Regular Article

Kinetic Aspects of Tetrahydrobenzo[b]pyran Formation in the Presence of Fructose as a Green Catalyst: a Mechanistic Investigation

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The kinetics and mechanism of the reaction between benzaldehyde 1, malononitrile 2 and dimedone 3 in a mixture of ethanol and water as solvents in the presence of fructose as a biodegradable catalyst has been studied by the spectroscopic method (UV-Vis spectrophotometry method). The influence of various parameters (temperature, solvent and concentration) was studied on the reaction by means of the pseudo-first order kinetic model. Based on the experimental data, the overall order of the formation reaction of tetrahydrobenzo[b]pyran followed the second-order kinetics and under pseudo-order conditions the partial orders with respect to 1, 2 and 3 were one, one and zero, respectively. Kinetic values (k and E_a), associated with the activation parameters ($\Delta H^{\ddagger}$, $\Delta S^{\ddagger}$ and $\Delta G^{\ddagger}$) of the reaction were calculated using the Eyring equation from variable temperature in kinetic studies. The initial step of the presented mechanism was determined as a rate-determining step (k_1) and t was confirmed using the steady state approximation.

INTRODUCTION

Tetrahydrobenzo[b]pyrans have recently attracted attention as a special class of heterocyclic scaffolds in drug research because of their various biological and pharmacological beneficiary usages. These compounds are applied as anticancer, anticoagulant, diuretic, spasmolytic and antianaphylactic agents [1-7]. In addition, some of 4H-benzo[b]pyrans are applicable as photoactive materials [8]. In particular, 4H-benzo[b]pyrans has potential applications in the treatment of rheumatoid, psoriasis and cancer [9]. Other properties such as laser dyes [10], optical brighteners [11], fluorescence markers [12], pigments [13], cosmetics and potent biodegradable agrochemicals [14] have been well known for decades.

A literature survey revealed recent reports on several modified procedures using a variety of reagents, for example, hexadecyldimethylbenzyl ammonium bromide (HDMBAB) [15], TBAB [16,17], fluoride ion [18], ionic

liquids [19-21], RE(PFO)$_3$ [22], Na$_2$SeO$_4$ [23], high surface area MgO [24], solid acid [25] and (NH$_4$)$_2$HPO$_4$ [26,27], as catalyst in the synthesis of these heterocyclic compounds. However, some of the reported methods require prolonged reaction times, reagents in stoichiometric amount, use of the expensive catalysts, low yields of the products and toxic solvents.

Recently, one-pot procedures for the synthesis of trahydrobenzo[b]pyran from benzaldehyde, malononitrile and dimedonein have been developed in the presence of fructose as a catalyst (Fig. 1) [28-30]. However, the kinetic studies of these reactions have not yet been investigated. The purpose of any kinetic studies is to offer predictions about the composition of reaction mixtures as a function of time and to understand the processes occurring during a reaction. Kinetic measurements play key roles in elucidating reaction mechanisms, the mechanism must agree with the experimentally determined rate law.

In recent years, we have endeavored to expand experimental and theoretical studies on the kinetics and mechanisms of some synthesized organic reactions [31-37].

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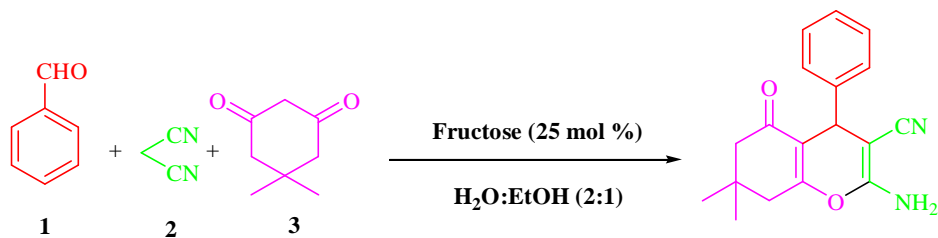*Corresponding author. E-mail: smhabibi@chem.usb.ac.ir

Fig. 1. Synthesis of tetrahydrobenzo[b]pyran in the presence of fructose in a mixture of (water/ethanol, 2:1).

