



**AN EXPERIMENTAL KINETICS AND A MECHANISTIC STUDY OF  
TETRAHYDROBENZO[B]PYRAN FORMATION IN THE PRESENCE OF AGAR  
AND WATER/ETHANOL AS GREEN CATALYST AND SOLVENT**

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**Abstract**

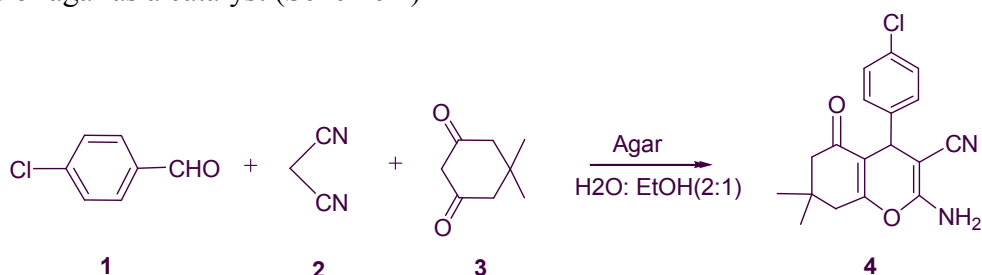
Ultraviolet–visible spectroscopy was used to monitor the kinetics of formation of tetrahydrobenzo[b]pyrans via condensation reaction of 4-chlorobenzaldehyde, malononitrile, and dimedone in the presence of agar as a green catalyst and in a mixture of water:ethanol (2:1) as a green solvent. The experiments were carried out at various concentrations, catalysts and solvents. Furthermore, a range of temperatures in order to estimate the rate constants of reaction were examined. The rate constants were found to decrease as the dielectric constant of solvent decreased, and also increased as a function of temperature and showed normal Arrhenius and Eyring behavior. According to observation data, the reaction followed second order kinetics and first step of the reaction was a rate determining step.

**Keywords:** Kinetics, Mechanism, Catalyst, Agar, Tetrahydrobenzo[b]pyran

**1. Introduction**

MCRs due to decrease waste and cost, as well as reduce consumption of energy, time, labor or manpower render green processes that are the major goal of new organic synthesis<sup>i</sup>. Along with other reaction parameters, it should be noted that the catalyst is the reagent which, not only, essentially lessens generation of superfluous substances, reaction costs and contamination that are significant requisites of green chemistry, but also, reduce activation energy of the reaction. Therefore, high yield of any process pertains to choosing suitable and inexpensive catalyst<sup>ii</sup>. Recently, chemical and pharmaceutical scholars owing to increasing requirement to roll up collections of structurally compounds required in drug exploration have reinvigorated these considerations. Pyran derivatives are essential ingredients of cosmetics, pharmaceuticals, and scents crafts. They have captured a fundamental position in medicine researches for the sake of diverse activities, for exemplary antioxidant, diuretic, spasmolytic, anticoagulant, antianaphylactic, anticancer, antileishmanial, antibacterial, antiviral, antifungal, antiallergenic, hypotensive, and antitumor activities. In addition, they can be applied as cognitive enhancers for the therapy of some illnesses comprising Alzheimer's, Huntington's and Parkinson's illness, AIDS-associated dementia, amyotrophic lateral sclerosis, schizophrenia, myoclonus and Down's syndrome<sup>iii-viii</sup>. A novel, uncomplicated, convenient and environmentally friendly technique for the synthesis of

tetrahydrobenzo[b]pyrans contains one-pot, three-component condensation of an aldehyde, malononitrile, and dimedone in different conditions<sup>ix</sup>. Chemical kinetics includes investigation of how different experimental conditions can influence the speed of a chemical reaction and yield information about the reaction's mechanism and transition states, as well as the construction of mathematical models that can describe the characteristics of a chemical reaction. The rate of change in the concentrations of the reactants and products can be used to characterize the rate of a chemical reaction<sup>x</sup>. In our previous works, mechanism examination via thoroughly experimental and theoretical kinetics studies has been discussed for numerous reactions<sup>xi-xv</sup>. Herein, we try to investigate the kinetic of the convenient synthesis of tetrahydrobenzo[b]pyran **4** from 4-chlorobenzaldehyde **1**, malonitril **2**, and dimedone **3**, in the presence of agar as a catalyst (Scheme 1)



