

## Research Article

# Full Kinetics and a Mechanistic Investigation of the Green Protocol for Synthesis of $\beta$ -Aminoketone in the Presence of Saccharose as a Catalyst by a One-Pot Three-Component Reaction

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For the first time, in a green protocol, an investigation of the kinetics and mechanism of the reaction between benzaldehyde **1**, 4-chloroaniline **2**, and acetophenone **3** compounds in the presence of saccharose as a catalyst was performed for generating  $\beta$ -aminoketone. For determining the kinetic parameters, the reaction was monitored by using the UV/Vis spectrophotometry technique. The second order rate constant ( $k_1$ ) was automatically calculated by the standard equations contained within the program. In the studied temperature range, the second order rate constant ( $\ln k_1$ ,  $\ln k_1/T$ ) depended on reciprocal temperature that was in good consistent with Arrhenius and Eyring equations, respectively. These data provided the suitable plots for calculating the activation energy and parameters ( $E_a$ ,  $\Delta G^\ddagger$ ,  $\Delta S^\ddagger$ , and  $\Delta H^\ddagger$ ) of the reaction. Furthermore, useful information was obtained from studying the effects of solvent, concentration, and catalyst on the reaction mechanism. The results showed that the first step of the reaction mechanism is a rate determining step (RDS). The obtained experimental data and also the steady state assumption confirmed the proposed mechanism.

## 1. Introduction

Mannich reaction is as one of the most important carbon-carbon bond forming reactions in organic synthesis [1]. The products of Mannich reaction are mainly  $\beta$ -Amino carbonyl compounds and their derivatives are mainly products of Mannich reactions and significant synthetic intermediates for various pharmaceuticals and natural products [2–6].

Over the past decades, the research on the new operationally simple, efficient, recyclable, and environmentally benign catalysts for the Mannich reaction has gained popularity in synthetic chemistry. Nowadays, it has been noted that this reaction can also be promoted by a wide array of catalysts, such as rare earth perfluorooctanoate (RE(PFO)<sub>3</sub>) [7], Brønsted acidic ionic liquid [8], HClO<sub>4</sub>-SiO<sub>2</sub> [9], SalenZn complex [10], cerium (IV) ammonium nitrate (CAN) [11],

Triton X10 (TX10) aqueous micelles [12], CeCl<sub>3</sub>·7H<sub>2</sub>O [13], Tröger's base derivatives [14], Cbz protected [15], and PEG-OSO<sub>3</sub>H [16–30]. However, they often suffer from the drawbacks of long reaction times, harsh reaction conditions, toxicity, and difficulty in product separation, which limit their use in the synthesis of complex molecules. Hence, development of a synthetic protocol that is nature friendly, simple, efficient, and cost effective remains an ever challenging objective. One of these methods uses organocatalysis for C–C bond formation [31] and synthesis of important compounds such as highly functionalized piperidines [32]. Beyond doubt, organocatalysis belongs to the most exciting and innovative chapters of organic chemistry today [31]. Herein our research group presents entirely green protocol, an eco-friendly, simple, and efficient protocol for synthesis of  $\beta$ -amino carbonyl compounds via a one-pot three-component reaction

among aromatic aldehydes, anilines, and acetophenone in the presence of saccharose as catalyst in water/ethanol at room temperature (Figure 1). It was noteworthy that the results of this work have been published recently [33]. Kinetics studies of these reactions are therefore important, but they have not yet been investigated. To fully understand or apply any chemical reaction, we must know more than just the identities of the reactants and the products. We must know, if the reaction will occur (is it thermodynamically favorable?), how long it will take to occur (is it kinetically feasible?). For a complete understanding, we should also know how it occurs. Hence, we now describe full kinetics and mechanistic of mentioned reaction in later section. The activation energy and the other related thermodynamic parameters for the reaction are experimentally determined through the Arrhenius and Eyring equations. Numerous kinetic investigations over a large area of different reactions have previously been reported using the UV/Vis technique [34–47].