We have implemented various methods and techniques such as UV-Vis spectrophotometry and theoretical calculations to elucidate the detailed kinetics and mechanisms of these reactions [38-48]. For the first time, we have described kinetic results along with detailed mechanistic studies of the synthesis reaction of 4H-tetrahydrobenzo[b]pyran based on a global kinetic analysis methodology using UV-Vis spectrophotometry apparatus in the present study.

EXPERIMENTAL

All reagents and solvent were purchased from (Merck, Darmstadt, Germany), (Acros, Geel, Belgium) and (Fluka, Buchs, Switzerland) and utilized without any purification. All yields refer to isolated products after purification by ethanol three times. Rate constants were presented as an average of several kinetic runs (at least 6-10) and were reproducible within a ±3% range. The overall rate of the reaction was followed by monitoring absorbance changes of the products with time on a Varian (Model Cary Bio-300) UV-Vis spectrophotometer with a 10 mm light-path cell.

Kinetics

A kinetic study of the reaction between benzaldehyde 1, malononitrile 2 and dimedone 3 in the presence of fructose as a green catalyst (Cat) was performed in a mixture of (water/ethanol, 2:1) by UV-Vis spectrophotometric technique. In the first experiment, 10^{-2} M solution of each reactant 1, 2, 3 and 2.5×10^{-3} M solution of fructose were prepared in a mixture of (water/ethanol, 2:1) as a solvent.

The relevant spectrum of each compound at 25 °C was recorded over the wavelength range 250-500 nm. In the second experiment, the concentration of all regents and fructose, as a catalyst, were 10^{-2} and 2.5×10^{-3} M,

respectively. The reaction was monitored along with recording scans of the entire spectra with 20 min intervals for the entire duration of the reaction at the ambient temperature (Fig. 2). As seen in Fig. 2, the appropriate wavelength was detected to be 380 nm (corresponding mainly to the product 4). Since at this wavelength, reactants 1, 2, 3 and fructose have relatively no absorbance value, it gave us the chance to find the practical conditions that allow kinetics and mechanistic investigation of the reaction. It is worth noting that, the concentration range was measured over (10^{-4} M ≤ product M ≤ 10^{-2} M) to prove a linear relation between the absorbance and concentrations values.

In the third experiment, under the same concentration (10^{-2} M) of 1, 2 and 3 in the presence of fructose (2.5×10^{-3} M) in a mixture of (water/ethanol, 2:1) at 35 °C, the reaction kinetics was followed by indicating the UV absorbance measurements as a function of time (Fig. 3).

The infinity absorbance (A_∞) that is the absorbance at reaction completion can be obtained from Fig. 3. With regard to this value, the zero, first or second curve fitting can be drawn automatically for the reaction by the software associated [49] with the UV instrument. A second order fit curve (solid line) was obtained from the absorbance data versus time provided at 380 nm that precisely described the experimental curve (dotted line) as reported in Fig. 3. It is obvious that the reaction is second order. Thus, overall order of the reaction is α + β + γ = 2. Therefore, the second-order can be reported ($k_{obs} = 26.57$ M^{-1} min^{-1}, T = 308.15 K) In this case, the rate law can be written as:

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

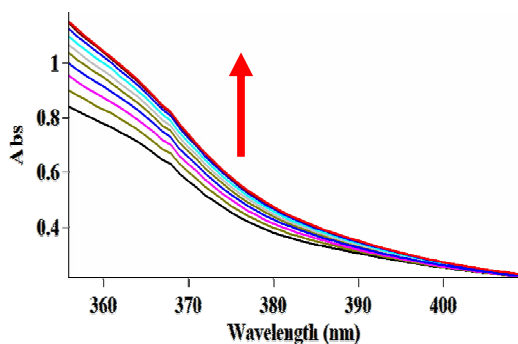where benzaldehyde is 1, malononitrile is 2, and dimedone

