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DFT analysis of intermolecular and intramolecular double proton transfer during the condensation process of 4-pyridinecarboxaldehyde with isomers of aminobenzoic acid

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Abstract. To understand in detail the double proton transfer in the condensation reaction of 4-pyridinecarboxaldehyde with isomers of aminobenzoic acid (in the gas phase and in solvent), the dynamic mechanism was studied using the DFT method implemented in the GAUSSIAN 09 program and the 6-31G basis set. All condensation processes described in this study proceed in two stages: the first stage involves the interaction of the reactants and the methanol-mediated proton transfer from the amine group to the aldehyde group, forming an intermediate compound; the second stage is identified by the intramolecular donation of the second proton from the (-NH) group to the hydroxyl oxygen, forming highly stable Schiff base products with the elimination of water and methanol molecules. From the perspective of activation energy, it is observed that the solvent has a positive influence on intermolecular transfer, which is not the case for intramolecular transfer. Additionally, the solvent positively contributes to the energetic stability of the final reaction products.

Keywords: DFT study, double proton transfer, activation energy, energetic stability.

Analiza DFT a transferului dublu de protoni inter și intramolecular în timpul procesului de condensare a 4-piridincarboxaldehidei cu izomerii acidului aminobenzoic

Rezumat. Pentru a înțelege în detaliu transferul dublu de protoni în reacția de condensare a 4-piridincarboxaldehidei cu izomerii acidului aminobenzoic (în fază gazoasă și în solvent), a fost studiat mecanismul dinamic, utilizând metoda DFT implimentată în programul GAUSSIAN 09 și setul de bază 6-31G. Toate processele de condesare descrise în acest studiu decurg în două etape: prima etapă decurge cu interacțiunea reactanților și transferul protonului mediat de metanol de la gruparea amină la gruparea aldehidică formându-se un compus intermediar; a doua etapă se indentifică prin donarea intramoleculară a celui de-al doilea proton din gruparea (-NH) la oxigenul hidroxilic, formându-se produși Baze Schiff cu stabilitatea mare, cu eliminarea moleculei de apă și matanol. Din punct de vedere a energiei de activare se constată că solventul influențează pozitiv în cazul transferului intermolecular, ceea ce nu putem spune în cazul intramolecular. De asemenea solventul are un aport pozitiv în cazul stabilității energetice a produșilor finali de reacție.

Cuvinte-cheie: studiul DFT, transfer dublu de protoni, energie de activare, stabilitate energetică.

1. Introduction

Aliphatic and aromatic aldehydes constitute a significant category of organic compounds involved in numerous essential chemical reactions. One of the most remarkable reactions is their condensation with primary amines, resulting in the formation of N-substituted imines, known as Schiff bases. These imines are crucial in chemical synthesis and biological processes, being widely used in organic chemistry to generate complex compounds. Moreover, Schiff bases are of major importance in the pharmaceutical industry for drug synthesis, in molecular recognition studies, and as intermediates in various catalytic processes. Theoretical analysis of the properties and reactivity of Schiff bases provides valuable information for understanding the mechanisms of chemical reactions and for developing new materials and functional compounds [1].

The condensation reactions leading to the formation of Schiff bases involve essential proton transfers, both within individual molecules and between different molecules. In the process of forming a Schiff base, a proton is transferred from the amino group to the carbonyl group, thereby facilitating the formation of the characteristic carbon-nitrogen double bond of N-substituted imines. This proton transfer can occur through intramolecular mechanisms, where the proton moves between functional groups within the same molecule, or through intermolecular mechanisms, via hydrogen bonds formed with water molecules or other molecules present in the environment. In these proton transfer processes, quantum tunneling plays an important role, accelerating the reactions and influencing the dynamics of Schiff base formation. Thus, understanding these proton transfer mechanisms, both inter- and intramolecular, is essential to fully elucidate the formation and reactivity of Schiff bases under various chemical and biological conditions [2].

The theoretical mechanism of double proton transfer in aldehyde-amine condensation reactions is described in the paper [3], where the authors have developed and described the reaction mechanism, comparing the energetic data of direct proton transfer and double proton transfer. Additionally, in the works [4, 5] the theoretical mechanisms of the condensation reaction between 4-pyridinecarboxaldehyde and o-, m-, and p-aminobenzoic acids are also studied and described. The authors mention the reduction of activation energy when the reaction occurs in a solvent.

