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Reagocatalysis: In Silico Mechanistic Study to Investigate that it is a Boon or a Bane

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Abstract

The word "Reagocatalysis" was derived (not from the Latin "Reago" which means reaction) after combining the two words i.e. reagent and catalysis. It involved a reagent now called a reagocatalyst that because of its catalyzing moiety could catalyze another identical reagocatalyst or a different molecule as well as it reacted further owing to the presence of the reacting moiety. It was divided into two categories: (a) homoreagocatalysis (b) heteroreagocatalysis. In homoreagocatalysis, one homoreagocatalyst catalyzed another molecule of the homoreagocatalyst and resulting catalyzed intermediate molecule could react further in variety of ways and whereas in heteroreagocatalysis, the heteroreagocatalyst first catalyzed another different molecule to give catalyzed intermediate molecule which then reacted with another heteroreagocatalyst molecule to give an identical product as given by an uncatalyzed reaction.

Keywords: *Catalysis, Reagocatalysis, Homoreagocatalysis, Heteroreagocatalysis.*

Introduction

The discovery of the phenomenon of catalysis remains one of the most powerful tool and substantial act in the human history of progress and development. The development of catalysis involved the collective and individual efforts of the researchers hailing from various parts of the world. An early English scientist, John Roebuck, invented a process of producing approximately 35% concentrated H_2SO_4 using large chambers containing lead surface (Jones, 1950). F. Kuhlmann in 1838 converted NH_3 via air oxidation to HNO_3 using Pt catalyst (Heinemann, 1979).

The team efforts involved the invention of the promoter effect in 1909 and olefinic alkylation using acid catalysis in 1935 by Vladimir Ipatieff (Kieboom, Moulijn, van Leeuwen, & Van Santen, 2000; Plank, 1983; Sciences, 1975). Raney Murray invented the catalytic hydrogenation of oils of vegetable origin with metals (Seymour & Montgomery, 1983). Irving Langmuir was the first to identify the process of the heterogeneous catalysis on solid surface owing to the attachment of gas molecules in the form of a single layer (Gaines Jr & Wise, 1983). The work of Emmett led to the substantial comprehension of the NH_3 synthesis (Garten, 1983). For almost 30 years, Pine contributed to the development of catalysis for various processes (Armor 2011). The process of the intramolecular catalysis was studied for kinetic independence of hydrolytic reactions (Bender, Chow, & Chloupek, 1958). Another prominent discovery of catalysts for the field of isomerization of the paraffins is contributed by F. G. Ciapetta (Hettinger, 1983).

One such finding in the field of catalysis involves the discovery of intramolecular catalysis. An intramolecular catalyst has a reacting and a catalyzing moiety present within the same molecule. It is found that the hydrolysis of phthalamic acid takes place much more rapidly than that of the benzamide and it is attributed to the carboxylic group (catalyzing moiety) that is present in the phthalamic acid and is involved in the intramolecular hydrolysis of the amide group (reacting moiety) (Bender, 1957; Bender, Chow, et al.,

1958). Intramolecular catalysis was then extended to the hydrolysis of esters and similar results were found (Bender, Chloupek, & Neveu, 1958; Morawetz & Oreskes, 1958). Furthermore, this phenomenon is tested on the hydrolysis of copolymer containing carboxylic groups (catalyzing moieties) in the presence and absence of a strong base. The absence of a strong base and pH range of 2 – 8 leads to a hydrolysis rate two to four times greater than in the presence of a strong base (Westhead Jr & Morawetz, 1958). The alkaline hydrolysis of Schiff bases is found to be catalyzed intramolecularly by the ionized ortho hydroxyl groups present in the Schiff bases (Reeves, 1965). The alkaline intramolecular catalysis is revealed to be approximately same or slightly less effective in the reactions of aspirin with nucleophilic reagents (Pierre & Jencks, 1968). The aminolysis reaction of benzoic acid esters is found to be accelerated 16000 times or even more in aprotic solvents due to intramolecular catalysis (Senatore, Ciuffarin, Isola, & Vichi, 1976). A molecule with a similar structure to an intramolecular catalyst can also undergo an intermolecular process and is given a name of "Reagocatalyst". The current article introduces the reagocatalysis to fill a gap in the field of catalysis.

Similar to an intramolecular catalyst, a reagocatalyst also has two parts i.e. a catalyzing moiety and a reacting moiety. A reagocatalyst, therefore, first catalyzes another molecule, alters its reactivity and then the catalyzed intermediate molecule reacts with the reacting moiety available either from another molecule of a reagocatalyst or a simple reactant. However, the catalyzing moiety remains intact at the end of the process. This phenomenon is given a name of reagocatalysis and it is an intermolecular catalytic process. Based on the catalytic action of reagocatalyst as well as the further reaction of the reagocatalyst catalyzed intermediate molecule, the reagocatalysis has two types i.e. homoreagocatalysis and heteroreagocatalysis. If the reagocatalyst catalyzes another identical molecule of its own kind and the catalyzed intermediate molecule reacts with the reacting part of another reactant, it is known as homoreagocatalysis and if the reagocatalyst catalyzes a different molecule and the catalyzed intermediate molecule reacts with the reacting part of another reagocatalyst, it is known as the heteroreagocatalysis.