Fig. 2. The UV-Vis spectra of the reaction between benzaldehyde 1 (10^{-2} M), malononitrile 2 (10^{-2} M) and dimedone 3 (10^{-2} M) in the presence of fructose (2.5×10^{-3} M) as a catalyst in a mixture of (water/ethanol, 2:1) as reaction proceeds into a 10 mm light-path cell. Herein, the upward direction of the arrow indicate the progress of product (concentration or absorbance) *vs.* times.
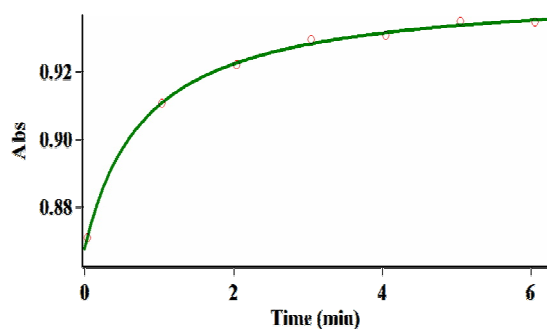

Fig. 3. The experimental absorbance changes (dotted line) along with the fit curve (solid line) against time for the reaction between benzaldehyde 1 (10^{-2} M), malononitrile 2 (10^{-2} M), and dimedone 3 (10^{-2} M) in the presence of fructose (2.5×10^{-3} M) and in a mixture of (water/ethanol, 2:1) at 380 nm and 35.0 °C.

is 3.

RESULTS AND DISCUSSION

Effect of Solvent and Temperature

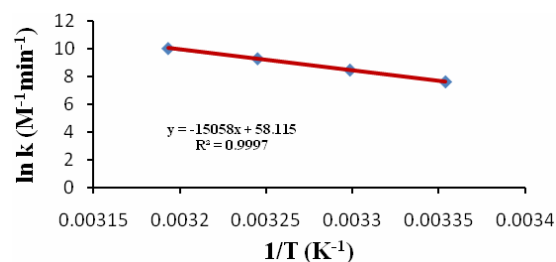To specify the effect of temperature variations and

Fig. 4. The affiliation of the second order rate constant (ln$k$) on reciprocal temperature for the reaction between 1, 2 and 3 in the presence of fructose measured at a wavelength of 380 nm in a mixture of (water/ethanol, 2:1), according to the Arrhenius equation.
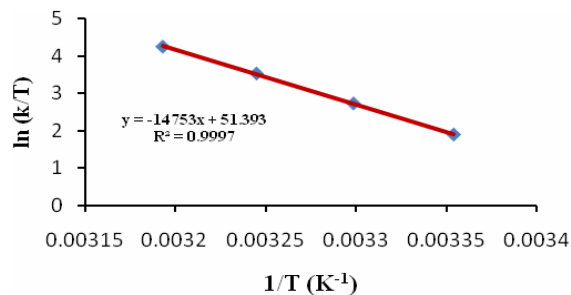

Fig. 5. An Eyring plot according to Eq. (3) for the reaction between 1, 2 and 3 in the presence of fructose in a mixture of (water/ethanol, 2:1).

solvent environment on the rate of reaction, both factors were investigated through various experiments using different conditions of temperature and solvent, under the same condition as the earlier experiments.

Since the transition state (Step 1, Fig. 9) in the reaction carries a dispersed charge, solvents with higher dielectric constant (a mixture of water/ethanol (2:1)) speed up the reaction rate (Table 1) by making the species at the transition state more stable than the reactants, and therefore E_a would be made lower.

In this investigation, Fig. 4 shows the linear relation between lnk_{ove} (the rate constant) and inverse of the temperature, $1/T$, in agreement with the Arrhenius Eq. (2).

$$\ln k = \ln A - \frac{E_a}{RT} \tag{2}$$

Table 1. k_{obs} (M^{-1} min^{-1}) for the Reaction between 1 (10^{-2} M), 2 (10^{-2} M) and 3 (10^{-2} M) and Fructose (2.5 × 10^{-3} M) in Different Media of Solvent and Temperature

Solvent: mix of water/ethanol (2:1) (60.9)[a]			
T	T = 298.15 K	T = 303.15 K	T = 308.15 K	T = 313.15 K
k_{obs}	4.98	11.68	26.57	55.63
	(0.0029)[b]	(0.0025)	(0.0016)	(0.0019)
Solvent: ethanol (24.3)[a]			
T	T = 298.15 K	T = 303.15 K	T = 308.15 K	T = 313.15 K
k_{obs}	1.89	4.37	10.81	23.96
	(0.0017)[b]	(0.0023)	(0.0029)	(0.0022)

[a]Dielectric constant (D). [b]Standard deviation (SD).