The aim of this research is to develop the mechanism of double proton transfer in the condensation process of 4-pyridinecarboxaldehyde with isomers of aminobenzoic acid, calculating the activation energy for each system.

2. Computational Methods

The optimization of geometric structures for condensation reactions was performed using Density Functional Theory (DFT), employing the hybrid exchange-correlation functional B3LYP (Becke's three-parameter exchange functional with Lee, Yang, and Parr's correlation functional) and the standard basis set 6-31G [6]. This combination provides a balance between accuracy and computational cost, and is widely used in theoretical studies to predict the electronic structure and properties of molecules. To characterize the optimized stationary points as minima and to evaluate the vibrational zero-point energies, there were calculated harmonic vibrational frequencies for all species involved in the reaction using the B3LYP/6-31G level. All calculations were performed using the GAUSSIAN 09 software package [7].

3. Results and Discussions

Proton transfer is one of the most common processes in chemical and biochemical reactions. A rigorous analysis of this phenomenon requires, first, a consistent explanation of the quantum-chemical behaviour of the proton. Secondly, proton transfer is often associated with charge transfer, which involves a change in the interaction between charge and the polarization of the environment, behaving in a classical manner. Based on the aim of this study, there have been developed general schemes for condensation reactions (Figure 1), which will be theoretically studied using advanced computational methods. The essence of these reactions involves the interaction of an aromatic aldehyde (4-pyridinecarboxaldehyde) with three isomeric amino acids: 2-aminobenzoic acid (1), 3-aminobenzoic acid (2), and 4-aminobenzoic acid (3). The resulting reaction products are N-substituted imines, known as Schiff bases: P1, P2, and P3.

Condensation of 4-Pyridinecarboxaldehyde with o-Aminobenzoic Acid

Theoretical investigation of the condensation mechanism between 4-pyridinecarboxaldehyde and o-aminobenzoic acid was conducted according to the scheme shown in Figure 2. The reaction yields 4-(pyridin-2-ylmethyleneamino)benzoic acid as the reaction product.

The condensation reaction proceeds in two stages. In the first stage, as illustrated in Figure 2, methanol, forming hydrogen bonds between the involved functional groups, facilitates the intermolecular transfer of a hydrogen atom from the amino group to the aldehyde oxygen. This reduces the energy barrier for the formation of the intermediate compound (**Inter1**), contributing to the stabilization of the intermediate structure and enhancing the efficiency of the reaction.

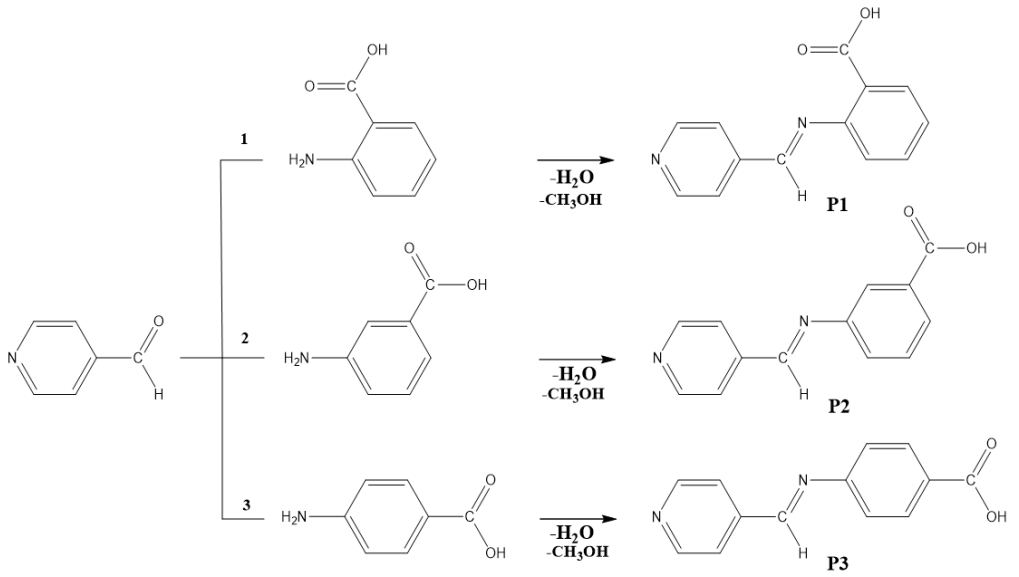

Figure 1. General scheme for the condensation of 4-pyridinecarboxaldehyde with aminobenzoic acid isomers.