The present work has a focus on the in silico approach using gaussian 16 (Frisch et al., 2016) for the mechanistic studies of reagocatalysis and its types.

Research Methodology

The in silico mechanistic approach was used to describe the reaction pathway for the types of reagocatalysis i.e. homoreagocatalysis and heteroreagocatalysis.

Reaction Pathway of Reagocatalysis

Homoreagocatalysis

For describing the reaction pathway of homoreagocatalysis, DFT/631G(d,p) level of the theory was used with ethanol solvent. The process of the homoreagocatalysis can actually be divided into three parts. First part describes the formation of enamine as a catalyzed intermediate molecule from the homoreagocatalyst.

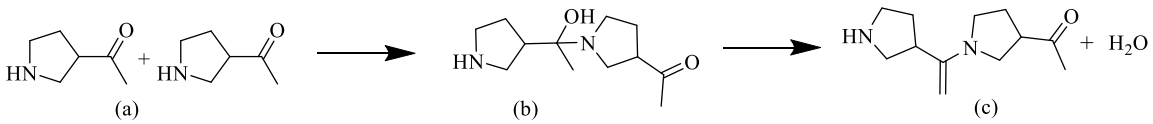


Figure 1: (a) Homoreagocatalysts (b) Adduct (c) Catalyzed intermediate molecule (Enamine)

3-Acetylpyrrolidine was used as a homoreagocatalyst for the mechanistic study of homoreagocatalysis. It had two moieties: a secondary amine (catalyzing moiety) and an acetyl group (reacting moiety). The secondary amine group present in the pyrrolidine ring of one homoreagocatalyst was reacted with the acetyl

group of another molecule of the homoreagocatalyst. It generated the catalyzed intermediate molecule i.e. enamine in two steps via the formation of adduct intermediate as shown in the figure 1. The homoreagocatalyst, the adduct intermediate and the enamine were optimized separately and directly using DFT/631G(d,p) level of theory. However, the transition states (TS) were first optimized at low level theory i.e. hf/sto3g and then optimized using DFT/631G(d,p).

Second part of the homoreagocatalysis involved the nucleophilic attack of the aniline (a simple reactant) on the catalyzed intermediate molecule i.e. enamine as shown in the figure 2.

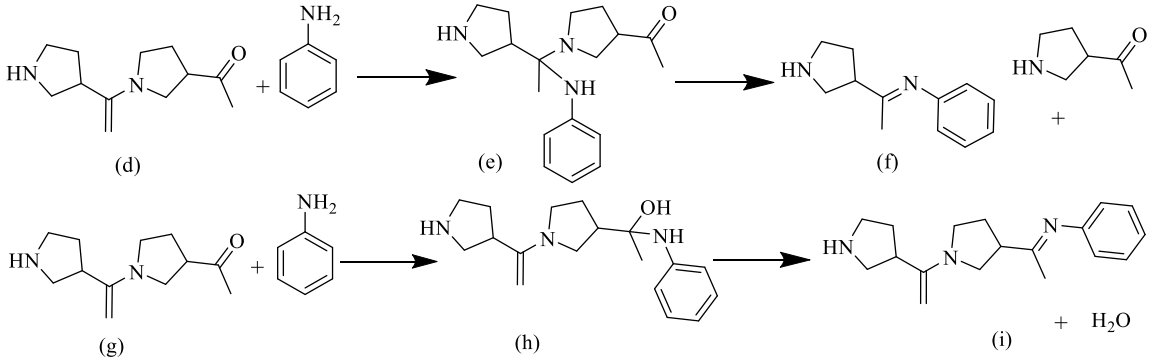


Figure 2: (d) Enamine and aniline (e) Adduct (f) Schiff base (product) and homoreagocatalyst (g) Enamine and aniline (h) Adduct from acetyl group of enamine (i) Schiff base

A careful look into the structure of enamine revealed the presence of another electrophilic site in the form of the acetyl group in it and the second part is further subdivided into two parts. Therefore, the nucleophilic attack of aniline on this site was also taken into the account during the mechanistic study as shown in the figure 2. All the species involved in the second part of the homoreagocatalysis were also optimized using the DFT/631G(d,p) theory but their corresponding transition states were first optimized using hf/sto3g theory followed by either again optimization using DFT/631G(d,p) theory or single point energy was calculated (when optimization using DFT/631G(d,p) failed after multiple efforts) for the optimized transition states.

The third part of homoreagocatalysis involved the formation of a homopolymer bearing enamine moieties after the successive reactions of the catalyzed intermediate molecule with the homoreagocatalyst as shown in the figure 3. Though, it was not made a part of the in silico investigation in this paper owing to its high computational cost.

