Investigation of the Mannich reaction for generating a $\beta$-aminoketone: further treatment of kinetic results

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ABSTRACT

The aim of this study is the derivation of the kinetic parameters for a special Mannich reaction, where the first step is rate-determining. The work involved studying the reactions among benzaldehyde, acetophenone and aniline in the presence of sodium acetate as a catalyst for the generation of a $\beta$-aminoketone. The novelty of this work lies in its investigation of the effect of the catalyst on kinetic behaviour that allows for estimations of the rate constant and activation parameters such as energy of activation, enthalpy, entropy and activation Gibbs free energy, relative to the formation of $\beta$-aminoketone. Experimentally, the reactions were found to be of second-order and the observed rate constants were determined using UV-vis spectrophotometry. The satisfactory agreement between the sets of experimental data obtained under different reaction conditions and the steady state assumption indicates that the assumptions made are correct and the whole treatment applied to the kinetic data is justified.

ARTICLE HISTORY

Received 9 September 2017
Accepted 11 January 2018

KEYWORDS

$\beta$-Aminoketone; kinetic study; benzaldehyde; acetophenone; aniline

1. Introduction

The synthesis of natural molecules, pharmaceuticals and other nitrogenous biologically active compounds using multi-component reactions (MCRs) has long been a significant branch of organic synthesis [1–3]. MCRs are important for the achievement of high levels of brevity and diversity. They allow for more than two simple and flexible building blocks to be combined in practical, time-saving one-pot operations, giving rise to complex structures by simultaneous formations of two or more bonds, according to the domino principle [4]. MCRs contribute to the requirements of an environmentally friendly process by reducing the number of synthetic steps, energy consumption and waste production. Researchers have transformed this powerful technology into one of the most efficient and economic tools for combinatorial and parallel synthesis [5]. Their inherent simple experimental procedures and one-pot character make them perfectly suitable for automated synthesis. Herein, an amine, two carbonyl compounds and catalysts are used to produce synthesized $\beta$-amino carbonyl compounds (Scheme 1) via a one-pot three-component reaction [6–19]. $\beta$-Amino carbonyl compounds are very useful in pharmaceutical and other biologically related areas of chemistry. One of the many synthetic routes to these compounds is the Mannich reaction which brings together three compounds under appropriate catalytic conditions. The Mannich reaction is one of the most important C–C bond forming reactions in organic synthesis for the preparation of secondary and tertiary amine derivatives [20]. These amines are further used in the synthesis of many intermediates, biologically active and natural products such as alkaloids and polyketides. The products of the Mannich reaction are mainly $\beta$-amino carbonyl compounds and its derivatives that are used for the synthesis of amino alcohols, peptides and lactams, and as precursors to optically active amino acids. The conventional catalysts for the classical Mannich reaction among aldehydes, ketones and amines involve mainly organic and mineral acids like proline, acetic acid [21]. 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.

Our research group presents an entirely green eco-friendly, simple and efficient protocol for the 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 a catalyst in a mixture of water/ethanol at room temperature. It should be noted that the results of such a synthesis have been published...
recently [22]. Kinetic research of these reactions is therefore valuable, but they have not yet been extended very much. The purpose of this work is to utilize the UV–vis spectrophotometric method to describe the kinetic results of the presented reaction in order to enhance the knowledge of their important biological behaviours. Numerous kinetic researches over a large area of different reactions have previously been reported using the UV–vis technique [23–43]. Also, a reason for the importance of kinetics is that it provides evidence for the mechanisms of chemical processes.

2. Experimental

2.1. Chemicals and apparatus used

Benzaldehyde 1, aniline 2, acetophenone 3 and sodium acetate were obtained from Merck (Darmstadt, Germany), Acros (Geel, Belgium) and Fluka (Buchs, Switzerland), and used without further purifications. All extra pure solvents 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. Optimization concentration of
the catalyst was chosen (1.5 × 10⁻² M) in each experiment on the basis of the synthesis report of the reaction [22], and it is shown in Figure 1.

3. Result and discussion

3.1. Preliminary studies

The progress of the reaction among benzaldehyde 1, aniline 2 and acetophenone compound 3 in the presence of sodium acetate as a catalyst in a mixture of ethanol and water (1:1). The upward direction of the arrow indicates the progress of the reaction.

The catalyst was chosen (1.5 × 10⁻² M) in each experiment on the basis of the synthesis report of the reaction [22], and it is shown in Figure 1.

3.2. Further investigations

3.2.1. Determination of partial order of reaction

In order to obtain a partial order of the reaction regarding each reactant, pseudo-order conditions were performed for the reaction via three different experiments and the results are presented below (Figures 4–6).

