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Computational Study of Green Production of *Vanilli Planifolia-Based* Schiff Base Using Ionic Liquid Solvent

Tinjauan Komputasi dari Produksi Hijau Basa Schiff Berbasis *Vanilli Planifolia* Menggunakan Pelarut Cairan Ion

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ABSTRAK

Basa Schiff adalah produk kondensasi dari senyawa amina primer seperti anisidina dengan senyawa karboksilat yang memiliki banyak kegunaan di bidang kimia. Untuk menaikkan nilai tambah produk lokal, senyawa dari tanaman Vanilli Planifolia dapat digunakan sebagai sumber gugus karboksilat. Sintesis secara konvensional memiliki banyak kekurangan semisal yield yang kecil dan limbah yang berbahaya bagi lingkungan. Berdasarkan hal tersebut, perlu dilakukan modifikasi reaksi untuk mengurangi dampak berbahayanya seperti dengan menggunakan cairan ion. Metode komputasi digunakan dalam riset dasar ini karena dapat mengurangi waktu dan biaya riset. Dari hasil dari perhitungan komputasi, didapatkan bahwa penambahan pelarut terbukti dapat memberikan efek penstabilan pada semua molekul terutama bila memiliki sifat kepolaran sejenis. Reaksi produksi basa Schiff terjadi dalam keadaan endoterm dan tidak spontan di suhu kamar. Reaksi tersebut melewati tiga tahap reaksi dengan tahapan penentu laju terjadi pada tahap ke-3. Energi pengaktifan ditemukan lebih kecil pada pelarut cairan ion dari pada pelarut polar lain. Pada tahap reaksi pertama, energi pengaktifan paling minimum ditemukan pada pelarut [EMIM][TfO] sebesar 119.915 kJ.mol^{-1}. Hal ini dikarenakan keadaan transisi pertama/TS-1 bersifat lebih polar dan cocok dengan [EMIM][TfO] yang bersifat lebih polar pula. Sedangkan, pada tahap reaksi ke-2 dan ke-3 energi pengaktifan lebih minim pada pelarut [BMIM][BF_4], sebesar 195.316 dan 354.290 kJ.mol^{-1}, karena sifat keadaan transisi dan pelarut yang tidak terlalu polar. Ke depannya, perlu dilakukan percobaan di laboratorium untuk mengetahui yield dan variabel lain yang tidak dapat ditemukan dengan metode komputasi.

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ABSTRACT

Schiff bases are a condensation product of primary amines, such as anisidine, with carbonyl compounds that have many chemical purposes. To increase the natural product value, the compounds from Vanilli Planifolia could be used as a carbonyl group source. The conventional Schiff Base reaction has several disadvantages, including low yield and producing waste that harms the environment. Due to these disadvantages, it is necessary to do reaction modification to reduce the harmful disadvantages, for example, by using ionic liquid. The computational method was used to reduce the time and cost consumption of the research. The results show that the addition of solvents was proven to increase stabilization effects on all molecules, especially if they have similar polarity properties. Schiff base reaction is classified as endothermic and non-spontaneous at room temperature. The reaction has three steps, with the rate-determining step occurring at stage 3. The activation energy was found to be smaller in the ionic liquid than in other polar solvents. In the first reaction, the minimum activation energy was found in [EMIM] [TFO] solvent at 119,915 kJ.mol^{-1}. It was because transition state-1/TS-1 was more polar and suitable for [EMIM][TFO] which was also more polar. Whereas in the reaction stage 2 and 3, the minimum activation energy was in [BMIM][BF4] at 195,316 and 354,290 kJ.mol$^{-1,}$ *respectively. The minimum energy was caused by TS and solvent properties that were not too polar. In the future, more research needs to be carried out in the laboratory to find out the yield and other variables that cannot be found by the computing method.*