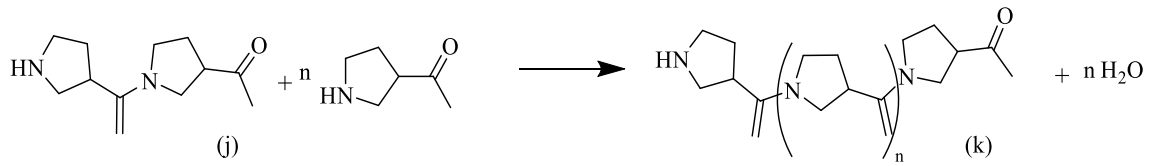


Figure 3: (j) Enamine and n molecules of the homoreagocatalyst undergoing homopolymerization (k) A homopolymer with enamine moieties

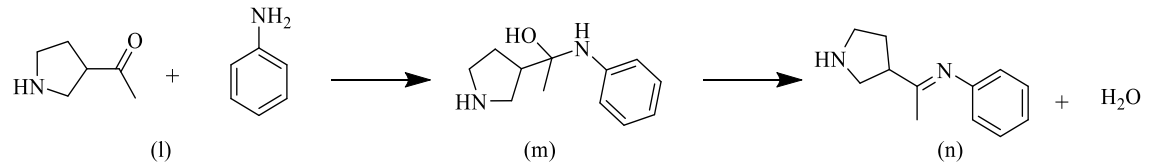


Figure 4: (l) A homoreagocatalyst and aniline (m) Adduct (n) Schiff base and water

The direct reaction between the aniline and the acetyl group of the homoreagocatalyst as shown in the figure 4 was also considered for the in silico mechanistic study.

Heteroreagocatalysis

3-Aminopyrrolidine was used as a heteroreagocatalyst along with the acetophenone (a simple reactant) for the mechanistic study of the heteroreagocatalysis using DFT/631G(d,p) level of theory and ethanol as a solvent. The normal reaction between the amino group (-NH_2 i.e. reacting moiety) of the 3-aminopyrrolidine and acetophenone to give Schiff base directly, as shown in the figure 5, was also included separately as a part of the in silico mechanistic study.

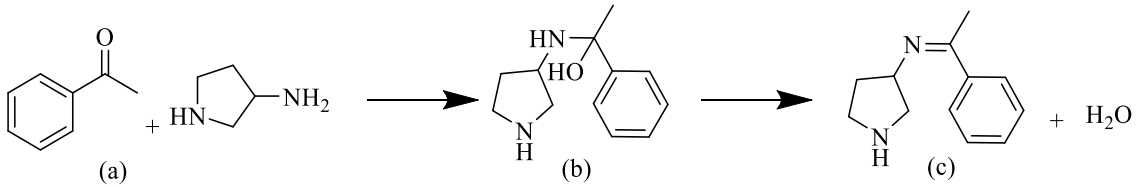


Figure 5: Acetophenone and a heteroreagocatalyst (b) Adduct (c) Schiff base and water

Heteroreagocatalysis is also divided into three parts. In first part, the secondary amine group (catalyzing moiety) present in the pyrrolidine ring of the 3-aminopyrrolidine reacted with the molecule of acetophenone and converted into the catalyzed intermediate molecule i.e. enamine in two steps as shown in the figure 6.

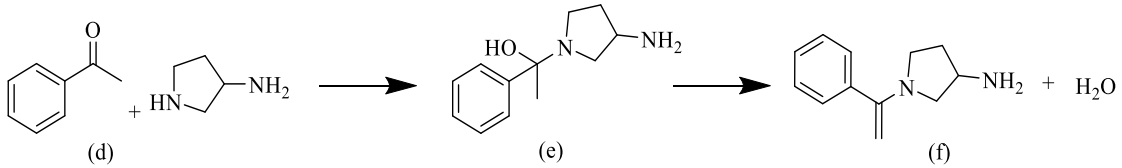


Figure 6: (d) Acetophenone and heteroreagocatalyst (e) Adduct (f) Enamine as a catalyzed intermediate molecule

The species involved in the first step were directly optimized with DFT/631G(d,p) level of theory except for their transition states which were first optimized at low level of theory using sto3g basis set and then either if it was possible optimized again with DFT/631G(d,p) level of theory or their single point energy was calculated using DFT/631G(d,p) level of theory.

The second part involved in the nucleophilic attack of amino group (-NH_2) of the 3-aminopyrrolidine on the catalyzed intermediate molecule i.e. enamine obtained in the first step as shown in the figure 7.

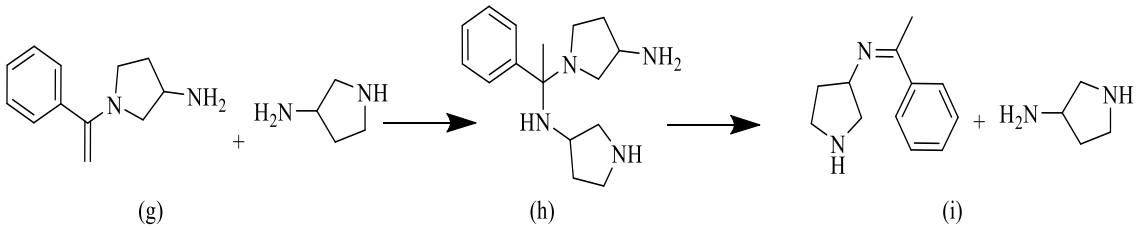


Figure 7: (g) Enamine and heteroreagocatalyst (h) Adduct (i) Schiff base and regenerated heteroreagocatalyst.