Table 1. Activation energy and imaginary frequency values for the transition state in stage I and II.

Reaction stage	**Reaction environment**	**Activation energy, kcal/mol**	**The imaginary frequency, cm^{-1}**
TS11	vacuum	25.98	-1016.87
	methanol	21.52	-833.45
TS21	vacuum	30.94	-1257.07
	methanol	31.62	-800.32

In the second stage, methanol continues to play an important role by facilitating the intramolecular donation of the second hydrogen atom from the (-**NH**) group to the hydroxyl oxygen, resulting in the formation of 4-pyridin-2-ylmethyleneaminobenzoic acid (P1) with the elimination of a water molecule.

Through these mechanisms, methanol not only supports the reaction but also optimizes the conditions for obtaining the final product in an energy-efficient manner. Table 1 presents the numerical values of the activation energies and vibrational frequencies for the studied reaction.

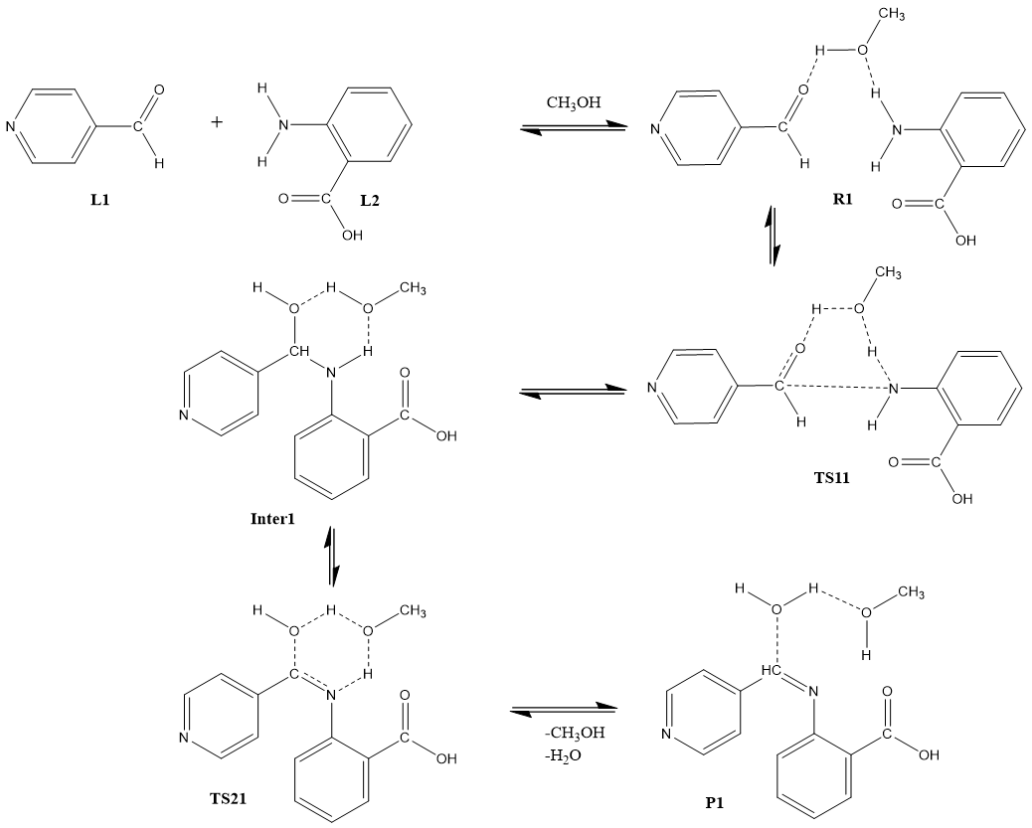

Figure 2. Mechanism of the double proton transfer condensation reaction of 4-pyridinecarboxaldehyde with o-aminobenzoic acid.