From Figure 6 it is deductible that the reaction is second-order kinetics with the same rate constant (kobs = 39.4 M⁻¹ min⁻¹) that was obtained from Figure 3. This is possible when the reaction is zero-order kinetics with respect to component 3 (γ = 0). Ultimately, it was deduced from all the experiments that the partial orders of reaction with respect to components 1, 2 and 3 are one, one and zero, respectively.

| Reactant | Benzaldehyde 1 | Aniline 2 | Acetophenone 3 | Sodium acetate |
|----------|----------------|-----------|----------------|----------------|
| Concentration (M) | 10⁻² | 10⁻² | 10⁻² | 1.5 × 10⁻² |

Figure 2. Expanded absorbance changes versus wavelengths for the reaction among 10⁻² M solution of reactants 1, 2 and 3 in the presence of sodium acetate as a catalyst in a mixture of ethanol and water (1:1). The upward direction of the arrow indicates the progress of the reaction.

Figure 3. The experimental absorbance change (dotted line) along with the second-order fit curve (solid line) versus time for the reaction among benzaldehyde 1 (10⁻² M), aniline 2 (10⁻² M) and acetophenone 3 (10⁻² M) in a mixture of water and ethanol (50:50) at 370 nm and 298.15 K, in the presence of a catalyst.

Table 1. Optimum concentrations of reactants.

| Reactant       | Benzaldehyde 1 | Aniline 2 | Acetophenone 3 | Sodium acetate |
|----------------|----------------|-----------|----------------|----------------|
| Concentration (M) | 10⁻² | 10⁻² | 10⁻² | 1.5 × 10⁻² |

Since γ = 0, β = 1, α = 1 and kobs = k_{o vr}(ca).
So the rate law can be written as

$$\text{Rate} = k_{\text{obs}}[1]^a,$$

$$k_{\text{obs}} = k_{\text{ave}}[2]^b[3]^c[\text{Cat}].$$ (2)

So the rate law can be written as

$$\text{Rate}_{\text{exp}} = k_{\text{obs}}[1][2].$$ (5)

### 3.2.2. Confirmation of mechanism

For writing a true mechanism or confirmation of the suggested mechanism (Figure 1), it is necessary to know which two-component reactions (three possibilities) start step1 of the reaction mechanism. So a series of two-component experiments were performed between the reaction components under the same conditions. These reactions are recorded in Table 2. Kinetic measurements were carried out using the UV–vis spectrophotometer.

Results showed that there are no reactions between benzaldehyde 1 and acetophenone 3 (R1, Figure 7) or acetophenone 3 and aniline 2 (R2, Figure 8) due to a lack of progress during recording a suitable trace. But the reaction between aniline 2 and benzaldehyde 1 shows a good progress (R3, Figure 9). The enhancement of absorbance in Figure 9 is clear evidence for the generation of the intermediate (I1).

If we assume that the RDS for the overall reaction depends on the formation of the intermediate (I1) in step1, the rate law can be written as

$$\text{Rate}_{\text{mech}} = k_1[1][2][\text{ca}],$$

$$k_{\text{obs}} = k_{\text{ave}}[1]^a[2]^b[3]^c[\text{Cat}].$$ (3)

$$\text{Rate}_{\text{mech}} = k_{\text{obs}}[1][2].$$ (6)

This is acceptable because the rate law for an elementary step is derived from the molecularity of that step. Equation (6) has compatibility with the experimental rate law, Equation (5). It seems that for a careful determination of the RDS, greater investigation such as solvent and temperature studies are required.

### Table 2. A series of two-component reactions.

| Number of reaction | Component of reaction | Result     |
|--------------------|-----------------------|------------|
| R1 (reaction 1)    | Benzaldehyde 1 + acetophenone 3 | No reaction |
| R2 (reaction 2)    | Aniline 2 + acetophenone 3 | No reaction |
| R3 (reaction 3)    | Benzaldehyde 1 + aniline 2 | Good progress |
4. Effect of temperature

In order to follow the effect of temperature on the reaction rate and determination of kinetic measurements and activation parameters, the reaction was carried out at different temperatures under the same conditions. Results showed that at higher temperatures, the reaction needs little time to complete. Also, the absorbance and rate constants increase due to the enhancement of temperature. Herein, all experimental absorbance curves versus time exactly fitted to the second-order fitting curves at various temperatures. The second-order rate constants of the reactions were obtained using the standard equations within the programme [52] at the time required for the completion of the reaction (Table 3).

The effect of temperature upon the rate constant is described by the Arrhenius equation, where \( E_a \) is the activation energy for the reaction and \( A \) is a constant known as the pre-exponential factor.

\[
\ln k = \ln A - \frac{E_a}{RT}.
\]  

(7)

When the \( \ln k \) (rate constant) is plotted versus the inverse of temperature, \( 1/T \), a straight line is obtained which is in agreement with the Arrhenius equation (7) (Figure 10).