## 2. Method

**2.1. Kinetics.** For further insight into the reaction mechanism between benzaldehyde **1**, 4-chloroaniline **2**, and acetophenone compound **3** in the presence of saccharose as a catalyst, a kinetics study of the reaction was performed using the UV/Vis spectrophotometry technique. Firstly, it was necessary to find the suitable wavelength for the kinetic study of the reaction. For this reason in the first experiment,  $10^{-2}$  M solution of each compound **1**, **2**, and **3** and  $1.5 \times 10^{-2}$  M solution of saccharose were prepared in a mixture of water and ethanol (50 : 50) as solvent. The relevant spectrum of each compound was recorded over the wavelength range 200–500 nm. Figures 2, 3, 4, and 5 exhibit the ultraviolet spectra of compounds **1**, **2**, and **3** and saccharose, respectively. In the second experiment, the reaction mixture was started into a 10 mm quartz spectrophotometer cell along with a  $10^{-2}$  M solution of each compound (**1**, **2**, and **3**) and  $1.5 \times 10^{-2}$  M saccharose according to stoichiometry of each compound in the overall reaction. The reaction was monitored by conducting scans of the entire spectrum with 10-second intervals during the whole reaction time at ambient temperature. The ultraviolet spectra shown in Figure 6 are typical. Herein, the upward of direction of the arrow indicates the progress of product versus time. From this, the appropriate wavelength was discovered to be 365, 375, and 380 nm. Since, at these wavelengths, compounds **1**, **2**, and **3** and saccharose have relatively no absorbance value, it gave us the chance to find the practical conditions that allows kinetics and a mechanistic investigation of the reaction. Herein, in all the experiments, the UV/Vis spectrum of the compound product was measured over the concentration range ( $10^{-3}$  M  $\leq$  M product  $\leq$   $10^{-2}$  M) to confirm a linear relationship between the absorbance and concentrations values.

In the third experiment under same concentration of each compound ( $10^{-2}$  M), experimental absorbance curve was recorded versus time at 25°C temperature and the biggest absorption wavelength 375 nm. This is shown in Figure 7

(dotted line) which exactly fits to second order fitting curve (solid line). In this case, overall order of rate low

$$(\text{rate} = k_{\text{ovr}} [\mathbf{1}]^{\alpha} [\mathbf{2}]^{\beta} [\mathbf{3}]^{\gamma} [\text{Cat}]) \quad (\text{I})$$

can be written as  $\alpha + \beta + \gamma = 2$ . It is obvious that the reaction is second order. Then, the rate constant ( $74.62 \text{ min}^{-1} \cdot \text{M}^{-1}$ ) of the reaction was automatically calculated by the software [48] associated within the UV/Vis equipment.

## 3. Results and Discussion

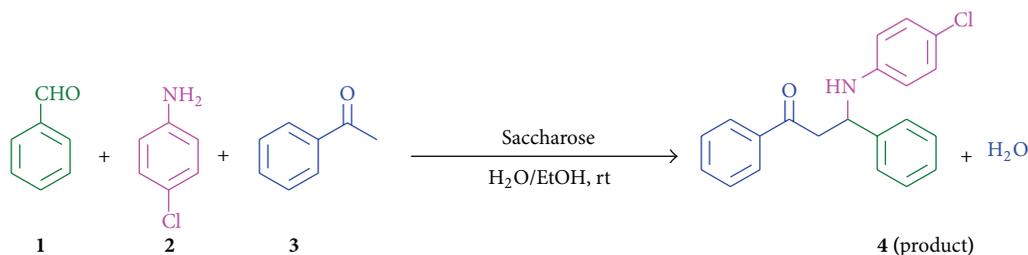
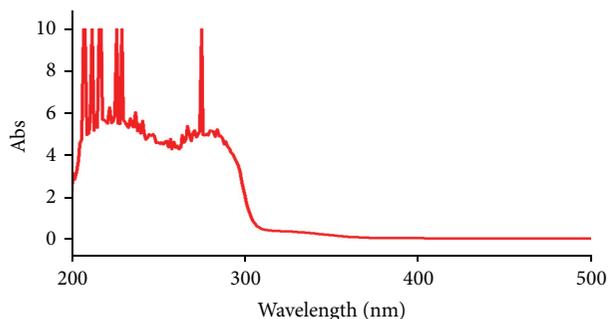
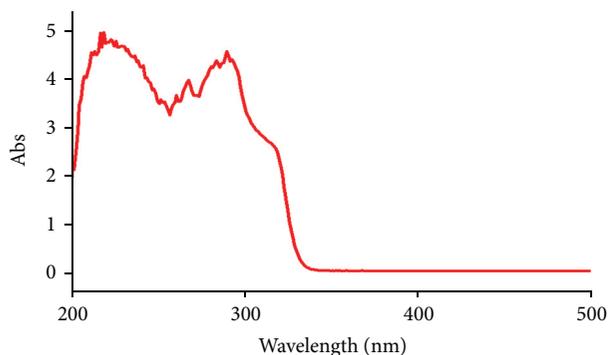
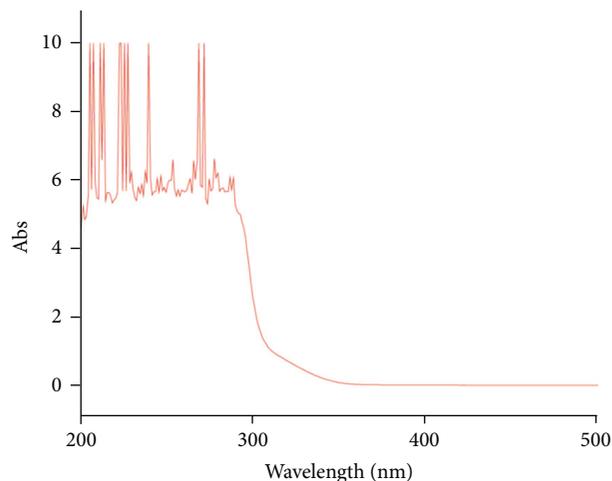
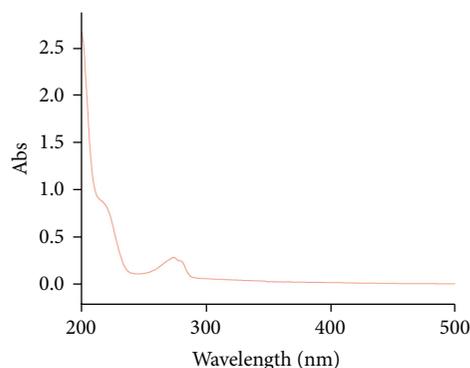
**3.1. Effect of Solvent and Temperature.** In order to determine the effect of change in temperature and solvent environment change on the reaction rate, various experiments were arranged with different temperatures and solvent polarity under the same conditions with the previous experiment. For this purpose, a mixture of methanol and water (methanol/water, 4:1) and a mixture of ethanol and water (ethanol/water, 1:1) have been used in the experiment. The results showed that rate of reaction speeds up in solvent with high dielectric constant (ethanol and water) with respect to lower dielectric constant (methanol/water, 4:1) at all temperatures investigated (see Table 1).