According to the data presented in Table 1, the solvent, in this case, methanol, plays a significant role in reducing the activation energy in the first stage of the condensation reaction. This reduction is from 25.98 to 21.52 kcal/mol and is due to the solvent's solvation capacity and its ability to form hydrogen bonds, which facilitates the formation of the final product in an energy-efficient and kinetically efficient manner. In the second stage of the reaction, where intramolecular transfer occurs, the activation energies do not show a similar decrease, increasing from 30.94 to 31.62 kcal/mol. This phenomenon suggests a different influence of the solvent depending on the specific stage of the condensation reaction.

Analyzing the transition states in this condensation reaction, in the first stage, the activated complex corresponds to the moment when the hydrogen atom moves from the amino group to the oxygen of the aldehyde group. At this point, the value of the imaginary frequency is negative (Table 1) and reflects a critical point in the double proton transfer,

indicating how the hydrogen atom oscillates between the donor and acceptor. In the second stage, the transition state occurs when the hydrogen atom moves from the amino group to the hydroxyl oxygen, forming a water molecule and eliminating methanol. The imaginary frequencies associated with this transition state reflect the oscillations of the hydrogen atom before the formation of a stable covalent bond.

Based on the energies obtained from the optimization of the species involved in the condensation reaction, an energy profile was constructed, both in the vacuum and in methanol (Figure 3).

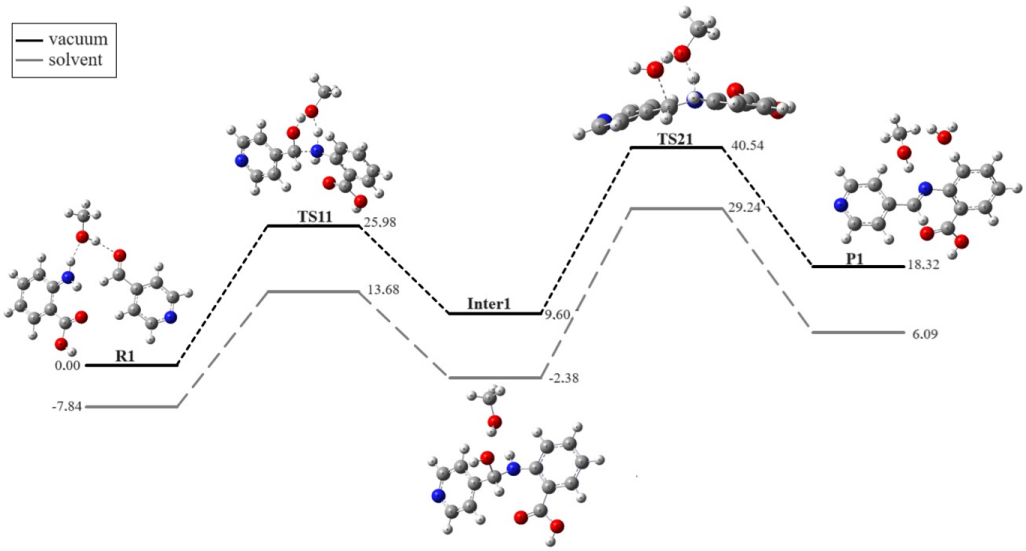

Figure 3. Energetic profile of the reaction between 4-pyridinecarboxaldehyde and o-aminobenzoic acid expressed in kcal/mol.

Analyzing this reaction, it is an endothermic one, meaning it absorbs heat, with the reaction energy values in the vacuum and methanol being 18.32 kcal/mol and 13.93 kcal/mol, respectively. This aspect is consistent with experimental data, indicating that the synthesis or reaction was carried out under severe conditions, at high temperatures.

Condensation of 4-pyridinecarboxaldehyde with m-aminobenzoic acid. Theoretical investigation of the condensation mechanism between 4-pyridinecarboxaldehyde and m-aminobenzoic acid was conducted according to the scheme shown in Figure 4. The reaction yields 4-(pyridin-3-yl methylene amino)-benzoic acid as the reaction product.