However, the Arrhenius equation is most often applied to gas-phase kinetics, whereas the Eyring
equation is used to describe the relationship between the reaction rate and temperature for the reactions in solution media. The activation parameters were determined from two linear forms of Eyring equations (8(a) and 8(b)), and is shown in Figures 11(a,b), respectively.

\[
\ln \left( \frac{k}{T} \right) = \ln \frac{k_B}{h} + \frac{\Delta S^\ddagger}{R} - \frac{\Delta H^\ddagger}{RT}, \quad (8a)
\]

\[
T \ln \left( \frac{k}{T} \right) = T \ln \frac{k_B}{h} + \frac{\Delta S^\ddagger}{R} - \frac{\Delta H^\ddagger}{R}, \quad (8b)
\]

The activation energy \(E_a\) and the activation enthalpy \(\Delta H^\ddagger\) are linked with each other as demonstrated by Equation (9)

\[
E_a = \Delta H^\ddagger + RT. \quad (9)
\]

All activation parameters for the reaction between reactants 1, 2 and 3 in the presence of a mixture of water and ethanol (50:50) are given in Table 4.

Pre-exponential factor \(A\) is related to the activation entropy as follows:

\[
A = \left( \frac{k_B}{h} \right) \exp \left( \frac{\Delta S^\ddagger}{R} \right). \quad (10)
\]

Since \(\ln A\) from an Arrhenius plot for a given reaction is less than 30.05, this corresponds to a large negative value for \(\Delta S^\ddagger\); herein, the recent work (see Table 4) and other experimental works \([53,54]\) confirm it. \(\ln A\) and \(\Delta S^\ddagger\) give information about the degree of order in the transition state, low values of \(\ln A\) correspond to the large negative values of \(\Delta S^\ddagger\) which indicate that the activated complex in the transition state has a more ordered or more rigid structure, which often alludes to an associative mechanism.

The values of \(\Delta H^\ddagger\) are positive, meaning energy is consumed in the process. In addition, because the values of \(\Delta H^\ddagger\) in the mentioned reaction are bigger than the \(T\Delta S^\ddagger\), then the reaction is enthalpy-controlled \([53,54]\).

### 5. Effect of solvents

Solvents may affect the reaction rate that can be explained on the basis of the transition state theory. In essence, the reaction rate is influenced by differential solvation of the starting material and transition state by the solvent. So, to find the solvent effect, a different mixture of methanol and water (methanol/water, 1:1) and a mixture of ethanol and water (ethanol/water, 50:50) are considered.
1:1) have been used in the experiment. The results showed that the rate of the reactions speed up in solvents with high dielectric constants [methanol/water, 1:1(ε = 57.5)] compared to those with lower dielectric constant [ethanol and water (ε = 52)] at all temperatures investigated (Table 3). This means that at the RDS, the activated complex must have more charges than the reactant. Therefore, the solvent stabilizes the activated complex more than the reactant.

6. Determination of RDS

Utilizing the above result, the simplified scheme of the proposed reaction mechanism (Figure 1) is shown in Figure 12.

On the basis of the suggested mechanism, several possibilities for the RDS and the general rate laws were acquired (listed in Table 5). The below instructions and rules were applied for the determination of the rate laws:

(1) If one step was considered as a RDS, certainly the previous step is a reversible process.

(2) The steady-state approximation was used to derive a rate law.

Some of the above rate laws [Rate_{mech}] when step2 and step3 are considered as RDS have very low probability that has been discussed below.

(1) If step3 is considered as a RDS, Equation (13) indicates the relevant rate law as Rate_{mech} which is not in agreement with the experimental rate law Rate_{exp} or Equation (5). Thus, step3 (k3) could not be accounted as a RDS, because the experimental rate law is a second-order kinetics, but the rate law from the mechanism on the basis of step3 as a RDS is a third-order kinetics.

(2) If Step2 (k3) is considered as a RDS, even though there is good agreement between Equation (12) [Rate_{mech}] and Equation (5) [Rate_{exp}], this step is a dissociative mechanism while the experimental data (Table 4, ∆S^‡ ≪ 0) indicate an association process. Therefore step2 is not a good candidate for RDS.

(3) Step1 (Figure 1) with a few factors has a good chance for being a RDS:

(a) This step obeys an associative mechanism which is confirmed by the negative value of ∆S^‡ (Table 4).

(b) There is good agreement between the experimental rate law [Equation (5), Table 5] and that obtained on the basis of the mechanism [Equation (11), Table 5].

(c) This step is compatible with the solvent studies on the reaction rate.

6.1. Effect of catalysts

In order to provide further information, we have reported the kinetic results of the reaction between 1, 2 and 3 compounds in the presence of other catalysts such as saccharose. Herein, the reactions are second-order with both catalysts (sodium acetate and saccharose) and the kinetic results are reported in Table 6.