1. INTRIDUCTION

1.1 Background

Schiff bases are a condensation product of primary amines with carbonyl compounds (Fabbrizzi, 2020) (see Figure 1), which are generally used in bio-inorganic chemistry (Naureen et al., 2021), biomedical applications (Dueke-Eze et al., 2013), supramolecular chemistry (Abdulghani & Hussain, 2015), catalysts (Al Zoubi et al., 2018), and the pharmaceutical industry (Kumar et al., 2017). Schiff bases in the pharmaceutical industry are well-known as antioxidants (Wahab et al., 2014), anti-cancer (Lemilemu et al., 2021), anti-microbial (Saadeh et al., 2012), and antifungal (Sharma et al., 2023). Based on this wide usage, the synthesis of Schiff's base has been widely studied, including from various reactants that can produce diverse Schiff's base molecules, one of them was using vanillin. Vanillin is an organic compound that is obtained from *Vanilli Planifolia*. Using Vanillin as a reactant can increase the economic value of *Vanilli Planifolia,* which is usually sold as a dry powder. Schiff base synthesis using vanillin was successfully reported for synthesis with cystine (Lee et al., 2019), aniline (Sabaa et al., 2009) (Abdurrafi et al., 2020) and p-aminoacetophenone (Ma'rufah et al., 2021). Generally, the Schiff base synthesis reaction from vanillin is a condensation reaction between the primary amine and the carbonyl group of the vanillin molecule. The resulting Schiff base molecule had the characteristic of azomethine (C=N) bonds.

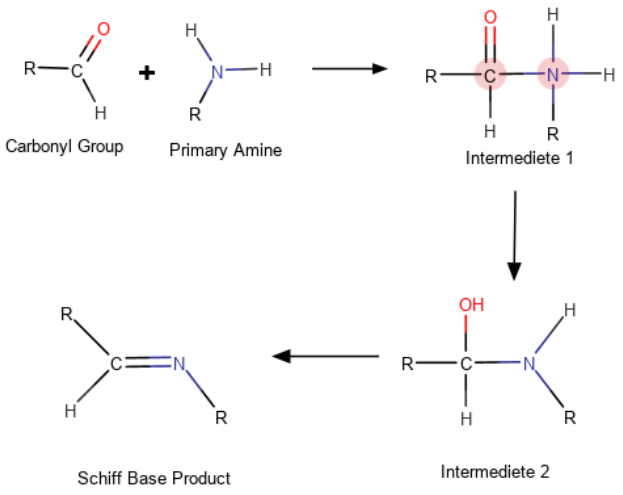


Figure 1. Reaction of Schiff base from primary amines with carbonyl compounds

Conventional Schiff base synthesis was reported successfully using varied solvents such as water (Lee et al., 2019), ethanol (Sabaa et al., 2009), methanol (Rao et al., 2010), DMSO-d_6 (Abdulghani & Hussain, 2015), and $CDCl_3$ (Saadeh et al., 2012). This conventional method has several disadvantages, including low yields, taking a long time, and producing waste harmful to the environment (Abdurrafi et al., 2020). Due to these disadvantages, modification of the synthesis method must be studied, such as using the ionic liquid method.

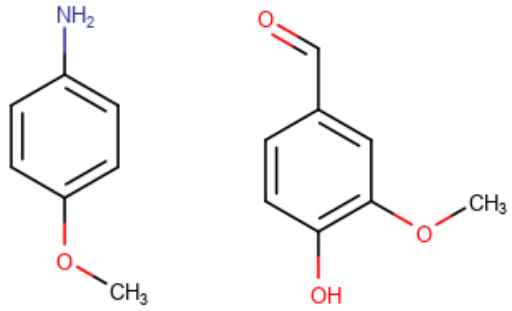


Figure 2. structure of: (a) P-Anisidine which contain primary amines and (b) Vanillin which contain carbonyl compounds

Ionic liquids (ILs) are molten salt with a melting point below ambient temperature that can increase thermal stability, ionic conductivity, and catalytic stability (Khungar et al., 2012). ILs are solvents that are safer than conventional organic solvents because of their low volatility and flammability (Llaver et al., 2021). ILs were made to avoid fire and explosion accident in laboratory(Chen et al., 2019). It also has low toxicity/eco-toxicity and is biodegradable in the environment (Flieger & Flieger, 2020). According to all of this evidence, ILs can be used as a substitute for conventional solvents to fulfill the criteria of green production (Wang et al., 2022).

Based on this, research on Schiff base synthesis using ionic liquid needs to be studied because it lacks reporting to minimize costs; research will be carried out using computational methods by performing solvent comparisons between ionic liquids and conventional solvents

1.2 Aim of Research

This research aimed to find the Schiff base reaction energetic aspect using quantum computational methods. Moreover, the data was processed to find the best solvent in the reaction based on the green production process.