To form the final product, the condensation reaction undergoes two consecutive stages. In the first stage, as shown in Figure 4, the intermolecular transfer of a hydrogen atom from the amino group (**-NH$_2$**) to the carbonyl oxygen (**HC=O**) occurs via hydrogen bonds

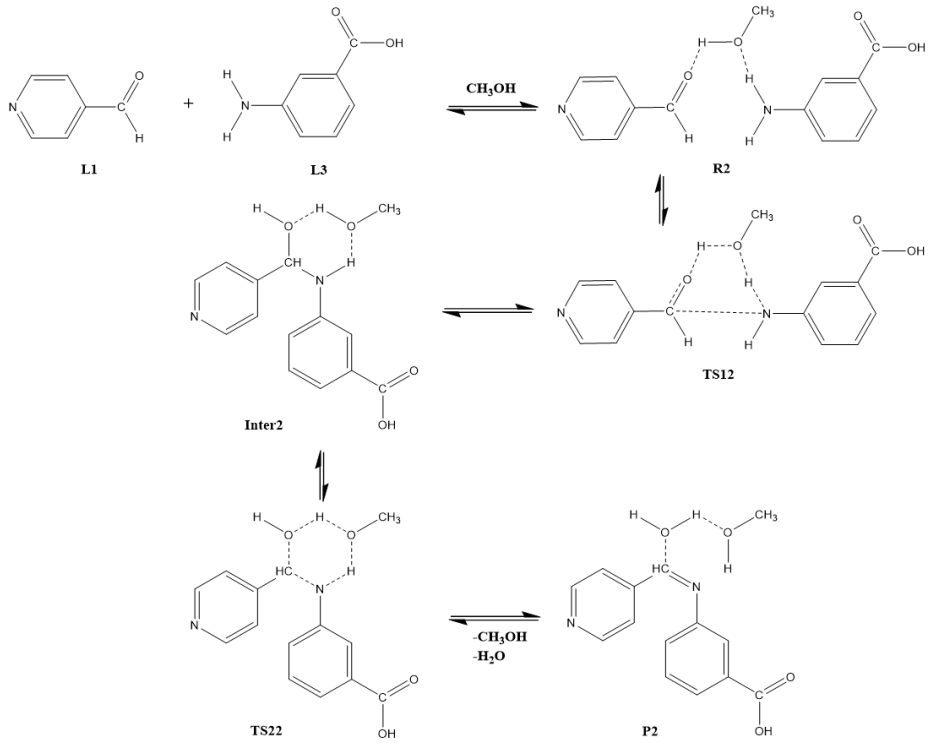

Figure 4. Mechanism of the double proton transfer condensation reaction of 4-pyridinecarboxaldehyde with m-aminobenzoic acid.

created by methanol, forming an intermediate compound (**Inter2**). Methanol continues to play an important role in enhancing the reaction in the second stage by facilitating the intramolecular donation of the second hydrogen atom from the (**-NH**) group to the hydroxyl oxygen, resulting in the formation of 4-(pyridin-3-yl methylene amino)-benzoic acid (**P2**), with the elimination of a water molecule and the release of methanol. Table 2 presents the numerical values of the activation energies for the given reaction.

According to the data presented in Table 2, it is obvious that methanol plays an important role in reducing the activation energy required in the initial phase of the condensation reaction. The energy variation in this case is 2.01 kcal/mol, with the decrease attributed to the solvent's solvation capacity and its ability to form hydrogen bonds, thus accelerating the formation of the final product in an energy-efficient and kinetically favourable manner. Moving to the next stage of the reaction, characterized by intramolecular transfer, the activation energy increases from 24.16 to 25.67 kcal/mol.

Transition states for this reaction were studied, characterizing the moment when the hydrogen atom undergoes a transfer from the amino group to the oxygen atom in the

Table 2. Activation energy and imaginary frequency values for the transition state in stage I and II of the condensation reaction with direct proton transfer.

Reaction stage	**Reaction environment**	**Activation energy, kcal/mol**	**The imaginary frequency, cm^{-1}**
TS21	vacuum	20.96	-995.69
	methanol	18.95	-881.73
TS22	vacuum	24.16	-891.65
	methanol	25.67	-839.76

aldehyde group. This critical juncture is characterized by a negative imaginary frequency, as shown in Table 2, symbolizing a stage in the double proton transfer mechanism. In the subsequent stage, the transition state occurs when the hydrogen atom moves from the amino group to the hydroxyl oxygen, leading to the formation of a water molecule and the simultaneous expulsion of methanol from the system.