Scheme 1. Synthesis of tetrahydrobenzo[b]pyran **4** from 4-chlorobenzaldehyde **1**, malonitril **2**, and dimedone **3**, in the presence of agar as a catalyst and in a mixture of water:ethanol (2:1) solvent

## 2. Experimental section

4-chlorobenzaldehyde **1**, malonitril **2**, dimedone **3**, caffeine and ethanol were obtained from Merck (Darmstadt, Germany) and Fluka (Buchs, Switzerland), and used without any purification. The pure solvents water and Ethanol were also obtained from Merck (Darmstadt, Germany). A Cary UV-vis spectrophotometer model Bio-300 with a 10 mm light-path quartz spectrophotometer cell was employed throughout the current work.

### 2.1. General procedure

**At first**,  $10^{-2}$  M solution of compounds **1**, **2**, **3** and catalyst was prepared in a mixture of 2:1 water: ethanol as a solvent, separately and then, single spectrum of each compound was recorded at wavelength range 200-800 nm. **In the second experiment**, 0.2 ml of the solution of catalyst ( $10^{-2}$  M) and each reactant **2** and **3** ( $10^{-2}$  M) was added into the cell, respectively (because there is no reaction between them); then, 0.2 ml of reactant **2** was added into the mixture according to stoichiometry of each compound in the overall reaction. The progress of reaction was monitored at the ambient temperature (Fig. 1). Therefore, the applicable wavelength at which reactants **1**, **2**, **3** and catalyst have relatively no absorbance was found to be 375 nm; so, full kinetics and mechanism of the reaction was investigated at this wavelength. Hereupon, in all the experiments, the UV-vis spectrum of the product was measured over the concentration range ( $10^{-3}$  M < M product <  $10^{-2}$  M) to display a linear relation between the absorbance and concentration values. **In the third experiment** under same condition with the previous experiment the absorbance curve was recorded versus time at 25°C and 375 nm (Fig. 2). Zero, first or second curve fittings can be drawn using the software associated with the UV-vis instrument, also, the related rate constants can be calculated automatically<sup>xi</sup>. As can be seen in Fig. 2 the experimental absorbance data (dotted line) accurately fitted to second order curve (solid line), so, overall order of reaction in accordance with rate law, indicated in equation (1), can be written as:  $\alpha + \beta + \gamma = 2$

$$\text{Rate} = k_{\text{ovr}} [1]^{\alpha} [2]^{\beta} [3]^{\gamma} [\text{cat}] \quad (1)$$

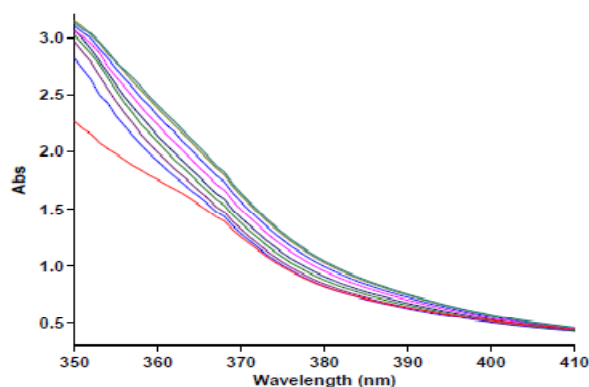


Fig. 1. UV-vis spectrum of the reaction between 4-chlorobenzaldehyde **1** ( $10^{-2}$  M), malononitrile **2** ( $10^{-2}$  M) and dimedone **3** ( $10^{-2}$  M) in the presence of agar catalyst ( $10^{-2}$  M), in a mixture of water: ethanol (2:1)