As can be seen in Table 1, increasing the temperature increases reaction rate in all solvents. In the studied temperature range, the second order equation rate constant ( $\ln k_1$ ) of the reaction was inversely proportional to the temperature, which is in agreement with the Arrhenius equation. This behavior is shown in Figure 8. The activation energy for the reaction between **1**, **2**, and **3** was obtained ( $35.85 \text{ kJ} \cdot \text{mol}^{-1}$ ) from the slope of Figure 8.

**3.2. Effect of Concentration.** In order to obtain a partial order of reaction regarding benzaldehyde, pseudoorder conditions were performed for the reaction. So in the fourth experiment, we followed the reaction kinetics by plotting the UV/Vis absorbance versus time at wavelength 375 nm for the  $10^{-3}$  M,  $10^{-2}$  M, and  $10^{-2}$  M solution of each compound (**1**, **2**, and **3**), respectively, at 25.0°C along with  $10^{-2}$  M solution of saccharose. For this case, the rate law can be expressed as

$$\begin{aligned} \text{rate} &= k_{\text{ovr}} [\mathbf{1}]^{\alpha} [\mathbf{2}]^{\beta} [\mathbf{3}]^{\gamma} [\text{Cat}], \\ \text{rate} &= k_{\text{obs}} [\mathbf{1}]^{\alpha}, \quad (\text{II}) \\ k_{\text{obs}} &= k_{\text{ovr}} [\mathbf{2}]^{\beta} [\mathbf{3}]^{\gamma} [\text{Cat}]. \end{aligned}$$

The infinity absorbance ( $A_{\infty}$ ), which is the absorbance at reaction completion, is obtainable from Figure 9 at  $t = 30$  min. With respect to this value, the zero, first, or second curve fittings can be drawn automatically for the reaction using the software [48] associated with the UV/Vis instrument. The original experimental absorbance against time data made a first pseudoorder available fit curve (solid line) at wavelength 375 nm, which exactly fits the experimental curve (dotted line) displayed in Figure 9 as a typical. Herein, observation rate constant ( $k_{\text{obs}}$ ) was automatically calculated by (II) which has been defined in the software program. It is

FIGURE 1: Synthesis of  $\beta$ -aminoketone 4.FIGURE 2: The UV/Vis spectrum of  $10^{-2}$  M, benzaldehyde compound 1 in a mixture of water and ethanol (50 : 50).FIGURE 3: The UV/Vis spectrum of  $10^{-2}$  M, 4-chloroaniline compound 2 in a mixture of water and ethanol (50 : 50).FIGURE 4: The UV/Vis spectrum of  $10^{-2}$  M, acetophenone compound 3 in a mixture of water and ethanol (50 : 50).FIGURE 5: The UV/Vis spectrum of  $10^{-2}$  M, saccharose as a catalyst in a mixture of water and ethanol (50 : 50).

obvious that the reaction is of the first order type with respect to benzaldehyde 1;  $\alpha = 1$ .