By analyzing the energies derived from the optimization process of the various species involved in the condensation reaction, there was constructed an energy profile, including calculations performed both in the vacuum and in the presence of methanol, as illustrated in Figure 3.

The thermodynamic study of the chemical reaction denotes that it is an endothermic process, when it takes place in vacuum and in the presence of methanol, the energy of the reaction being equal to 8.22 kcal/mol and 8.41 kcal/mol, respectively. These numerical values align with experimental observations, suggesting that the synthesis took place under demanding conditions, likely involving high temperatures to facilitate the desired chemical transformation.

Condensation of 4-pyridinecarboxaldehyde with p-aminobenzoic acid. The theoretical investigation of the process of condensation of 4-pyridinecarboxaldehyde with p-aminobenzoic acid has been studied in detail according to the mechanism shown in Figure 6. The reaction results in the formation of 4-(pyridin-4-yl methylen amino)-benzoic acid, commonly known as Schiff Base.

The condensation reaction involves two sequential steps, as illustrated in Figure 6, the process begins with the intermolecular transfer of a hydrogen atom from the amino group (**-NH_2**) to the oxygen of the aldehyde group (**HC=O**). This transfer is facilitated by methanol-mediated hydrogen bridging, resulting in the creation of an intermediate compound (**Inter2**). Subsequently, in the second step, methanol continues to be an

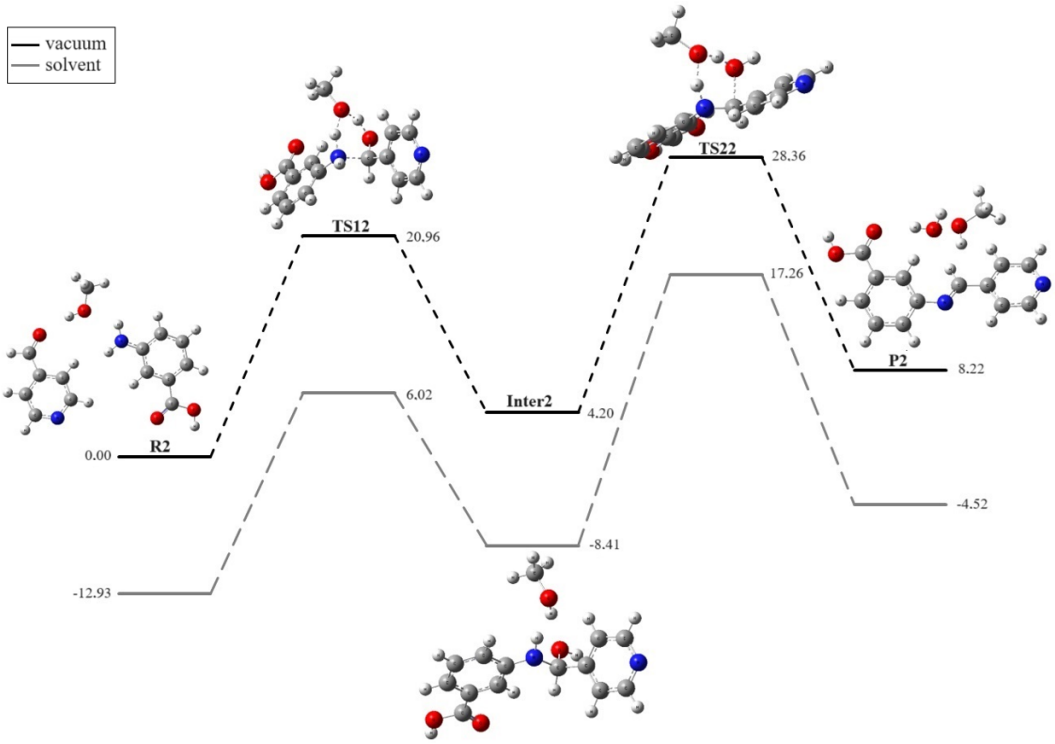

Figure 5. Energetic profile of the reaction between 4-pyridinecarboxaldehyde and m-aminobenzoic acid expressed in kcal/mol.