A similar method was opted for the optimization of all the species involved in the second part as mentioned earlier in the first step using the DFT/631G(d,p) level of theory.

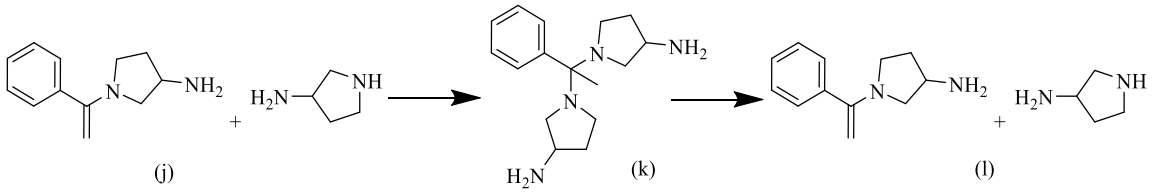


Figure 8: (j) Enamine and heteroreagocatalyst (k) Adduct resulted from reaction of secondary amine of heteroreagocatalyst (l) Enamine and heteroreagocatalyst regenerated

The third part of the heteroreagocatalysis involved the attack of secondary amine (-NH-) group of the pyrrolidine ring with the catalyzed intermediate molecule i.e. enamine which thus regenerated the reactants of this step again as shown in the figure 8. Therefore, it was also not made a part of the in silico investigation here.

Results and Discussion

Homoreagocatalysis as described earlier was divided into two parts.

The part 1 resulted in the formation of catalyzed intermediate molecule i.e. enamine in two steps. The energy of activation (E_a) of the second step i.e. 44.5004175 Kcal/mol is higher than that of the first step 35.0000675 Kcal/mol as shown in the figure 9. The energy change (ΔE) of the two steps of part 1 as given in the Eq.1 showed it to be slightly endothermic indicating that its formation will be favorable at higher temperatures during the experiments owing to its crossing of the two high energy transition state barriers.

$$\Delta E_{Part1} = E_{Enamine} - E_{(3\text{-Acetylpyrrolidine} \times 2)} = 10.0029775 \text{ Kcal/mol} \qquad \text{(Eq. 1)}$$

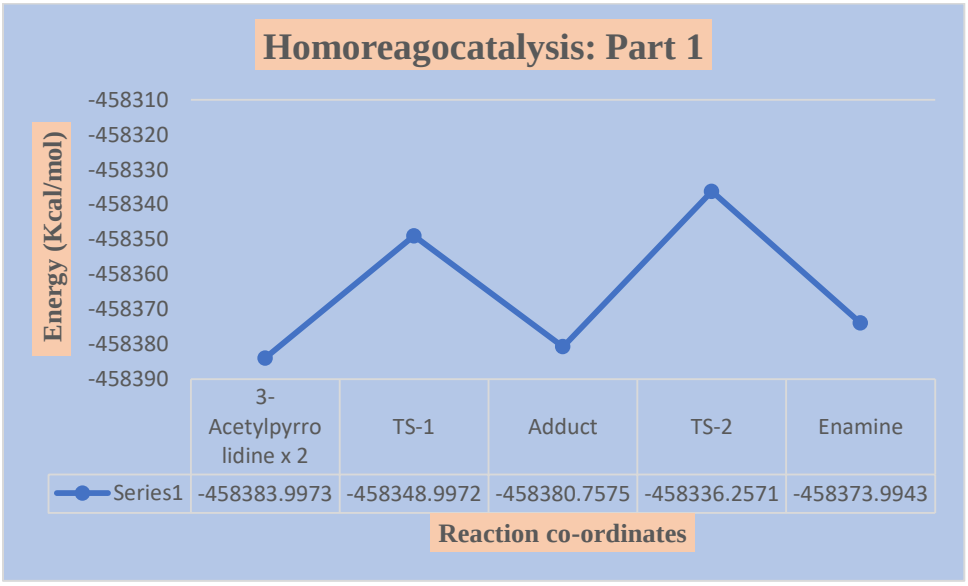


Figure. 9: Homoreagocatalysis leading to the formation of enamine as catalyzed intermediate molecule via two transition states

The second part of the homoreagocatalysis can actually be subdivided into three parts and two of which are discussed here i.e. 2a and 2b. The part 2a involved a reaction between the enamine and the aniline resulting in the formation of the Schiff base in two steps. The energy of activation (E_a) of the second step i.e. 31.00603 Kcal/mol was almost the half lower than that of the first step i.e. 63.4986075 Kcal/mol because of

the crowded nature of the transition state (TS-1) of as shown in the figure 10. The energy change (ΔE) for two steps of the part 2a (see Eq. 2) showed it to be slightly endothermic indicating its formation will also be favorable at higher temperatures during the experiments owing to the energy barriers it had to cross via the transition states (TS-1 and TS-2).

$$\Delta E_{Part2a} = E_{Schiff\ base} - E_{(Enamine+aniline)} = 1.9596825\ Kcal/mol \qquad (Eq.\ 2)$$