Also to gain a partial order of reaction with respect to 4-chloroaniline 2, ( $10^{-3}$  M), under pseudoorder condition, compounds 3 and 1 were used in excess ( $10^{-2}$  M). Same procedure was employed as a previous experiment. The rate law can be written as

$$\text{rate} = k_{\text{ovr}} [\text{1}]^{\alpha} [\text{2}]^{\beta} [\text{3}]^{\gamma} [\text{Cat}] \quad \text{or} \quad \text{rate} = k_{\text{obs}} [\text{2}]^{\beta}, \quad (\text{III})$$

$$k_{\text{obs}} = k_{\text{ovr}} [\text{3}]^{\gamma} [\text{1}]^{\alpha} [\text{Cat}].$$

The original experimental absorbance (solid line) against time data (Figure 10) creates a first order fit curve (full line) at 370 nm, which fits the experimental curve precisely. Therefore, the reaction is of the first order type in relation to the 4-chloroaniline 2;  $\beta = 1$ .

In the fifth experiment, the reaction was followed in the presence of an excess of compounds 1 and 2 ( $10^{-2}$  M of each) along with  $10^{-3}$  M of compound 3, so the rate law can be expressed as

$$\text{rate} = k_{\text{ovr}} [\text{1}]^{\alpha} [\text{2}]^{\beta} [\text{3}]^{\gamma} [\text{Cat}],$$

$$\text{rate} = k_{\text{obs}} [\text{3}]^{\gamma}, \quad (\text{IV})$$

$$k_{\text{obs}} = k_{\text{ovr}} [\text{1}]^{\alpha} [\text{2}]^{\beta} [\text{Cat}].$$

TABLE 1: Rate constants for the reaction between **1** ( $10^{-2}$  M), **2** ( $10^{-2}$  M), and **3** ( $10^{-2}$  M) in the presence of saccharose as a catalyst and both solvents containing a mixture of methanol and water (methanol/water, 4 : 1) and a mixture of ethanol and water (1 : 1).

Solvent	$\epsilon$	$k_1 \times 10^2 (\text{min}^{-1} \cdot \text{M}^{-1})$			
		$T = 20^\circ\text{C}$	$T = 25^\circ\text{C}$	$T = 30^\circ\text{C}$	$T = 35^\circ\text{C}$
Methanol : water, 4 : 1	42.08	9.084	16.64	24.18	31.71
Ethanol : water, 1 : 1	52.12	36.85	49.74	62.64	75.53

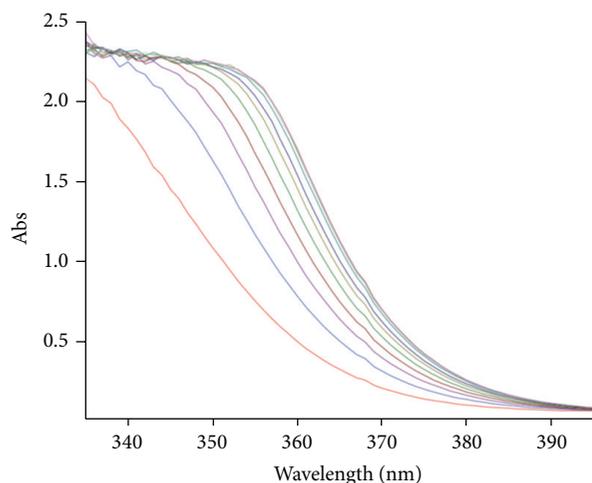


FIGURE 6: The UV/Vis spectra of the reaction between benzaldehyde **1** ( $10^{-2}$  M), 4-chloroaniline **2** ( $10^{-2}$  M), and acetophenone **3** ( $10^{-2}$  M) in the presence of saccharose as a catalyst in a mixture of water and ethanol (50 : 50), and reaction proceeds into a 10 mm light-path cell. The upward of direction of the arrow indicates the progress of product versus time.