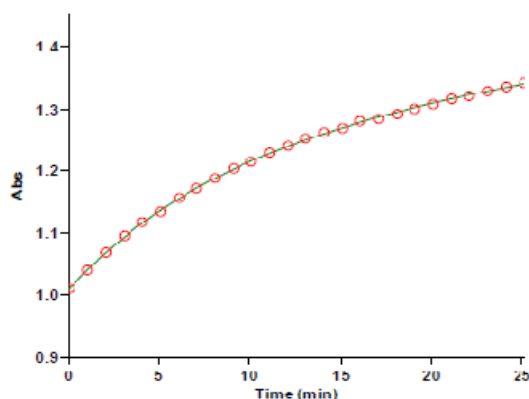


Fig. 2. Pseudo second order fit curve (solid line) along with the original experimental curve (dotted line) for the reaction between reactants **1** ( $10^{-2}$  M), **2** ( $10^{-2}$  M) and **3** ( $10^{-2}$  M) in the presence of agar ( $10^{-2}$  M) in a mixture of water:ethanol (2:1) at 375 nm

### 3. Results and Discussion

#### 3.1. Effect of Solvent and Temperature

Various experiments at different temperatures and solvent polarities were performed, but otherwise under the same conditions as for the previous experiment. The pertinent rate constants obtained from software were given in Table 1. The affiliation of the rate constants ( $\ln k_{\text{obs}}$  and  $\ln k_{\text{obs}}/T$ ) on temperature display compatibility with Eyring and Arrhenius equations. Moreover, the linearized form of Eyring equations was examined to compare these two methods with to gather <sup>xi</sup> (Figs. 3,4). Activation parameters were given in Table 2.

Table 1. Values of observed rate constants for the reaction between **1**, **2** and **3** in the presence agar catalyst at 375 nm

| $k_{obs}(M^{-1}.min^{-1})$ |                  | (a) 45.0    | (a) <b>40.0</b> | (a) 35.0    | (a) 30.0    | (a) 25.0    | (a) 20.0    | (b)                               |
|----------------------------|------------------|-------------|-----------------|-------------|-------------|-------------|-------------|-----------------------------------|
| $\lambda(nm)$              | Solvent          | $^{\circ}C$ | $^{\circ}C$     | $^{\circ}C$ | $^{\circ}C$ | $^{\circ}C$ | $^{\circ}C$ | <b>40.0<math>^{\circ}C</math></b> |
| 375                        | Water: ethanol   | 9.41        | <b>6.29</b>     | 4.38        | 3.25        | 2.30        | 2.16        | <b>6.28</b>                       |
| 375                        | (2:1)<br>ethanol | 2.54        | <b>1.62</b>     | 1.13        | 0.85        | 0.56        | 0.50        | <b>1.59</b>                       |

a: **1** ( $10^{-2}$  M), **2** ( $10^{-2}$  M), **3** ( $10^{-2}$  M), catalyst ( $10^{-2}$ M)

b: **1** ( $10^{-2}$  M), **2** ( $10^{-2}$  M), **3** ( $5 \times 10^{-3}$ M), catalyst ( $10^{-2}$ M)

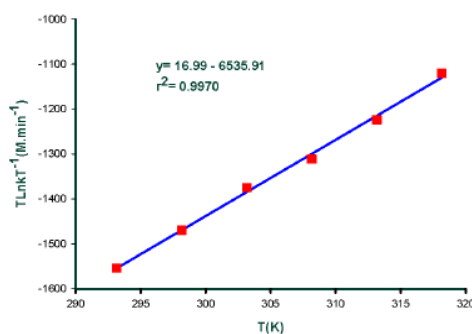
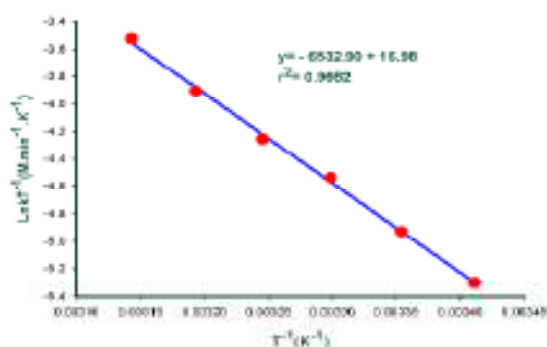