2. METHOD

2.1 Molecules Optimization

All molecule involved in the reaction was drawn using *Avogadro: Molecular Editor and Visualization* (ver. 1.90) (Hanwell et al., 2014). The molecules drawing was generated from a computation input file. The input file added some command scripts for ORCA (Neese et al., 2020). The calculation was done using DFT (Density Functional Theory) method with B3LYP (Becke, 3-parameter, Lee-Yang-Parr) exchange functional and def2-SVP basis sets. The optimized structure was recalculated in the solvation system using Conductor-like Polarized Continuum Model (CPCM) algorithm. The CPCM algorithm needed variables, which were the dielectric constant and Index of Refraction of every solvent, which was shown in Table 1.

Table 1. Dielectric constant and Index of Refraction of various solvent

Solvent	Dielectric constant	Index of Refraction
Water	78.36	1.333
Toluene	2.37	1.496
[EMIM][TfO]	16.50 (Curtis, 2011)	1.433 (Carissimi et al., 2019)
[BMIM][BF4]	6.00 (Göllei, 2017)	1.422 (Carissimi et al., 2019)

2.2 Calculating Energy During Reaction

The optimized structure molecules in every solvent were calculated with frequency energy command to find inner energy, enthalpy, entropy, and Gibbs free energy. The energetic (enthalpy, entropy, and Gibbs free energy) of reaction was calculated using the equation below:

$$\Delta E_{reactions} = \Delta E_{product} - \Delta E_{reactant} \ldots\ldots\ldots(1)$$

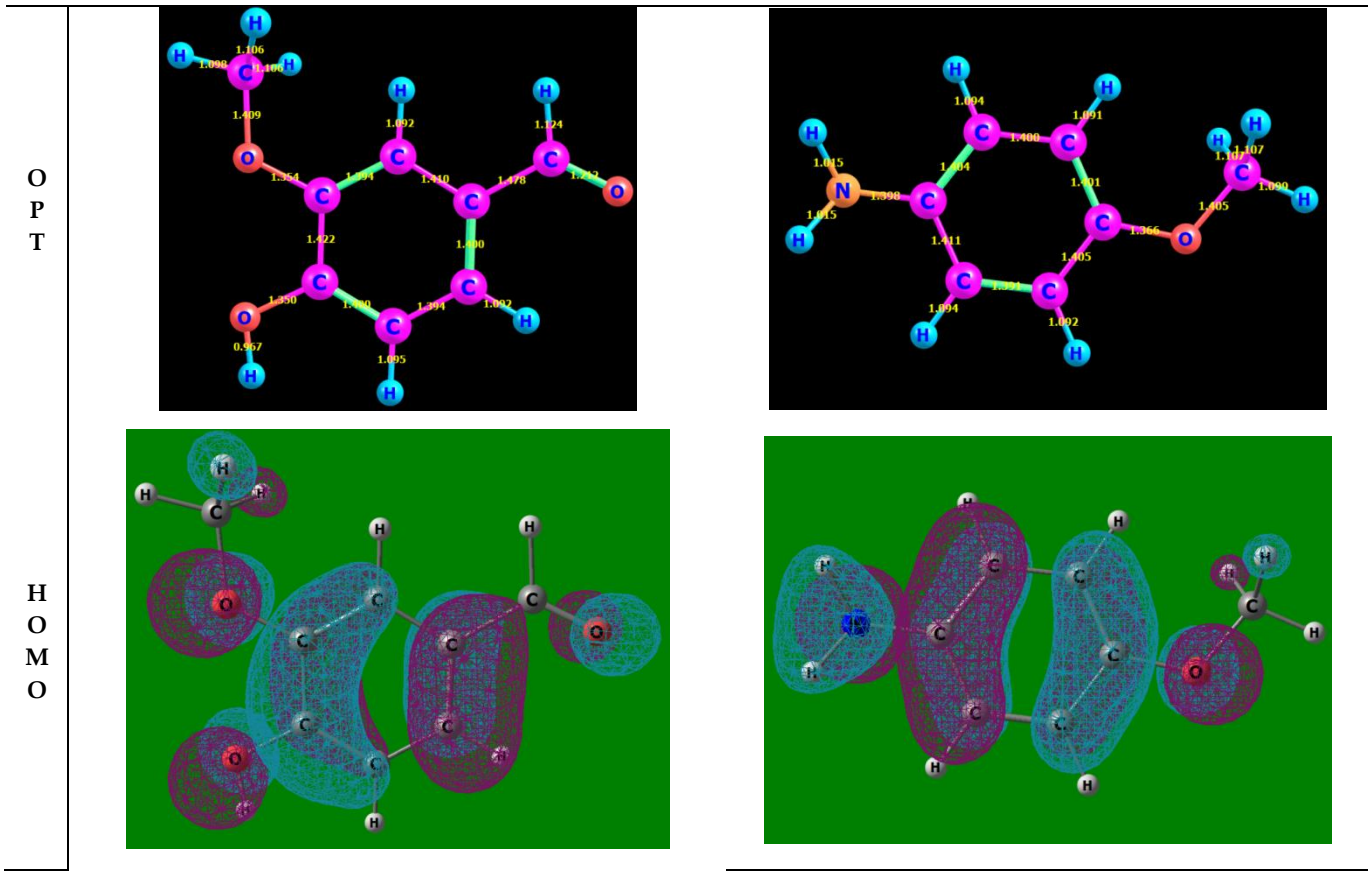
Where:
$\Delta E_{reactions}$ = Energy of reaction (kJ.mol^{-1})
$\Delta E_{product}$ = Energy in product species (kJ.mol^{-1})
$\Delta E_{reactant}$ = Energy in reactant species (kJ.mol^{-1})