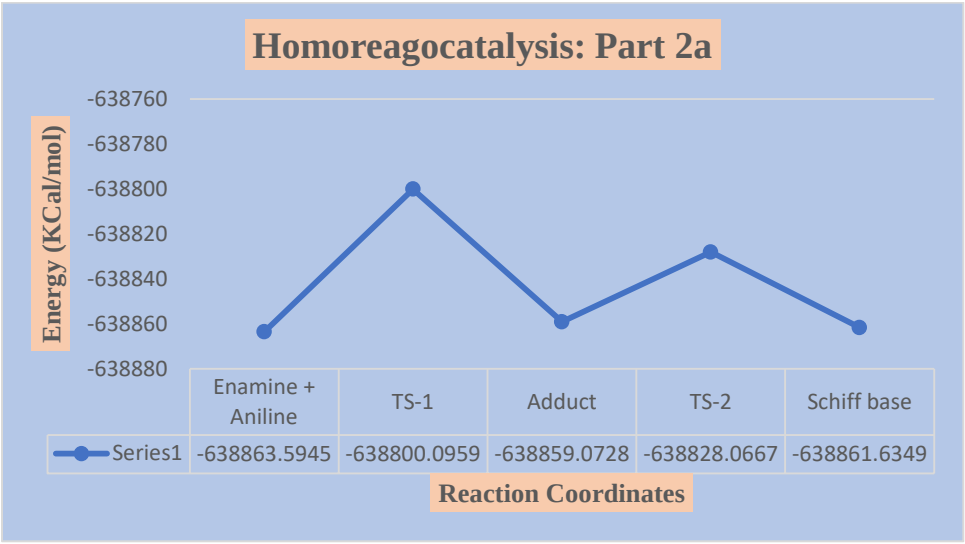


Figure 10: Formation of Schiff base after reaction between aniline and enamine moiety via two transition states

The part 2b involved reaction between the acetyl group of enamine and aniline again resulting in the formation of a Schiff base but a different one. The energy of activation (E_a) of the second step i.e. 49.1213275 Kcal/mol is a bit higher than that of the first step 41.8774675 Kcal/mol as shown in the figure 11.

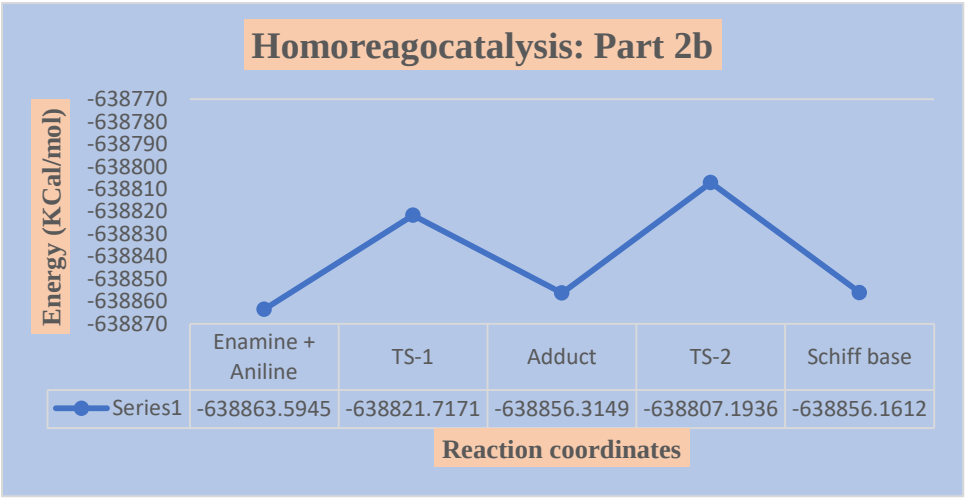


Figure 11: Part 2b involving reaction between acetyl group of enamine and aniline.

The energy change (ΔE) of two steps of the part 2b (see Eq. 3) showed it to be slightly endothermic indicating its formation will be much favorable at higher temperatures during the experiments. This energy change is slightly lower than the 25 °C which is equal to 11.34 Kcal.

$$\Delta E_{Part1} = E_{Schiff\ base} - E_{Enamine+Aniline} = 7.433365\ Kcal/mol \quad \text{(Eq. 3)}$$

The direct reaction without homoreagocatalysis between the 3-acetylpyrrolidine and the aniline resulted in the formation of Schiff base, nevertheless, retaining the secondary amine moiety in the product that may lead to the formation of the enamine after reacting with another molecule of the 3-acetylpyrrolidine. This direct reaction occurred in two steps and was also characterized with the in silico mechanistic approach.

The energy of activation (E_a) of the second step i.e. 57.46978426 Kcal/mol is a bit higher than that of the first step 51.51472385 Kcal/mol as shown in the figure 12. The energy change (ΔE) of two steps of this reaction was 3.308227448 Kcal/mol and it showed to be slightly endothermic indicating that its formation will be much favorable at higher temperatures during the experiments due to the fact that it had also to cross the energy barriers offered by the transition states. This energy change is slightly lower than the 25 °C which is equal to 11.34 Kcal.