The activation energy for the reaction between 1, 2 and 3 was acquired from the slope of (Fig. 4).

According to Eyring Eqs. (3) and a different linearized form of Eyring Eq. (4), the activation parameters $\Delta H^{\ddagger}$ (activation enthalpy) and $\Delta S^{\ddagger}$ (activation entropy) were determined by means of the intercept and slope of Figs. 5 and 6.

$$\ln\left(\frac{k}{T}\right) = \left(\frac{\ln k_B}{h} + \frac{\Delta S^{\mp}}{R}\right) - \frac{\Delta H^{\mp}}{RT} \qquad (3)$$

$$T \times \ln\left(\frac{k}{T}\right) = T \times \left(\ln\frac{k_B}{h} + \frac{\Delta S^{\mp}}{R}\right) - \frac{\Delta H^{\mp}}{RT} \qquad (4)$$

therein k_B, T, h and R are Boltzmann's constant, temperature, Planck's constant and universal gas constant, respectively.

From the Eyring equation [50-52], it is concluded that the standard errors of $\Delta S^{\ddagger}$ and $\Delta H^{\ddagger}$ correlate *via* the following equation:

$$\sigma(\Delta S^{\ddagger}) = 1/T_{av}\sigma(\Delta H^{\ddagger}) \qquad (5)$$

where T_{av} is the center of the temperature range used in this experiment.

Furthermore, $\Delta G^{\ddagger}$ (Gibbs free energy) was determined using Eq. (6):

$$\Delta G^{\ddagger} = \Delta H^{\ddagger} - T\Delta S^{\ddagger} \qquad (6)$$

According to Eq. (23), k_1 is the same as the overall rate constant (k_{ove} in Eq. (9)), hence, the activation parameters which include $\Delta G^{\ddagger}$, $\Delta S^{\ddagger}$ and $\Delta H^{\ddagger}$ can now be computed for the first step (step of rate determination, k_1), as an initial reaction.

High value of E_a depicts that the reactant needs higher amount of energy to increase its temperature in the transition state. The positive value of $\Delta H^{\ddagger}$ means that energy is consumed during the process and the high values of E_a and $\Delta H^{\ddagger}$ correspond to slow rate of reaction. A large positive value for entropy of activation $\Delta S^{\ddagger}$ results in a higher disorder of the transition state than the ground state. This is indicative of a large degree of dissociative interchange during process.

Effect of Concentration

The concentration factor has a key role in the kinetical study, particularly for finding the partial order of reactant 3 under pseudo-order condition, in a separate experiment (fourth experiment), a similar procedure was employed with these concentrations [(10^{-2} M, reactant 1), (10^{-2} M, reactant 2)], [(5 × 10^{-3} M, reactant 3)] and fructose (2.5 × 10^{-3} M). To obtain Eq. (7), the rate law can be expressed:

$$rate = k_{ovr}[1]^{\alpha}[2]^{\beta}[3]^{\gamma}[Cat]$$
$$rate = k_{obs}[3]^{\gamma}$$
$$k_{obs} = k_{ovr}[1]^{\alpha}[2]^{\beta}[Cat] \qquad (7)$$

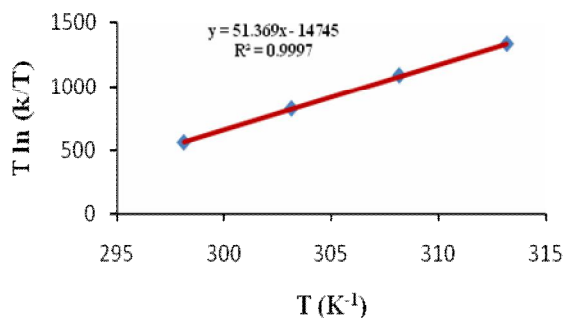In this study, the original experimental absorbance curve