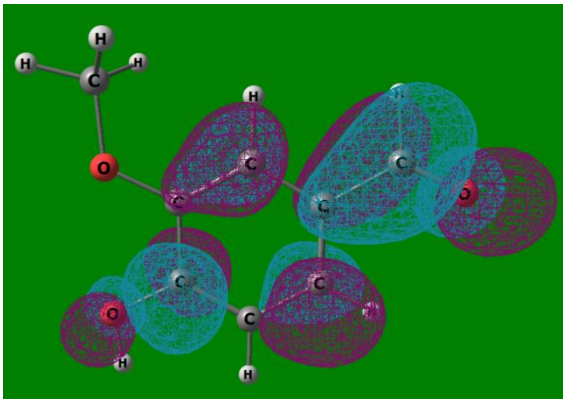
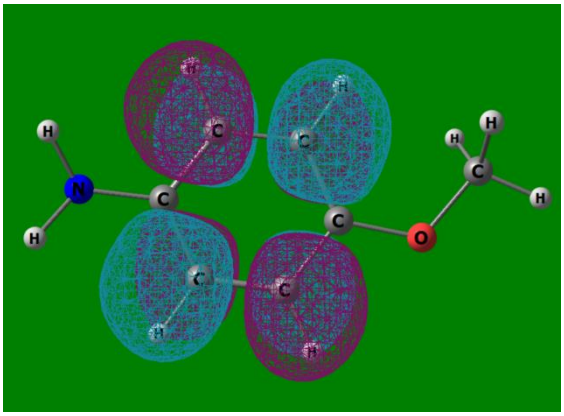
The transition state was searched using the OPTTS commands in ORCA program with input file where the guess structure of the transition state has been added. The potential energy surface reaction diagram was calculated based on Gibbs free energy and reactant species as 0 point.

3. RESULT AND DISCUSSION

3.1 Optimized Structure and Atomic Properties

All molecules that contributed to Schiff base reaction were successfully optimized, as seen in Figure 3. Following this, the optimized molecules were reoptimized in various solvents, and the energetic result comparison can be seen in Figure 4. According to Figure 4, adding solvent can cause stabilization effects characterized by decreasing energy from each molecule (Nilchi et al., 2019). In addition, in the toluene solvent system, the energy was more unstable than the others. It is because toluene is a non-polar solvent that was unsuitable with Schiff base that was classified as a polar molecule (Zarrinmehr et al., 2022).