Fig. 3. Eyring plot for the reaction between **1**, **2**, **3** and agar in a mixture of water: ethanol (2:1) at 375 nm

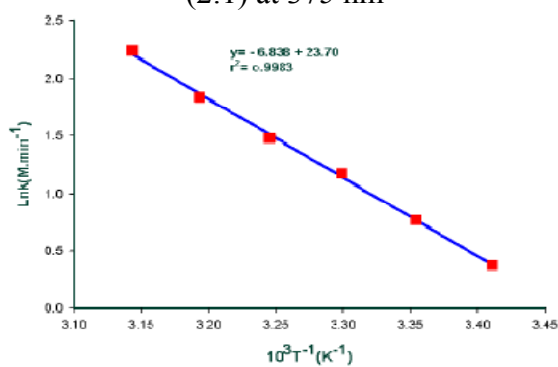


Fig. 4. Arrhenius plot for the reaction between **1**, **2**, **3** and agar in a mixture of water: ethanol (2:1) at 375 nm

Table 2. Activation parameters for the reaction between **1**, **2** and **3** in the presence of agar catalyst at 375nm

| Solvent             | $\Delta H^\ddagger$ (kJ.mol <sup>-1</sup> ) | $\Delta S^\ddagger$ (J.mol <sup>-1</sup> .K <sup>-1</sup> ) | $\Delta G^\ddagger$ (kJ.mol <sup>-1</sup> ) | $E_a$ (kJ.mol <sup>-1</sup> ) |
|---------------------|---|---|---|-------------------------------|
| Water: ethanol(2:1) | (a) 54.31                                   | (a) -56.37  | (a) 71.12                                   | (a) 56.85                     |
|                     | (b) 54.34                                   | (b) -55.54  | (b) 70.90                                   | (b) 56.90                     |

<sup>a</sup>: according to Eyring equation, b: according to linearized form of the Eyring equation

It can be seen from Table1 that the reaction rate increases whit increasing temperature. In addition, in a solvent whit lower dielectric constant (ethanol) in comparison with higher dielectric constant (mixture 2:1 water: ethanol) the reaction rate is decreased. That can be due to different stability of reactants and activated complexes in these environments. Furthermore, large negative value of  $\Delta S^\ddagger$  determines a transition state that is more strongly ordered than the reactants, and the positive value of  $\Delta H^\ddagger$  (Table 2) indicates an endothermic prosses.

### 3.2. Effect of Concentration

In order to determine the kinetic order with respect to a particular reactant and to establish an overall rate law three experiments were performed in which the concentration of one of reactants was selected much less ( $5 \times 10^{-3}$  M) than the others ( $10^{-2}$  M) separately. In other words, pseudo-order conditions were established for these reactions. The absorbance curves were shown in Figs. 5-7.

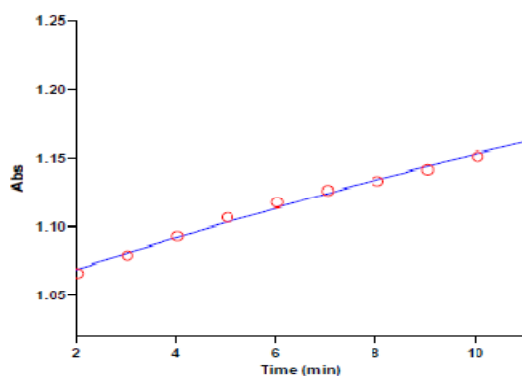


Fig. 5. Pseudo first order fit curve (solid line) along with the original experimental curve (dotted line) related to 4-chlorobenzaldehyde **1**, for the reaction between **1** ( $5 \times 10^{-3}$  M), **2** ( $10^{-2}$  M) and **3** ( $10^{-2}$  M) in the presence of agar at 375 nm