Fig. 6. A different linearized form of Eyring equation plot in accord with Eq. (4) for the reaction between 1, 2 and 3 in the presence of fructose in a mixture of (water/ethanol, 2:1).
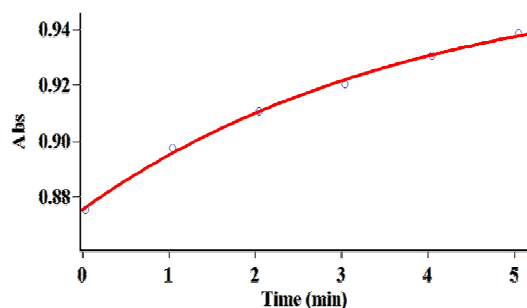

Fig. 7. Pseudo-second order fit curve (solid line) along with the original experim ental curve (dotted) for the reaction between dimedone 3 (5 × 10^{-3} M), malononitrile 2 (10^{-2} M) and benzaldehyde 1 (10^{-2} M) in the presence of fructose (2.5 × 10^{-3} M) at 380 nm and 35.0 °C in a mixture of (water/ethanol, 2:1).

(dotted) versus times provided a pseudo-second order (solid line) at 380 nm and 35.0 °C, as shown in Fig. 7. Additionally, the observed rate constant (k_{obs}) was automatically calculated by the software associated [49] with UV-Vis instrument (k_{obs} = 26.31 M^{-1} min^{-1}).

Herein, the experimental data proved that the observed pseudo-second order rate constant (k_{obs} = 26.31 M^{-1} min^{-1}, fourth experiment, pseudo-order condition) is identical with second order rate constant, (k_{obs} = 26.57 M^{-1} min^{-1}, third experiment) implying that probably γ = 0 in Eq. (7).

In the fifth experiment, to evaluate a partial order of the reaction in relevance to benzaldehyde 1, a pseudo-order
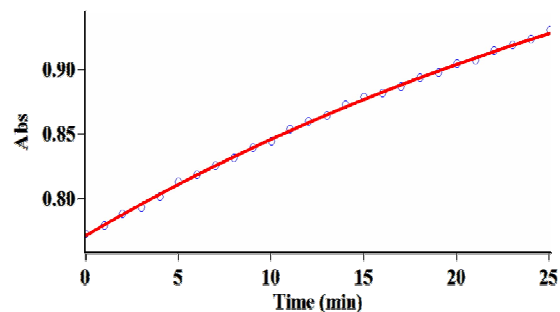

Fig. 8. Pseudo-first order fit curve (solid line) accompanied by the original experimental curve (dotted line) for the reaction between 1 (5 × 10^{-3} M), 2 (10^{-2} M) and 3 (10^{-2} M) in the presence of fructose (2.5 × 10^{-3} M) at 380 nm and 35.0 °C in a mixture of (water/ethanol, 2:1).

condition was defined for the reaction between 2 (10^{-2} M), 3 (10^{-2} M) and 1 (5 × 10^{-3} M) in the presence of fructose (2.5 × 10^{-3} M) and in a mixture of (water/ethanol, 2:1). According to the fifth experiment, the rate law follows:

$$rate = k_{ovr}[1]^{\alpha}[2]^{\beta}[3]^{\gamma}[Cat]$$
$$rate = k_{obs}[1]^{\alpha}$$
$$rate = k_{ovr}[2]^{\beta}[3]^{\gamma}[Cat] \tag{8}$$

Herein, the experimental absorbance curve *vs.* time provided a first-order fit (Fig. 8) at 380 nm and 35.0 °C.