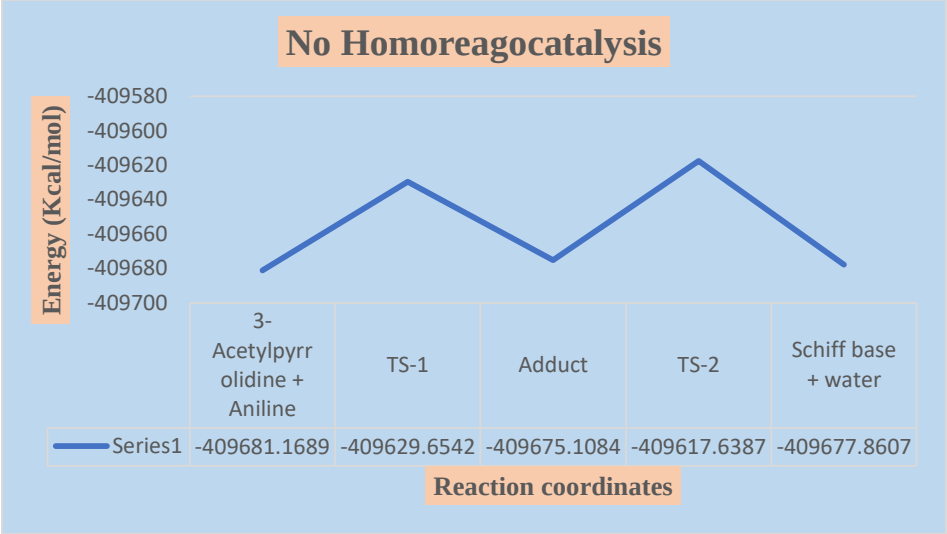
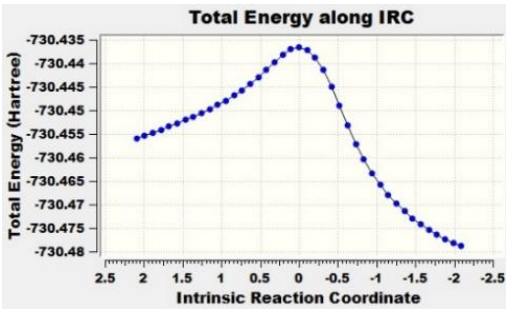


Figure 12: Schiff base formation when aniline reacts with the acetyl group of the homoreagocatalyst

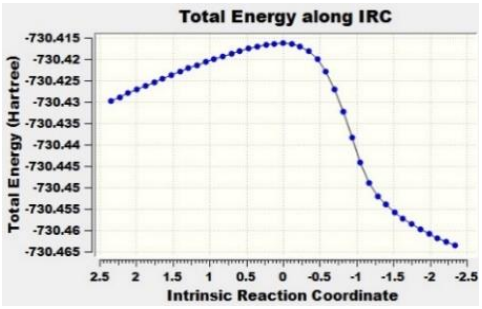
Finally, the intrinsic reaction coordinates (IRC) were calculated for the confirmation of all transition states involved in the homoreagocatalysis and are shown in the figure 13.

The normal reaction occurring with no heteroreagocatalysis between the amino group (-NH_2) of 3-aminopyrrolidine and acetophenone resulted in the formation of the Schiff base. It occurred in two steps via the formation of an adduct. The energy of activation for the first step i.e. 36.5279264 Kcal/mol is lower than that of the second step i.e. 46.35534485 Kcal/mol as depicted in the figure 14. The energy change (ΔE) of two steps of the part 1 (see Eq. 4) showed it to be slightly endothermic indicating that its formation will be greatly favorable at higher temperatures during the experiments. This energy change is, however, lower than the 25 °C which is equal to 11.34 Kcal.

$$\Delta E = E_{Schiff\ base} - E_{Acetophenone+3\text{-}aminopyrrolidine} = 2.732174186\ Kcal/mol \quad \text{(Eq. 4)}$$



(a)



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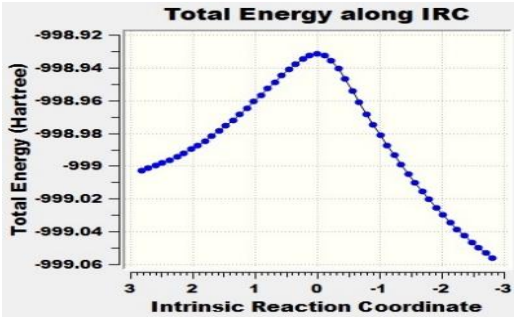

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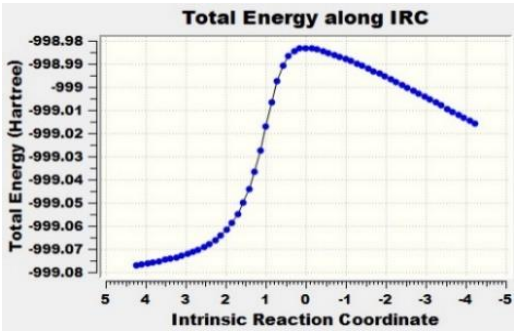