LUMO		
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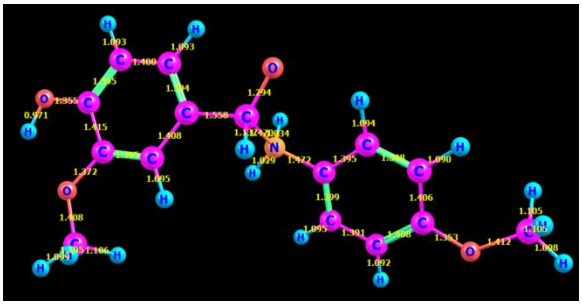
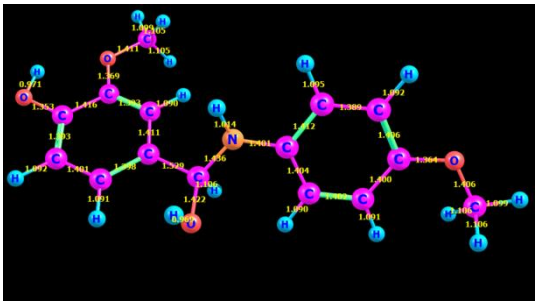
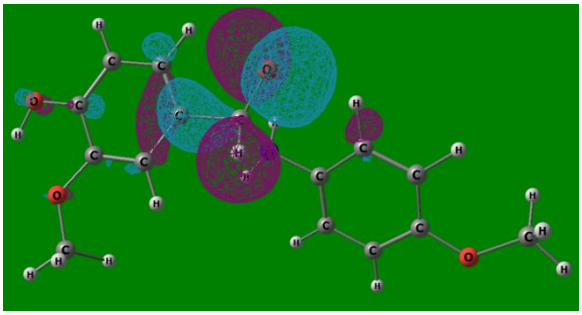
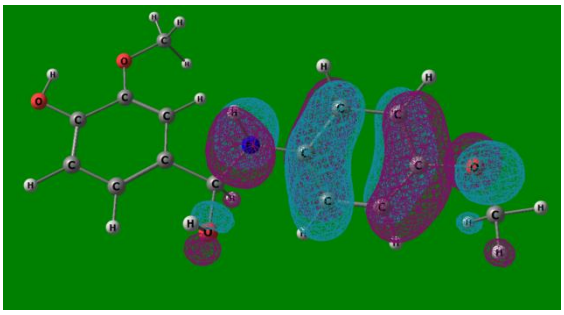
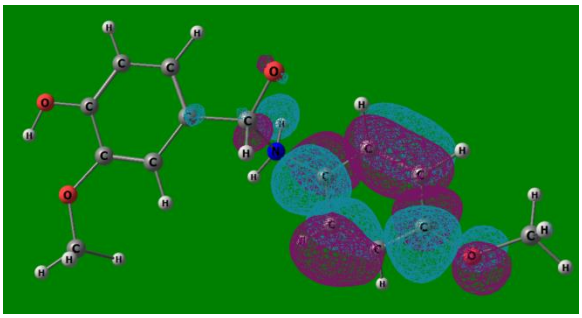
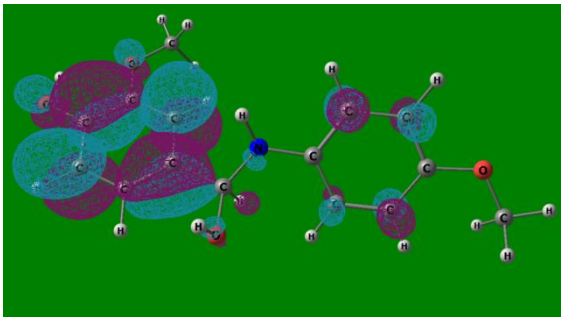
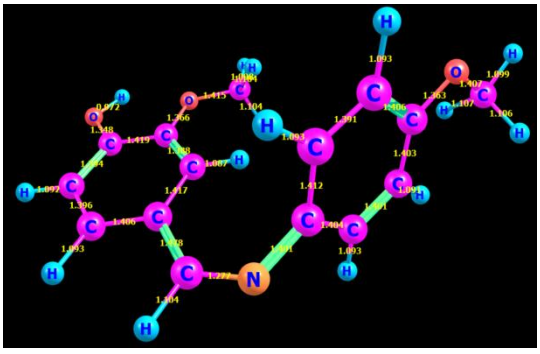
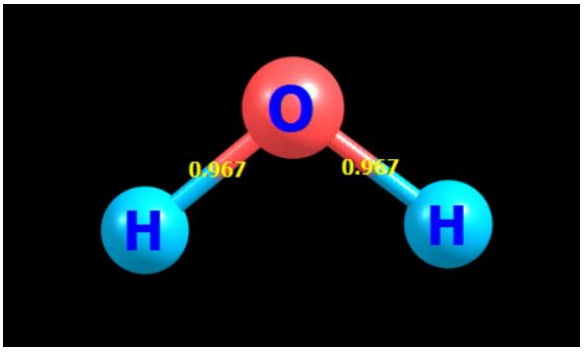
OPT		
HOMO		
LUMO		
	Intermediete-1	Intermediete-2
OPT		