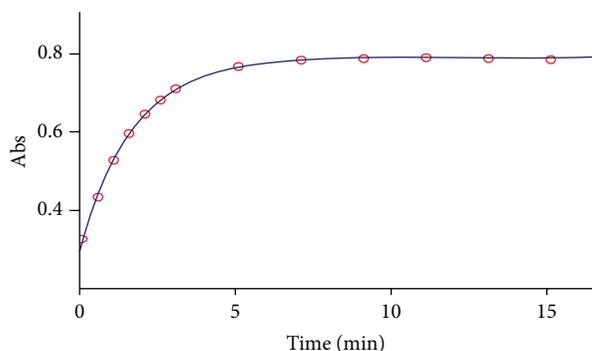


FIGURE 7: The experimental absorbance change (dotted line) along with the fit curve (solid line) against time for the reaction between benzaldehyde **1** ( $10^{-2}$  M), 4-chloroaniline **2** ( $10^{-2}$  M), and acetophenone **3** ( $10^{-2}$  M) in a mixture of water and ethanol (50 : 50) at 375 nm and  $25.0^\circ\text{C}$ .

The experimental absorbance curve (dotted line) versus times was recorded at  $25^\circ\text{C}$  and wavelength 375 nm (Figure 11). Then, the rate constant ( $k = 74.24 \text{ min}^{-1} \cdot \text{M}^{-1}$ ) of the reaction was automatically obtained by the software program. The value of the rate constant was similar to that of the pervious experiment (Figure 7, for this case, concentration of each compound is same corresponding to  $10^{-2}$  M). This curve led

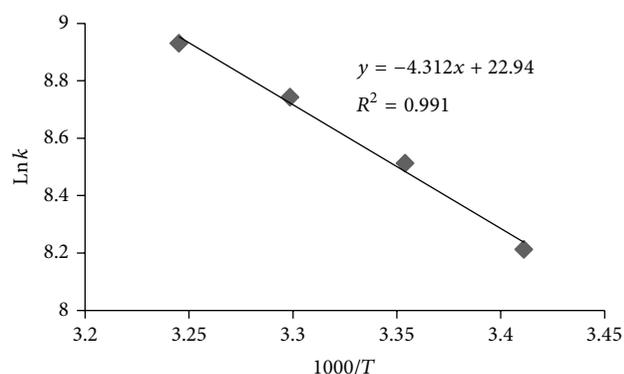


FIGURE 8: The dependence of the second order rate constant ( $\ln k_1$ ) on reciprocal temperature for the reaction between compounds **1**, **2**, and **3** measured at a wavelength of 375 nm in a mixture of water and ethanol (50 : 50), according to the Arrhenius equation.

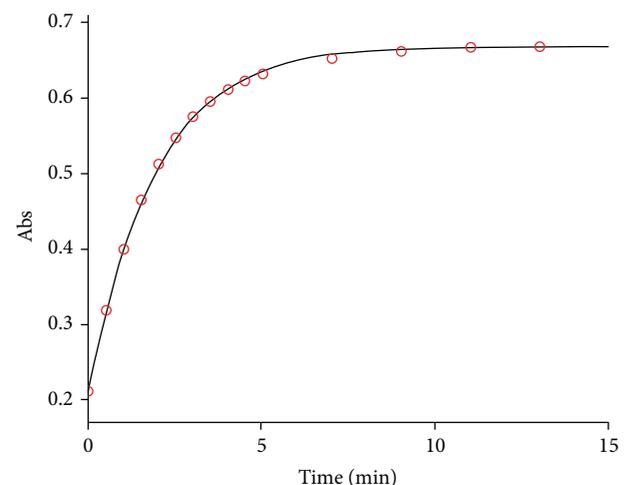


FIGURE 9: First pseudo order fit curve (solid line) along with the original experimental curve (dotted line) in relation to benzaldehyde **1** ( $10^{-3}$  M), for the reaction between **1** ( $10^{-3}$  M), **2** ( $10^{-2}$  M) and **3** ( $10^{-2}$  M) which was processed in a mixture of water and ethanol (50 : 50) at 375 nm.

to similar fit curve and rate constant. In fact, the experimental data indicated that the second order rate constant ( $k = 74.6 \text{ min}^{-1} \cdot \text{M}^{-1}$ , Figure 7) of this reaction under mentioned condition in (I) (page 7,  $10^{-2}$  M concentration of each compound) is equal to the second order rate constant ( $k_{\text{over}} = 74.2 \text{ min}^{-1} \cdot \text{M}^{-1}$ , Figure 11), (equation (IV),  $10^{-2}$  M of each compound (**1** and **2**) and  $10^{-3}$  M of compound **3**) under fifth experiment. This is possible when  $\gamma$  is zero in both (I) and