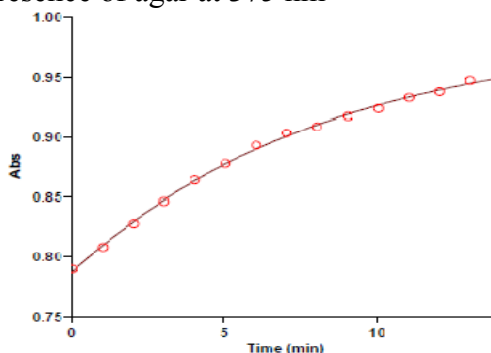


Fig. 6. Pseudo first order fit curve (solid line) along with the original experimental curve (dotted line) related to malonitrile **1**, for the reaction between **1** ( $10^{-2}$  M), **2** ( $5 \times 10^{-2}$  M), **3** ( $10^{-2}$  M) in the presence of agar at 375 nm

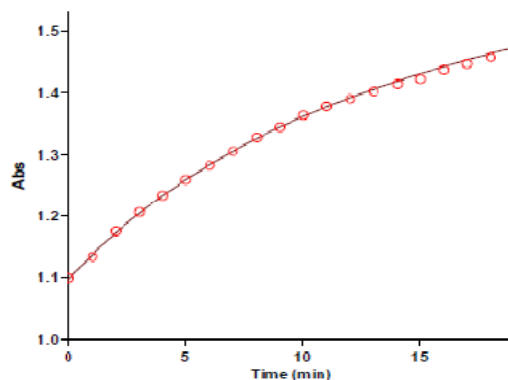


Fig. 7. Pseudo second order fit curve (solid line) accompanied by the original experimental curve (dotted line) for the reaction between compounds **1** ( $10^{-2}$  M), **2** ( $10^{-2}$  M) and **3** ( $5 \times 10^{-3}$  M) in the presence of agar ( $10^{-2}$  M) in a mixture of water: ethanol (2:1) at 375 nm

As expected from Fig. 2 (**1** ( $10^{-3}$  M), **2** ( $10^{-2}$  M) and **3** ( $10^{-3}$  M)) in comparison with Fig. 7 (**1** ( $10^{-2}$  M), **2** ( $10^{-2}$  M) and **3** ( $5 \times 10^{-2}$  M)), and Table 1, rate constants were independent of concentration of compound **3** and its value was the same in both experiments at 40.0 °C. So, order of reaction with respect to this compound could be zero ( $\gamma=0$ ). Also, from information in Figs. 5 and 6 we can conclude that order of reaction with respect to compounds **1** and **2** must be one ( $\alpha=\beta=1$ ). Therefore, we can rearrange equation (1) as follow:

$$\text{Rate} = k_{\text{ovr}}[1][2][\text{cat}], \quad k_{\text{obs}} = k_{\text{ovr}}[\text{cat}] \quad (2)$$

$$\text{Rate} = k_{\text{obs}}[1][2] \quad (3)$$

### 3.3 Effect of catalyst

In the presence of caffeine as a second catalyst, the reaction between **1**, **2** and **3** was carried out in a mixture of water: ethanol (2:1). Results show a decrease in rate constant compared to agar (Table 3). This is due to the fact that interactions of caffeine with polar solvent (water: ethanol, 2:1) compared to agar is stronger, so that, it has less opportunity to carry out its catalytic effects.