Figure 8 clearly confirms that the partial order of reactant 1 with respect to equation 8 is one (α = 1). Also γ is found to be zero from the fourth experiment. Then, the value of α = 1 is obtained in fifth experiment, and finally, this parameter leads to β = 1 in the whole UV-Vis experiments. So, the experimental general rate law is given as below Eq. (9):

$$rate = k_{ovr}[1][2][Cat]$$
$$k_{obs} = k_{ovr}[Cat]$$
$$rate = k_{obs}[1][2] \tag{9}$$

With respect to the above experiments' results, the simplified scheme of the speculative reaction (Fig. 9)

Table 2. Activation Parameters for the Reaction between the Compounds 1, 2, 3 and Fructose Measured in Different Solvent Media

Solvent	$\Delta H^{\ddagger}$ (kJ mol^{-1})	$\Delta S^{\ddagger}$ (Jmol^{-1})	$\Delta G^{\ddagger}$ (kJ mol^{-1})	Ea (kJ mol^{-1})	
# 1 water/ethanol (2:1) (58.6)[a]	122.65 ± 0.54	229.74 ± 1.79	54.15 ± 1.09	125.06 ± 0.55^{b}	125.19 ± 0.54^{c}
# 2 ethanol (24.3)[a]	129.82 ± 0.67	245.52 ± 2.21	56.61 ± 1.33	132.30 ± 0.67^{b}	132.35 ± 0.68^{c}

[a]Dielectric constant (D). [b]According to this equation: $E_a = \Delta H^{\ddagger} + RT$. [c]In accord with the Arrhenius equation.

mechanism for further studies is illustrated in Fig. 10. This mechanism is just a supposition based on known facts and results for an explanation of how the reaction proceeds. Therefore, it should comply with the experimental results of the reaction obtained by the kinetic study. On the basis of the obtained results, a speculative mechanism containing five steps can be proposed in accordance with the Knoevenagal condensation. First, benzaldehyde 1 and malonitrile 2 generate 2-benzylidenmalonitrile I_1, then the Michael addition of I_1 with dimedone 3 produces I_2 which is subsequently followed by tautomerization and cyclization affording the corresponding product 4 (Fig. 9). A simplified scheme of the presented reaction mechanism (Fig. 9) is shown in Fig. 10.

To investigate which step of the presented mechanism is a rate-determining step, the rate law was written using the final step of reaction:

$$rate = k_5[I_4] \tag{10}$$

The steady-state approximation can be applied for $[I_1]$ that yields the Eq. (11) in the following:

$$\frac{d[I_4]}{dt} = k_4[I_3][Cat] - k_5[I_4] = 0 \tag{11}$$

$$k_4[I_3][Cat] = k_5[I_4] \tag{12}$$

The value of $[I_4]$ can be replaced in Eq. (10) to attain Eq. (13):

$$rate = k_4[I_3][Cat] \tag{13}$$

To attain the intermediate concentration $[I_3]$ the following equation is yielded by applying the steady state estimation:

$$\frac{d[I_3]}{dt} = k_3[I_2][Cat] - k_4[I_3][Cat] = 0$$
$$k_3[I_2][Cat] = k_4[I_3][Cat] \tag{14}$$

By substituting Eqs. (14) in (13) and employing some straight forward math the following equation emerges:

$$rate = k_3[I_2][Cat] \tag{15}$$

The steady state approximation can then be applied in order to attain the concentration of $[I_2]$ which is represented in the following formula:

$$\frac{d[I_2]}{dt} = k_2[I_1][Cat][1] - k_3[I_2][Cat] = 0 \tag{16}$$

$$k_2[I_1][Cat][1] = k_3[I_2][Cat] \tag{17}$$

$$rate = k_2[I_1][Cat][1] \tag{18}$$

$$\frac{d[I_1]}{dt} = k_1[1][2][Cat] - k_{-1}[I_1][Cat] - k_2[3][I_1][Cat] = 0 \tag{19}$$