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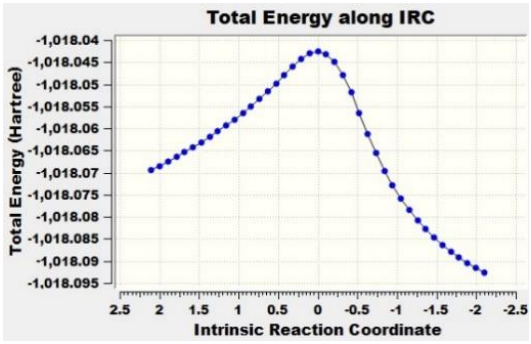

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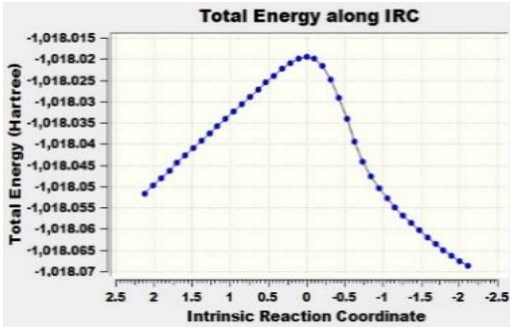


(f)

Figure 13: IRC of the transition states (TS) for Homoreagocatalysis (a) Part 1 TS-1, (b) Part 1 TS-2 (c) Part 2a TS-1, (d) Part 2a TS-2, (e) Part 2b TS-1 and (f) Part 2b TS-2

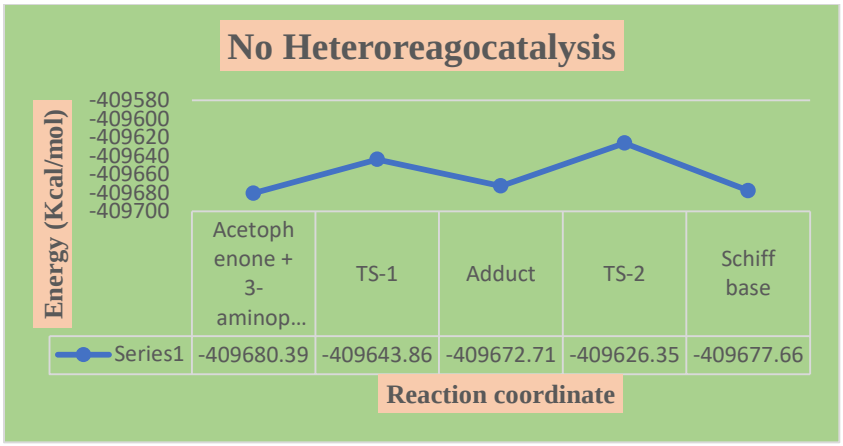


Figure 14: Reaction between acetophenone and amino group of the heteroreagocatalyst via two transition states

Heteroreagocatalysis as described earlier was also divided into the two parts. The part 1 led to the formation of catalyzed intermediate molecule i.e. enamine, after the reaction between the secondary amine group (-NH-) of 3-aminopyrrolidine. The energy of activation (E_a) of the second step i.e. 56.63707981 Kcal/mol is nearly double than that of the first step 34.86314502 Kcal/mol as shown in the figure 15.

The energy change (ΔE) of two steps of part 1 (see Eq. 5) showed it to be slightly endothermic and also very slightly higher than that of the 25 °C which is equal to 11.34 Kcal, indicating its formation will be favorable at higher temperatures during the experiments.

$$\Delta E_{Part1} = E_{Enamine} - E_{(Acetophenone + 3\text{-}aminopyrrolidine)} = 11.5461656 \text{ Kcal/mol} \qquad \text{(Eq. 5)}$$

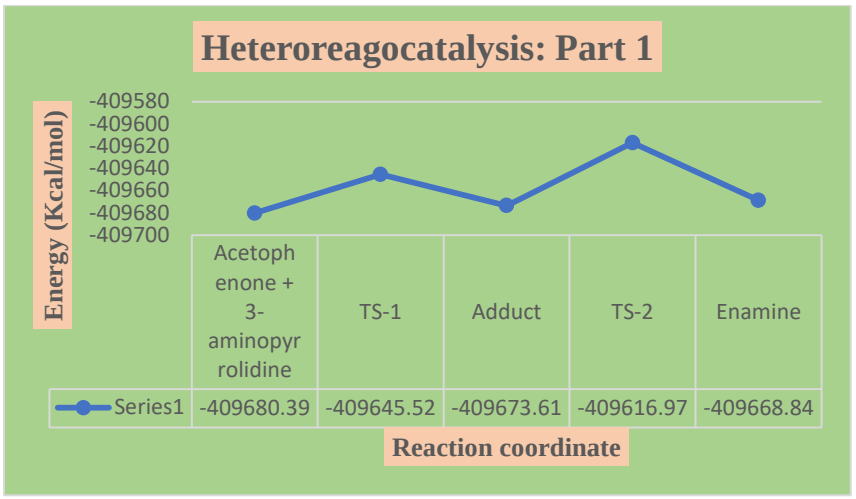


Figure 15: Reaction between secondary amine of the heteroreagocatalyst and acetophenone

The part 2 involved a reaction between the enamine and the amino group ($-NH_2$) of 3-aminopyrrolidine resulting in the formation of Schiff base in two steps as depicted in the figure 16. The energy of activation (E_a) of the second step i.e. 64.30084723 Kcal/mol was found to be lower than that of the first step i.e. 82.45280007 Kcal/mol because of the crowded nature of the transition state (TS-1).