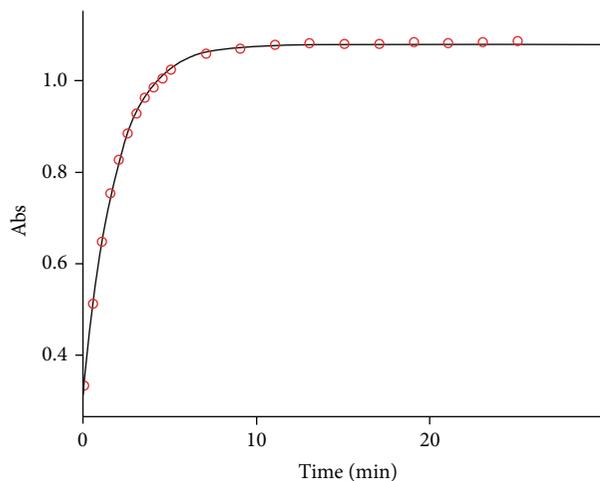


FIGURE 10: First pseudoorder fit curve (solid line) accompanied by the original experimental curve (dotted line) with respect to 4-chloroaniline **2** ( $10^{-3}$  M), for the reaction between **1** ( $10^{-2}$  M), **3** ( $10^{-2}$  M), and **2** ( $10^{-3}$  M), which proceeded in a mixture of water and ethanol (50 : 50).

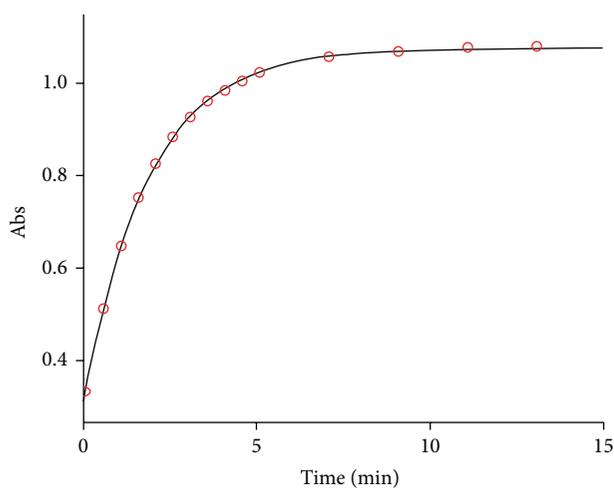


FIGURE 11: Second pseudoorder fit curve (solid line) along with the original experimental curve (dotted) for the reaction between benzaldehyde **1** ( $10^{-2}$  M), 4-chloroaniline **2** ( $10^{-2}$  M), and acetophenone **3** ( $10^{-3}$  M), at 375 nm, 25.0°C in a mixture of water and ethanol (50 : 50).

(IV). It means that the reaction is zero and of the second order type in relation to compound **1** and sum of **2** and **3** ( $\alpha + \beta = 2$ ), respectively. As a result, the overall order of reaction is two that is same with the previous experiment (third experiment, page 7).

Utilizing the above mentioned results, the simplified scheme of the proposed reaction mechanism (Figure 12, [33]) is shown in Figure 13.

To investigate which step of the proposed mechanism is the rate-determining step, the rate law was written using the final step of reaction (Figure 13)

$$\text{rate} = k_5 [I_2] [I_4] [\text{Cat}]. \quad (\text{V})$$

The steady state approximation can be applied for obtaining the concentration of  $[I_2]$  which is generated from the following equations:

$$\frac{d[I_2]}{dt} = k_2 [I_1] [\text{Cat}] - k_5 [I_2] [I_4] [\text{Cat}] = 0, \quad (\text{VI})$$

$$k_2 [I_1] [\text{Cat}] = k_5 [I_2] [I_4] [\text{Cat}].$$

The value of (VI) can be replaced in (V) so the rate equation becomes

$$\text{rate} = k_2 [I_1] [\text{Cat}]. \quad (\text{VII})$$

For obtaining the concentration of intermediate  $[I_1]$ , the following equation is yielded by applying the steady state assumption:

$$\frac{d[I_1]}{dt} = k_1 [1] [2] [\text{Cat}] - k_2 [I_1] [\text{Cat}] = 0, \quad (\text{VIII})$$