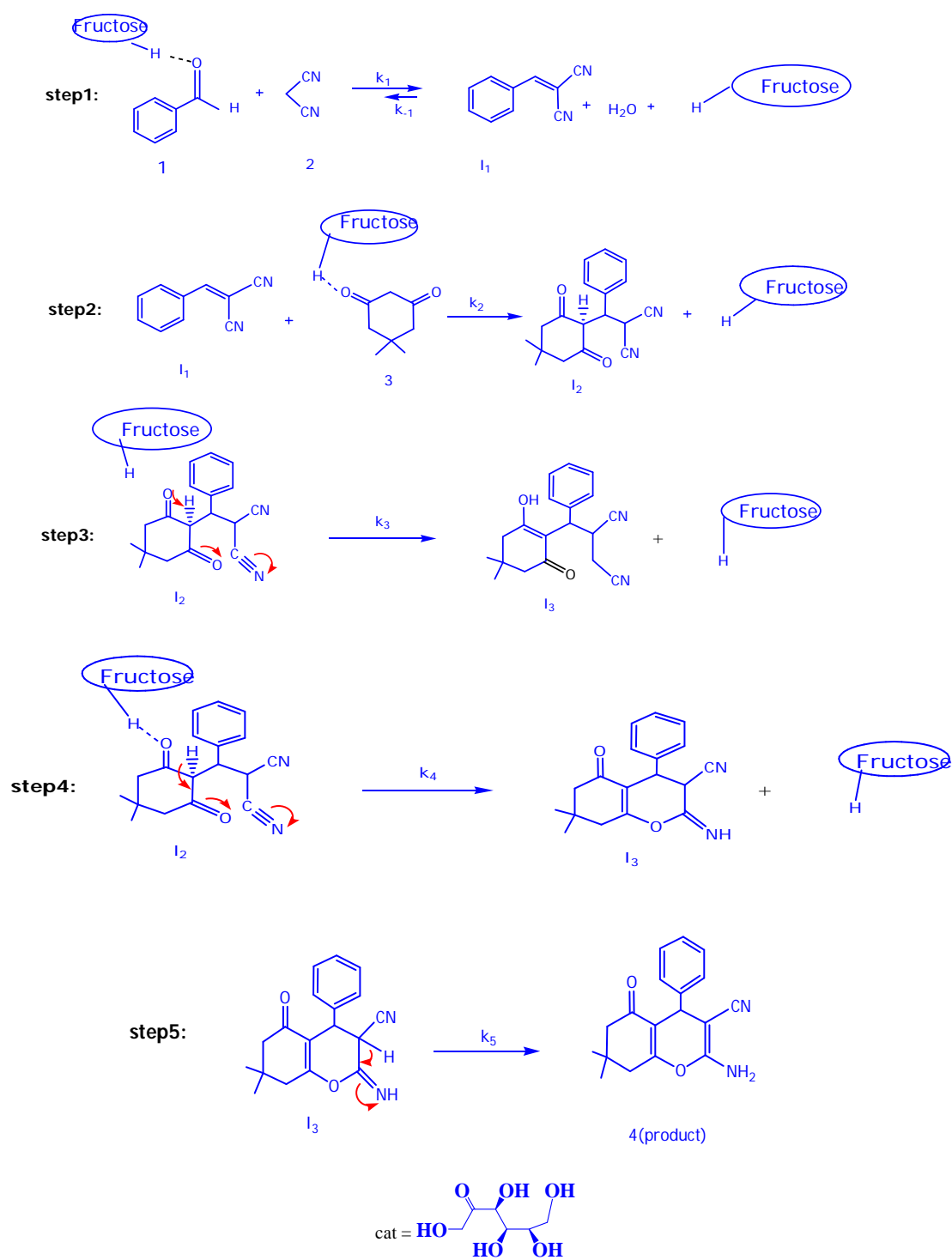$$[I_1] = \frac{k_1[1][2]}{k_{-1} + k_2[3]} \tag{20}$$