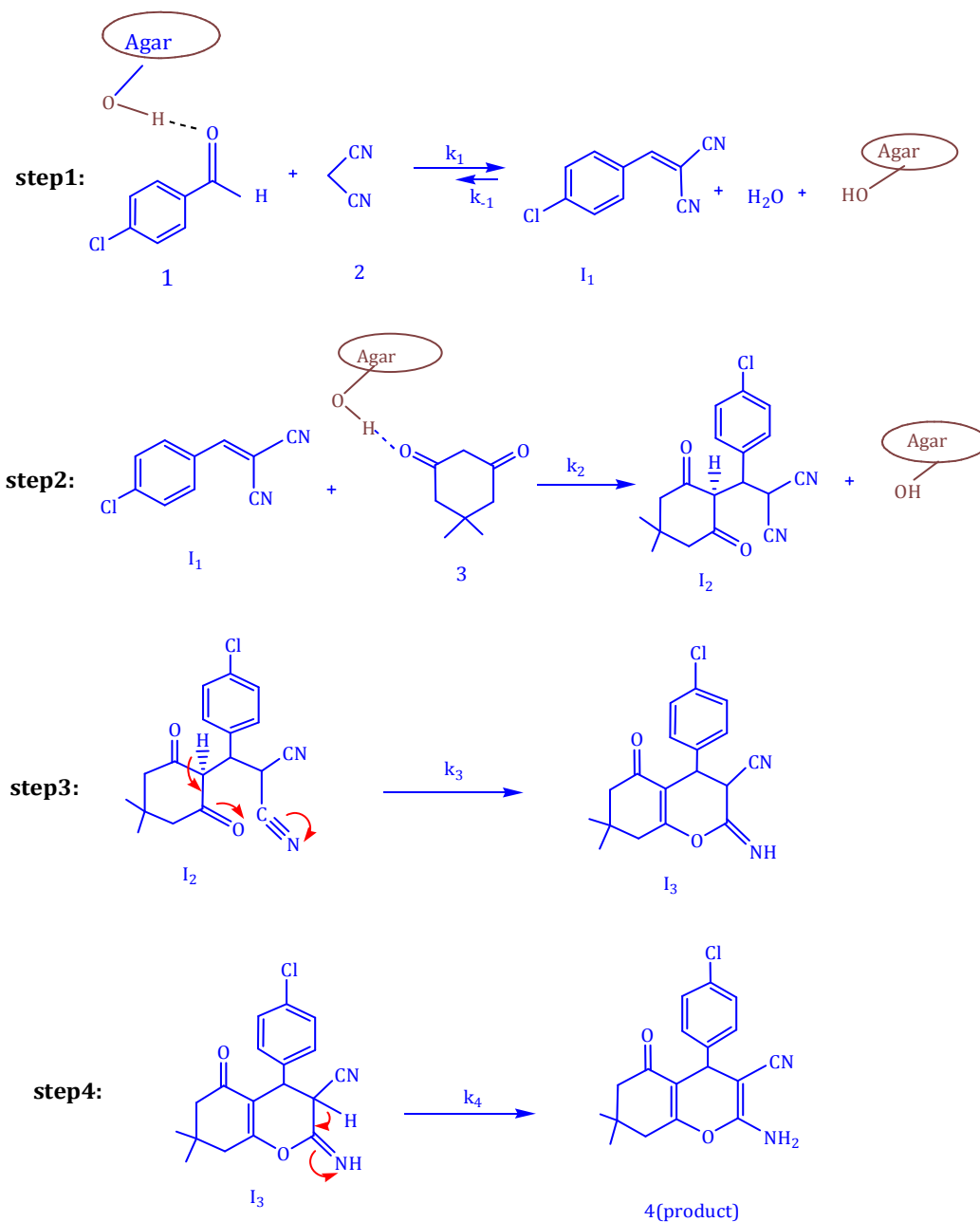
Table 3. Effect of various catalysts on the reaction between **1**, **2** and **3** at 45°C and 375 nm

| Solvent              | catalyst | $k_1 = k_{\text{ovr}}^a$ ( $\text{M}^{-2} \cdot \text{min}^{-1}$ ) |
|----------------------|----------|--|
| Water: ethanol (2:1) | caffeine | $1.04 \times 10^{+3}$  |
|                      | agar     | $1.31 \times 10^{+3}$  |

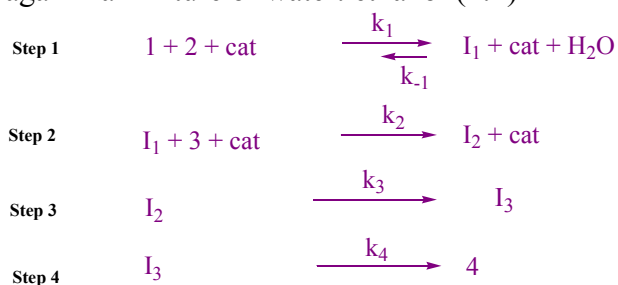
$$^a: k_{\text{ovr}} = k_1 = k_{\text{obs}}/[\text{cat}]$$

### 3.4. Proposed Mechanism

By using the above results, the proposed reaction mechanism and simplified derive as a possible comment are shown in schemes 2 and 3, respectively.