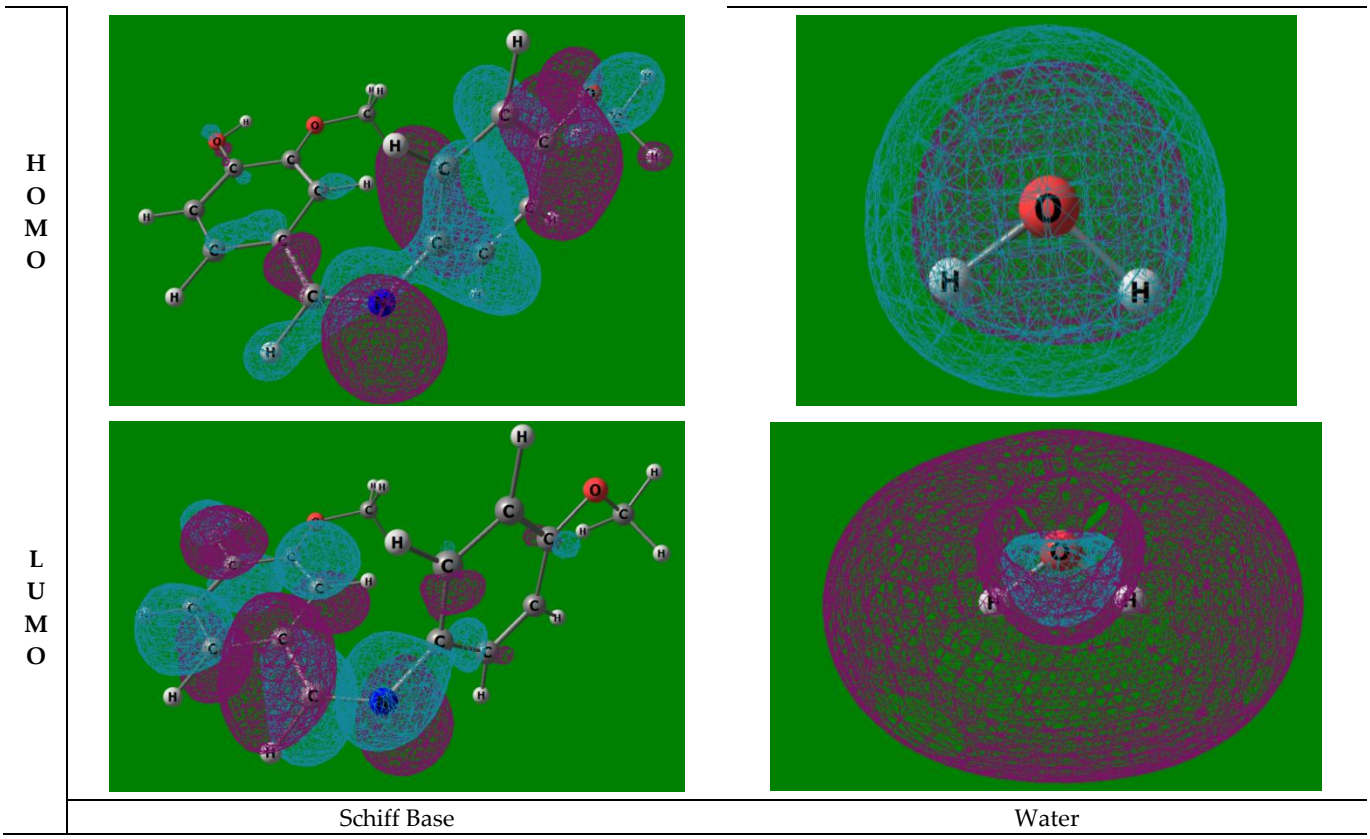


Figure 3. Optimized structure, highest occupied molecular orbital (HOMO), and lowest unoccupied molecular (LUMO) visualization of all molecules.