$$[I_1] = \frac{k_1 [1] [2]}{k_2}.$$

And with the replacement of (IX) in (VIII), the following equation is obtained:

$$\text{rate} = k_1 [1] [2] [\text{Cat}]. \quad (\text{IX})$$

The final equation (IX) indicates that the overall order of the reaction is two, additionally, in accordance with this equation; the order of reaction with respect to each compound (**1**, **2**, and **3**) is 1, 1, and zero, respectively, which was previously confirmed by the experimental data. Due to the presence of  $k_1$  in the rate law (IX), it is obvious that first step ( $k_1$ ) is a rate determining step. In this case, the transition state (see step 1, Figure 11) in reaction carries a dispersed charge, effect of solvent (mixture of water and ethanol, 50%: 50%), which has higher dielectric constant ( $\epsilon = 52.12$ ) rather than a mixture of water and methanol (20: 80) (with lower dielectric constant  $\epsilon = 42.08$ ) on this dispersed charge which would be much stronger compared to that on reactants (**2** and **1**) that do not have any charge. The solvent thus stabilizes the species at the transition state more than it does the reactants, and therefore  $E_a$  would be lower and speeding up the reaction rate (see Table 1, effect of both solvents). With respect to (IX)  $k_1$  is proportional to the overall reaction rate; therefore, the activation parameters which involve  $\Delta G^\ddagger$ ,  $\Delta S^\ddagger$ , and  $\Delta H^\ddagger$  can be now calculated for the first step (rate determining step,  $k_1$ ), as an elementary reaction, on the basis of Eyring equation. The results are accumulated in Tables 2 and 3.

**3.3. Effect of Catalyst.** Under similar conditions with previous experiments, the reactions between **1**, **2**, and **3** were proceeded in the presence of saccharose or maltose as a catalyst. The results show that the reaction rate speeds up in the maltose medium (see Table 4). It seems that maltose with six-membered ring can increase the reaction rate more than the saccharose with five-membered ring; perhaps the considerable and large size of maltose ring creates more room for easier interactions between the hydroxyl groups with both reactants **1** and **2** (see step 1, Figure 12).