Table 3. Values of activation energies and imaginary frequencies for the transition state in stage I and II of the double proton transfer condensation reaction.

Reaction stage	**Reaction environment**	**Activation energy, kcal/mol**	**The imaginary frequency, cm-1**
TS31	vacuum	19.95	-1029.07
	methanol	19.33	-949.15
TS32	vacuum	25.58	-1054.70
	methanol	27.30	-824.29

indispensable component, aiding the intramolecular transfer of the second hydrogen atom from the (**-NH**) group to the oxygen of the hydroxyl group. This transfer results in the formation of 4-pyridin-(-4-yl-methylene-)-aminobenzoic acid (**P3**), simultaneously eliminating a water molecule and methanol. Detailed information on the activation energies of the reaction can be found in the data presented in Table 3.

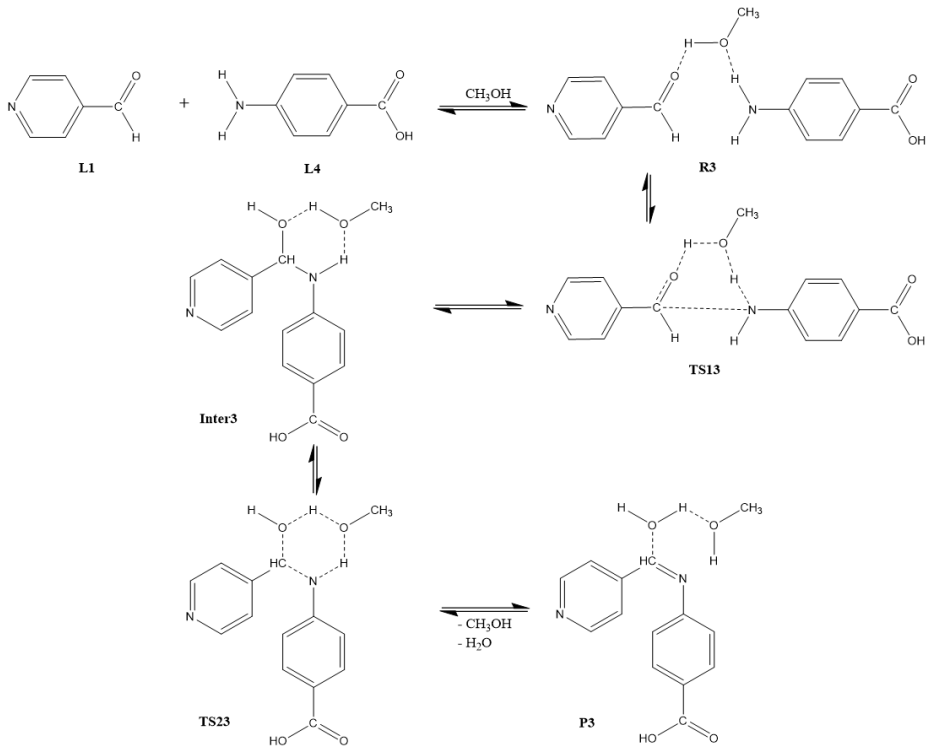

Figure 6. Mechanism of the double proton transfer condensation reaction of 4-pyridinecarboxaldehyde with p-aminobenzoic acid.

According to the information in Table 3, it is obvious that methanol as a solvent plays an essential role in reducing the activation energy required in the initial stage of the condensation process, with values of 19.95 and 19.33 kcal/mol in vacuum and methanol, respectively. The ability of the solvent to form hydrogen bonds thus accelerates the production of the final product in an energy-efficient and kinetically advantageous manner. Progressing to the later phase of the reaction, which is characterized by intramolecular proton transfer, there is a noticeable increase in the activation energy values from 25.58 to 27.30 kcal/mol.

