enthalpy values of the reaction in a vacuum, water solvent, and ethanol solvent are -36.5397 kJ/mol, -35.6022 kJ/mol, and -35,626 kJ/mol, respectively. At a temperature of 298.15 K, the pyridine synthesis reaction from pyrylium salt has an enthalpy change value and Gibbs free energy that varies in each reaction step. This reaction combines exothermic and exergonic reactions, requiring energy from the environment in several reaction steps to form pyridine as a product of the reaction and potential to be done at room temperature without extreme condition control.

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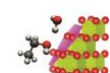
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