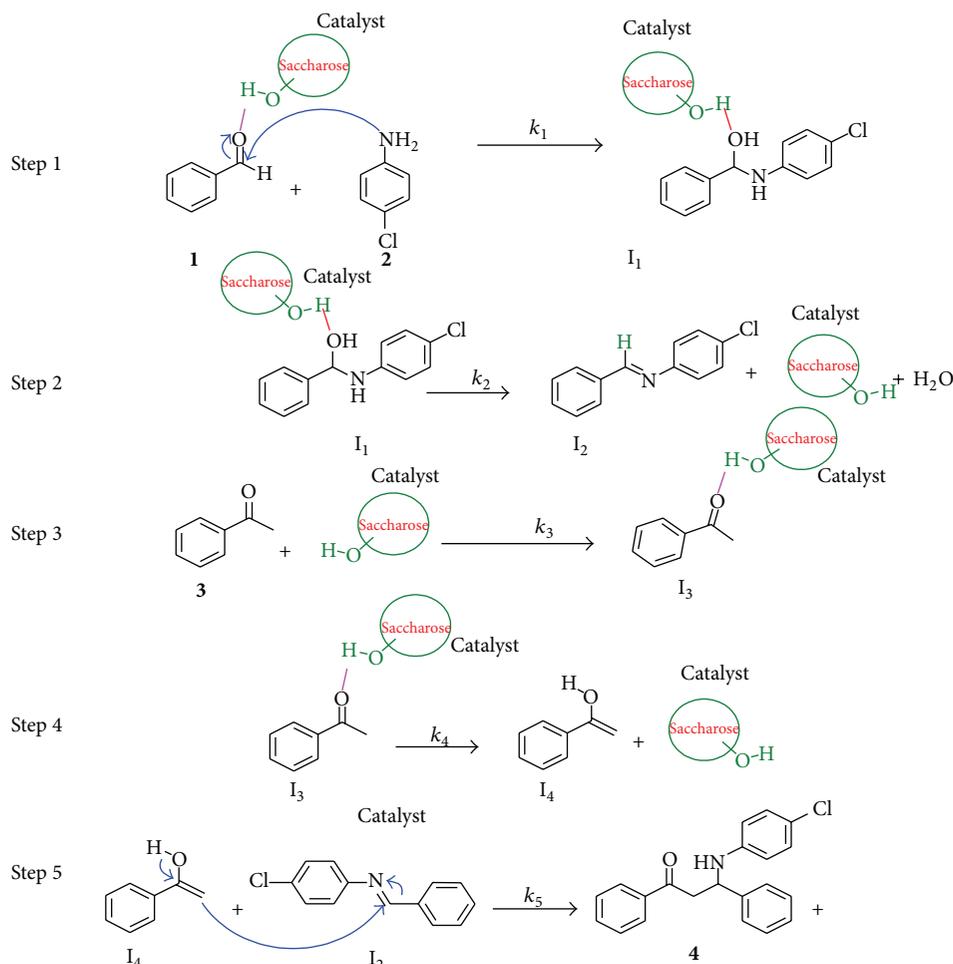


FIGURE 12: The proposed mechanism of the reaction between **1**, **2**, and **3** for generation of 3-(4-chlorophenylamino)-1,3-diphenylpropan-1-one (**4**) [33].

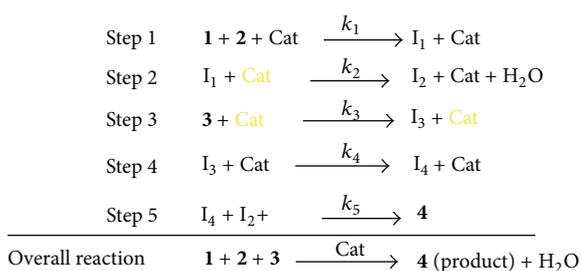


FIGURE 13: Simplified Figure 12 for the proposed reaction mechanism [33].

## 4. Conclusions

In this work, we report an efficient kinetics study for the various conditions. This method has several advantages including mild reaction conditions, operational simplicity, high yields, clean and neutral reaction conditions, and no environmental pollution, and also is an attractive process for the synthesis of  $\beta$ -aminoketone. Kinetic investigation of the recent reaction

TABLE 2: The dependence of the second order rate constant of the reactions (**1**, **2**, and **3**) on temperature.

$k$	$T$	$\ln k$	$k/T$	$\ln k/T$	$1/T$	$1000/T$
3685	293.15	8.21	12.57	2.53	0.003411	3.411
4974	298.15	8.51	16.68	2.81	0.003354	3.354
6264	303.15	8.74	20.66	3.03	0.003299	3.298
7553	308.15	8.93	24.51	3.20	0.003245	3.245

TABLE 3: The activation parameters involving  $\Delta G^\ddagger$ ,  $\Delta S^\ddagger$ , and  $\Delta H^\ddagger$  for the reactions between **1**, **2**, and **3** in a mixture of ethanol and water (1:1) at 375 nm and 298.15 K.

Reaction	$\Delta G^\ddagger$ (kJ·mol <sup>-1</sup> )	$\Delta H^\ddagger$ (kJ·mol <sup>-1</sup> )	$\Delta S^\ddagger$ (kJ·mol <sup>-1</sup> ·K <sup>-1</sup> )
<b>1</b> , <b>2</b> and <b>3</b>	16.44	597.84	1.95

\*Transition state.

was undertaken using UV spectrophotometry. The obtained results can be stated as follows.

- (1) The overall order of the reaction followed second order kinetics and the reaction orders each of

TABLE 4: Effect of catalyst under the same conditions for reaction between **1**, **2**, and **3** in a mixture of ethanol and water (1:1) at 375 nm and 298.15 K.

Reaction	Catalyst	$k_1 \times 10^{-2}$ ( $\text{min}^{-1} \cdot \text{M}^{-1}$ )
<b>1</b> , <b>2</b> and <b>3</b>	Maltose	56.30
<b>1</b> , <b>2</b> and <b>3</b>	Saccharose	49.74

the reactants involving benzaldehyde **1**, 4-chloroaniline **2**, and acetophenone **3** as one, one, and zero, respectively.

- (2) The reaction rate was increased in the presence of solvent with higher dielectric constants reaction rate.
- (3) Based on the experimental data, the first step of suggested mechanism was identified as a rate-determining step ( $k_1$ ) and this was confirmed by the steady state assumption.
- (4) The activation parameters  $\Delta G^\ddagger$ ,  $\Delta S^\ddagger$ , and  $\Delta H^\ddagger$  have been calculated for the reaction.
- (5) The reaction rate was sped up in the presence of a green catalyst with a considerable and large size of flexible ring.

## Conflict of Interests

The authors declare that there is no conflict of interests regarding the publication of this paper.

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