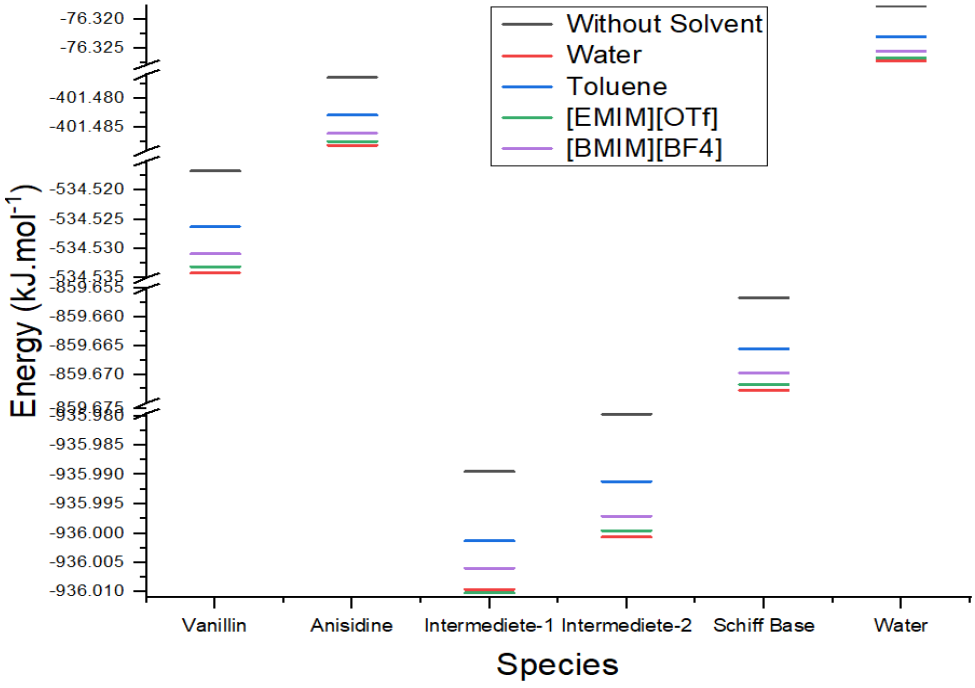


Figure 4. Energy of all molecules in various solvent.

3.2 Reaction Energetic Aspects

Quantum computation methods have found each molecule's energetic properties in Schiff base reaction. The energetic properties were electronic energy, inner energy, enthalpy, entropy, and Gibbs free energy. The result in the nonsolvent system is shown in Table 2.

Based on Equation 1, the enthalpy, entropy, and Gibbs free energy of Schiff base reaction in various solvents is shown in Table 3.

Table 2. Energetic properties of all molecules on non-solvent system

Molecule	Electronic Energy (E) [kJ/mol]	Inner Energy (U) [kJ/mol]	Enthalpy (H) [kJ/mol]	Entropy (S) [kJ/mol.K]	Gibbs free energy(G) [kJ/mol]
Vanillin	-534.628	-534.472	-534.471	1.54.E-04	-534.517
Anisidine	-401.593	-401.436	-401.435	1.40.E-04	-401.476
Intermediete-1	-936.240	-935.922	-935.921	2.31.E-04	-935.989
Intermediete-2	-936.235	-935.916	-935.915	2.18.E-04	-935.980
Schiff Base	-859.886	-859.596	-859.595	2.06.E-04	-859.657
Water	-76.321	-76.297	-76.296	7.19.E-05	-76.318

Table 3. Energetic aspect of Schiff base reaction in various solvent

Solvent	Enthalpy (H) [kJ/mol]	Entropy (S) [kJ/mol.K]	Gibbs free energy(G) [kJ/mol]
Gases/without solvent	36.691	-0.042	49.360
Water	46.743	-0.040	58.605
Toluene	41.610	-0.041	53.870
[EMIM][TfO]	45.936	-0.040	57.854
[BMIM][BF4]	44.734	-0.041	56.536

Overall, the Schiff base reaction was an endothermic reaction that absorbed heat from its surrounding, amounting to 58.605 kJ.mol^{-1} in water solvent (Maleque, 2013). The Schiff base reaction was classified as a nonspontaneous reaction in all temperatures. This is proven by the positive value of enthalpy and Gibbs free energy. Meanwhile, the entropy value was negative (Raff, 2014).