In examining the transition states for this condensation reaction, the initial phase aims to identify the activated complex, which indicates the specific case when the hydrogen atom passes from the amino group to the oxygen atom in the aldehyde group. This transition point is distinguished by a negative value of the imaginary frequency, (Table 2), representing an essential step in the double proton transfer mechanism. Moving to step II, the transition state materializes as the hydrogen atom moves from the amino group to the hydroxyl oxygen, leading to the formation of a water molecule and the expulsion

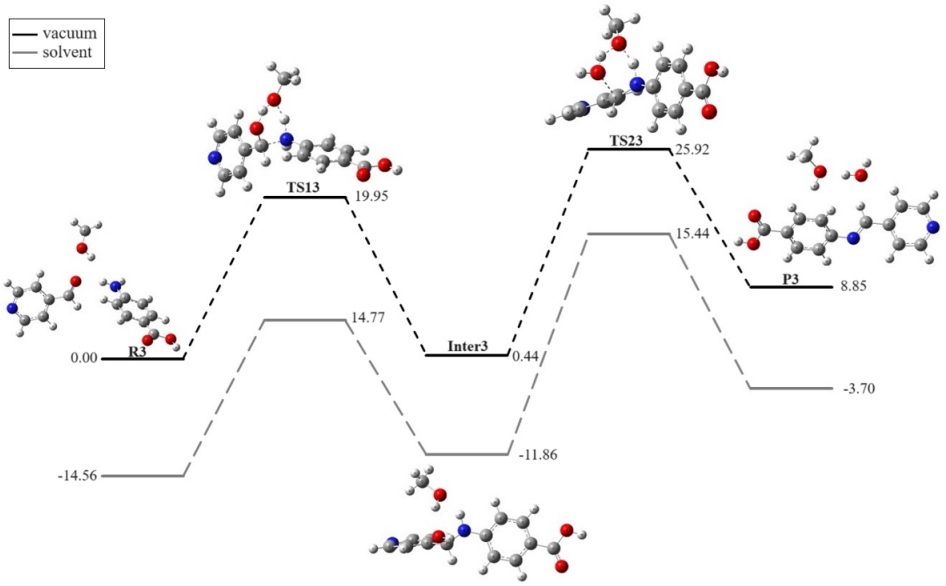

Figure 7. Energetic profile of the reaction between 4-pyridinecarboxaldehyde and p-aminobenzoic acid expressed in kcal/mol.

of methanol from the system. Theoretically investigating the energies obtained from the optimization process of the different entities participating in the condensation reaction and the energy profile was developed, including energy data both in vacuum and in methanol (Figure 3).

The examination of the chemical reaction involves the investigation of a phenomenon characterized by the absorption of thermal energy. The quantification of the energy associated with this particular reaction, which occurs under vacuum conditions and in the presence of methanol, amounts to 8.22 kcal/mol and 8.41 kcal/mol, respectively. These numerical values are in agreement with the experimental data, indicating that the synthesis or reaction took place under specific conditions requiring high temperatures to facilitate the desired chemical synthesis.

4. Conclusions

Double proton transfer is a scientific approach that can provide important insights into the mechanism of condensation reactions and can contribute to the understanding of key aspects of reactions in biological and chemical systems. The use of Density Functional Theory (DFT) has proven to be effective in optimizing geometries and determining the transition states involved in condensation reactions.

Harmonic vibrational frequency harmonic calculations confirmed that all transition states are characterized by single negative imaginary frequencies, indicating that they are veridical saddle points on the potential energy surface. These data confirm the relative energy stability of intermediate and transition species.

The study revealed the complex mechanism of double proton transfer at both intermolecular and intramolecular levels. In the first step, intermolecular proton transfer is facilitated by the formation of an unstable intermediate compound, which initiates intramolecular proton transfer in the second step. The study has shown that methanol, as a solvent, reduces the activation energy at the intermolecular proton transfer step due to its solvation and hydrogen bond formation ability ΔE_a(1st step)=4.46; 2.01; 0.62 kcal/mol. However, at the intramolecular transfer step, the activation energy increases, indicating a complex influence of the solvent on the different reaction steps ΔE_a(II stage)= 0.68; 1.51; 1.72 kcal/mol.

The study confirmed the endothermic nature of the condensation reaction, requiring harsh conditions and high temperatures to be realized. This observation is consistent with the experimental data, emphasizing the need for strict control of the reaction conditions in practical synthesis, thus validating the accuracy of the DFT method for this type of study.

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