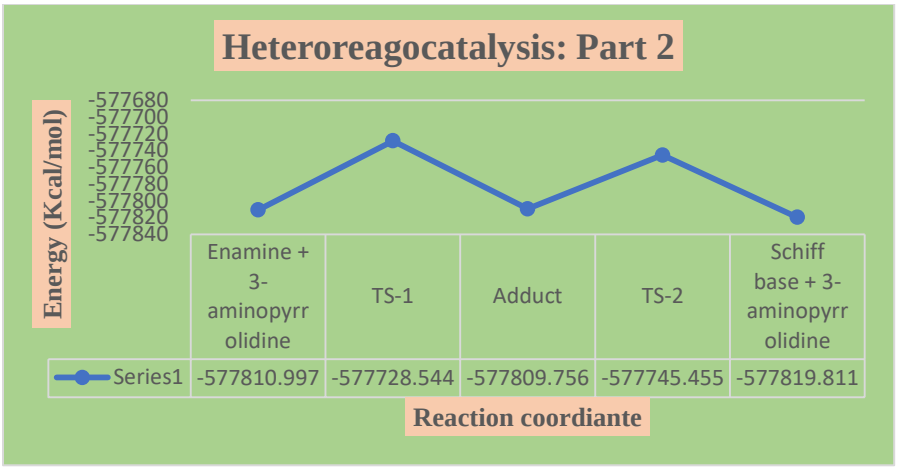
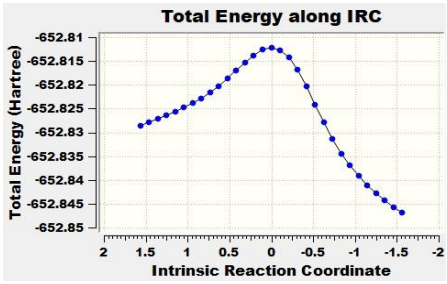


Figure 16: Reaction between enamine and amino group of the heteroreagocatalyst

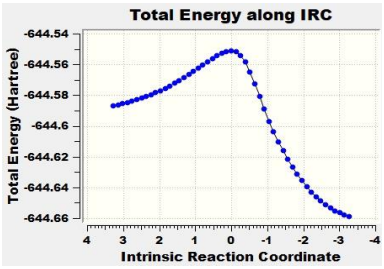
The energy change (ΔE) for two steps of the part 2 (see Eq. 6) showed it to be also slightly exothermic but the energy barriers offered by the transition states led to the indication that its formation will also be favorable at higher temperatures during the experiments.

$$\Delta E_{Part2} = E_{(Schiff\ base+3\text{-}aminopyrrolidine)} - E_{(Enamine+3\text{-}aminopyrrolidine)} = -8.81399141\ Kcal/mol \quad (Eq.\ 6)$$

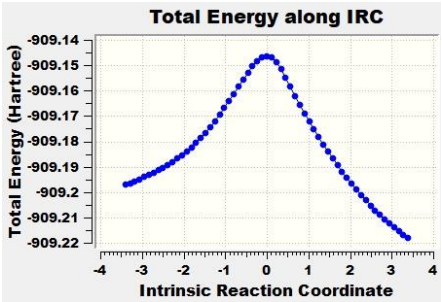
Finally, the intrinsic reaction coordinate (IRC) calculations for the heteroreagocatalysis were performed to verify the authenticity of involved transition states as shown in figure 17.



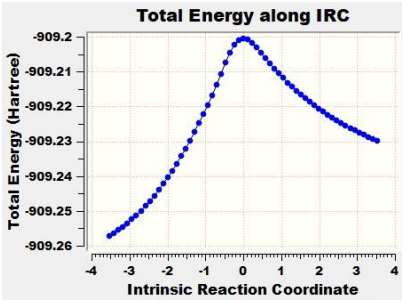
(a)



(b)



(c)



(d)

Figure 17: IRC calculations for the transition states of the heteroreagocatalysis (a) Part 1 TS-1 (b) Part 1 TS-2 (c) Part 2 TS-1 (d) Part 3 TS-2

Conclusion

As far as the homoreagocatalysis is concerned, the formation of Schiff base as a main product from the crowded catalyzed intermediate molecule i.e. enamine via opting a long route will also lead to the formation of the side products like a homopolymer and a Schiff base still containing the enamine moiety. Although, the latter side product may be converted into the two molecules of the Schiff base as main product if the crowded enamine moiety is still accessible by the aniline. The long route as well as the formation of the side products will definitely decrease the efficiency of the reaction in terms of the main product i.e. Schiff base formation.

However, the heteroreagocatalysis will end up in the same product i.e. the Schiff base formation just like the normal reaction that proceeded without enamine formation. The only problem heteroreagocatalysis created that it was a long way to reach the same product.

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