Fig. 9. A speculative mechanism of the reaction between 1, 2 and 3 in the presence of fructose for the synthesis of 2-amino-5,6,7,8-tetrahydro-7,7-dimthyl-4-(4-H)-5-oxo-4H-chromene-3-carbonitrile 4 in a mixture of (water/ethanol, 2:1).
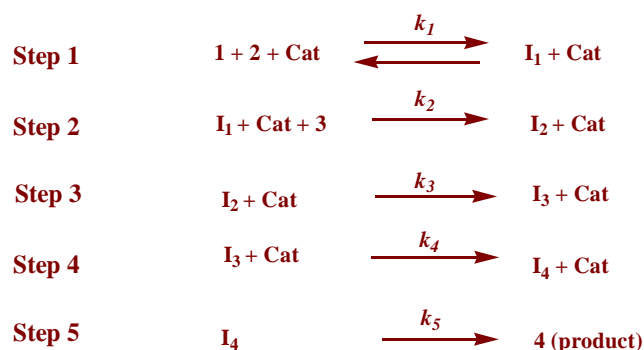
Fig. 10. A simplified Scheme for the presented reaction mechanism.

$$rate = \frac{k_2[3][Cat] \times k_1[1][2]}{k_{-1} + k_2[3]} \tag{21}$$

k_4, k_5 and k_3 are not attained in Eq. (21), therefore there rate constants have no chances of being a rate determining step, but step1 (k_1) and step2 (k_2) have a good opportunity to be a rate determining step.

If k_2 is the rate determining step, then the following speculation is reasonable:

$k_2[3] \ll k_{-1}$

The new equation can be presented:

$$rate = \frac{k_1 k_2[1][2][3][cat]}{k_{-1}} \tag{22}$$

This equation is not compatible with the experimental rate law (Eq. (9)), because the presented Eq. (22) is a third-order reaction with respect to compounds 1, 2 and 3, while the obtained results from the UV experiments indicate that the overall order of reaction is two.

If k_1 is a rate determining step, the following assumption is logical:

$k_2[3] \gg k_{-1}$

So, the new generation of the rate law can be expressed:

$$rate = k_1[1][2][Cat] \tag{23}$$

In this case, it is reasonable to write:

$k_1 = k_{ovr}$ and if $k_{obs} = k_{ove}[Cat]$

Then, rate $= k_{obs}[1][2]$ (24)

The last Eq. (24) deducted by the steady-state approximation is the same as the rate law obtained from the UV experiment (Eq. (9)). It is obvious that the overall order of the reaction is two. In addition, the order of the reaction with respect to each reactant (1, 2 and 3) is 1, 1 and zero, respectively. Because of the presence of k_1 in the rate law (23), it proves that the first step (k_1) is a rate-determining step.

Furthermore, effect of solvent study with higher dielectric constant on the reaction rate (a mixture of water/ethanol, 2:1) indicated that how the transition state in a rate-determining step (step 1, Fig. 9) with the larger full dispersed charges can be stabilized more than the reactants containing the lack or partial dispersed charges, Table 1.

CONCLUSIONS

Kinetic investigation of the reaction between benzaldehyde 1, malononitrile 2 and dimedone 3 compounds in the presence of fructose as a highly effective, green and homogenous catalyst was undertaken using the UV-Vis spectrophotometric technique. The reaction for the formation of a 4H-tetrahydrobenzo[b]pyran followed the second-order kinetics and the partial orders with regard to benzaldehyde 1, malononitrile 2 and dimedone 3 were one, one and zero, respectively. In conclusion, the rate of reaction speeds up in a solvent with a high dielectric constant (water/ethanol, 2:1) in comparison to those with a lower dielectric constant (ethanol and methanol) at all temperatures. In the studied temperature range, the second-order rate constant of the reaction was inversely proportional to the temperature, which was in agreement with the Arrhenius and Eyring equations. Activation parameters ($\Delta H^{\ddagger}$, $\Delta S^{\ddagger}$ and $\Delta G^{\ddagger}$) were calculated from the Eyring equation. The values of $\Delta S^{\ddagger}$ was extremely positive often indicating a dissociative mechanism. It was obvious that the large positive values of activation parameters lead to a stiff reaction progress. Finally, the first step of the proposed mechanism was identified as a rate-determining step (k_1) and this was confirmed based on the steady-state approximation.

ACKNOWLEDGEMENTS

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