3.3 The Ionic Liquid Effect on Green Production

The activation energy of Schiff base reaction in all ILs solvents and water is presented in Figure 5.

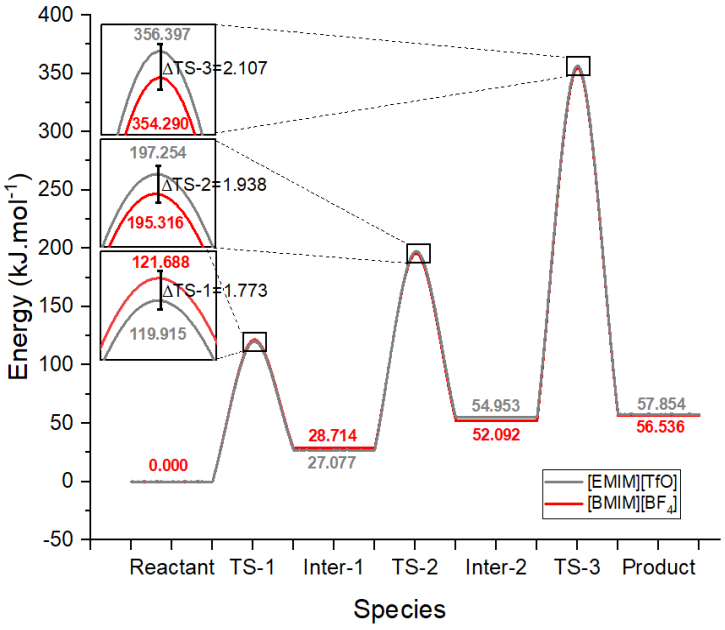


Figure 5. Energy diagram of Schiff Base Reaction in Ionic Liquids solvents.

According to Figure 5, the rate-determining step was in the third reactions step. It meant the step needed a longer reaction time and the highest energy consumption (Murzin, 2020). Moreover, all reactions in ILs solvent needed lower energy than other polar solvents. It is because ILs are more polar than others (DeVos et al., 2014).

Table 4. Dipole moment of transition states in ionic liquids solvent (Debye)

Solvent	[EMIM][TfO]	[BMIM][BF4]
Transition State-1	7.816	7.351
Transition State-2	3.602	3.380
Transition State-3	4.112	4.004

On the one hand, the activation energy for the first reaction step in [EMIM][TfO] solvent was lower than [BMIM][BF4] solvent. On the other hand, at the second and third reaction steps, the lowest was [BMIM][BF4] solvent. According to Table 4, the transition state-1 was the most polar molecule, evidenced by the highest value of dipole moment (Siebler et al., 2015). Thus, the transition state-1 is stable in the more polar solvents. The polarity of a solvent is evident by the higher dielectric constant value. In this case, cationic salt of EMIM/1-Ethyl-3-methylimidazolium has a shorter alkyl chain than BMIM/1-Butyl-3-methylimidazolium tetrafluoroborate, the value of dielectric constant was proportional to 1/chain length (Olmo et al., 2015). In the same manner, the dielectric constant of BMIM was lower than EMIM. For anionic salt effect, the dielectric constant of $[TfO]^-$ was highest than $[BF4]^-$ (Pavez et al., 2015).

Therefore, using the [EMIM][TfO] solvent should decrease the activation energy in the more polar transition state. Moreover, [BMIM][BF4] should also decrease the activation energy, especially in the transition state that did not tend to polar reaction.

4. CONCLUSION

In conclusion, the quantum computational has successfully found an optimized structure for all species, predicted molecules properties, and forecasted energetic aspect of reaction, which is linear with the efficiency of the production process. Ionic liquid performance as a reaction solvent should reduce the activation energy and substitute non-environment friendly solvents such as strong acids in conventional processes. Furthermore, it is necessary to conduct further research in the laboratory to determine the exact yield of the reaction and other important aspects.

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