Scheme 2. The proposed mechanism for the reaction between **1**, **2** and **3** in the presence of agar in a mixture of water: ethanol (2:1)



Scheme 3. A simplified stepwise scheme for the proposed reaction mechanism  
 To specify the rate-determining step, rate law was written for final step of reaction:  
 Rate= $k_4$  [I<sub>3</sub>]

(4)

By utilization the steady state approximation to acquire the concentration of all intermediates ( $I_1$ ,  $I_2$  and  $I_3$ ), the rate equation becomes:

$$\text{Rate} = \frac{k_1 k_2 [1][2][3][\text{cat}]}{k_{-1}[\text{H}_2\text{O}] + k_2[3]} \quad (5)$$

This equation is independent of  $k_3$  and  $k_4$ . Thus, steps 3 and 4 have no chance to be a rate determining step, nevertheless, the equation depends on the first and second steps; if second step is a rate determining step, this speculation is logical:  $k_{-1}[\text{H}_2\text{O}] \gg k_2[3]$  therefore we can express:

$$\text{Rate} = \frac{k_1 k_2 [1][2][3]}{k_{-1}[\text{H}_2\text{O}]} \quad (6)$$

This equation is not a valid state because is relevant to the reaction that follows third-order kinetics, while the experiment results emphasised the second order kinetics. Furthermore, if he first step is a rate determining step, this speculation is right,  $k_{-1}[\text{H}_2\text{O}] \ll k_2[3]$ ; then, we can write:

$$\text{Rate} = k_1 [1][2][\text{cat}] \quad (7)$$

So, according to equations (2) and (7) we can conclude:

$$k_1 = k_{\text{ovr}}, \quad k_{\text{obs}} = k_1[\text{cat}], \quad \text{Rate} = k_{\text{obs}}[1][2] \quad (8)$$

According to this equation, the order of reaction with respect to compounds (**1**, **2** and **3**) is 1, 1 and zero, respectively; and the overall order of the reaction is two, which was previously confirmed by the experimental data.

The presence of  $k_1$  in the rate law (equation 7) demonstrates that first step is a rate-determining step and step 2 must be a fast step. In this case, the transition state (Schemes 2 and 3, step 1) carries a dispersed charge; bonding of solvent with this dispersed charge is much stronger than the reactants with any charge. Thus the solvent stabilizes the transition state more than the reactants and, therefore,  $E_a$  is reduced which speeds up the reaction. Our experimental results show that the solvent with higher dielectric constant exerts a powerful effect on the rate of reaction but the contrariwise occurs in solvent with lower dielectric constant (Tables 1).

#### 4. Conclusion

In summary, we have described, for the first time, full kinetics of the condensation reaction of 4- chlorobenzaldehyde, malononitrile, and dimedone in the presence of agar catalyst, by UV-vis spectroscopy. The results show that the overall order of reaction is two and partial order with respect to 4- chlorobenzaldehyde, malononitrile, and dimedone is 1, 1 and 0, respectively. In a mixture of water: ethanol, with higher dielectric constant, compared to ethanol, with lower dielectric constant, and in the presence of agar catalyst in comparison with caffeine catalyst the reaction rate were accelerated. The automatically calculated rate constants were in adaptability with the Arrhenius and Eyring equations. According to the steady state approximation and also experimental data, first step of the reaction mechanism were recognized as a rate determining step. Activation parameters ( $\Delta H^\ddagger$ ,  $\Delta S^\ddagger$  and  $\Delta G^\ddagger$ ) along with kinetics values ( $E_a$  and  $k$ ) were successfully identified for the reaction.

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