Table 5. All possibilities for the RDS of the proposed mechanism.

| RDS   | Equation | Rate_{mech} | Rate_{exp} [Equation (5)] | k_{obs} |
|-------|----------|-------------|--------------------------|---------|
| Step1 | (11)     | Rate_{mech} = k_1[cat][1][2] | Rate_{exp} = k_{obs}[1][2] | k_1[cat] |
| Step2 | (12)     | Rate_{mech} = k_2k_3[cat][1][2] / (k_2 + k_1) | Rate_{exp} = k_{obs}[1][2] | k_2k_3[cat] / (k_1 + k_3) |
| Step3 | (13)     | Rate_{mech} = k_1k_3[cat][1][2][3] / (k_2[H_2O]) | Rate_{exp} = k_{obs}[1][2] | k_1k_3[cat] / (k_2[H_2O]) |

Figure 12. Simplified scheme of Figure 1 for the proposed reaction mechanism.
The rate of reaction in the presence of saccharose is higher than sodium acetate. Saccharose can establish hydrogen bonding with an oxygen atom in benzaldehyde; therefore, benzaldehyde becomes more active in the presence of saccharose and it will be more active for the nucleophilic attack of the aniline compound. Sodium acetate is a strong electrolyte which dissociates completely in the solution. Both sodium and acetate ions become more strongly hydrated in an aqueous solution and their mobility and ability decrease, so the catalytic activity of sodium acetate becomes smaller than saccharose. The activation energy and parameters (activation energy and parameters ($E_a$)) for the reaction between reactants 1, 2 and 3 are reported in Table 7 in the presence of saccharose as a catalyst. Herein, the value of $\Delta S^\ddagger$ in the presence of saccharose is a large and negative more than that obtained in the presence of sodium acetate (Table 4). This again demonstrates the truth of an associative mechanism for step1 of the reaction mechanism. It seems that the non-ionic catalyst such as saccharose tends to reduce the hardness of the reaction media in comparison with the ionic catalyst (sodium acetate). Thus, MCRs such as a β-aminoketones from the reaction among benzaldehyde 1, acetophenone 3 and aniline 2 promote more easily in the presence of a non-ionic catalyst.

### Table 6. $k_{obs}$ (min$^{-1}$ M$^{-1}$) for the reaction among 1, 2 and 3 at different temperatures in the presence of different catalysts in a mixture of ethanol/water.

| T (K) | Sodium acetate | Saccharose |
|-------|----------------|------------|
|       | $k_{obs}$     | $\sigma$  | $k_{obs}$ | $\sigma$  |
| 283.15| 20$^{(a)}$     | 0.011$^a$ | 33.52$^{(a)}$ | 0.015$^a$ |
| 288.15| 25.1$^{(a)}$   | 0.009$^a$ | 39.33$^{(a)}$ | 0.012$^a$ |
| 293.15| 30.2$^{(a)}$   | (0.013)$^a$ | 41.21$^{(a)}$ | (0.013)$^a$ |
| 298.15| 40.1$^{(a)}$   | (0.005)$^a$ | 48.68$^{(a)}$ | (0.010)$^a$ |
| 303.15| 62.1$^{(a)}$   | (0.015)$^a$ | 70.06$^{(a)}$ | (0.011)$^a$ |

(a)Standard deviation.

### Table 7. Activation parameters ($\Delta H^\ddagger$, $\Delta G^\ddagger$, $\Delta S^\ddagger$ and $E_a$) for the reaction between reactants 1, 2 and 3 in the presence of saccharose as a catalyst.

| $\Delta H^\ddagger$ (kJ mol$^{-1}$) | $\Delta G^\ddagger$ (kJ mol$^{-1}$) | $\Delta S^\ddagger$ (J mol$^{-1}$ K$^{-1}$) | $T\Delta S^\ddagger$ (kJ mol$^{-1}$) | $E_a$ (kJ mol$^{-1}$) | $E_v$ (kJ mol$^{-1}$) | $A$ |
|-------------------------------------|-------------------------------------|-------------------------------------|-------------------------------------|-----------------|-----------------|------|
| 21.63$^c$ ± 0.78                   | 65$^c$ ± 1.54                       | −139$^c$ ± 2.69                     | 41.42$^c$                           | 24.16$^c$       | 24.11$^c$ ± 0.78 | 8.9 × 10$^5$ |
| 21.95$^c$ ± 0.89                   | 63$^c$ ± 1.27                       | −138 3.09                           | 41.12$^c$                           | 24.44$^c$       |                 |      |

The kinetic investigation of the reactions between aniline 2, benzaldehyde 1 and acetophenone 3 in the presence of a catalyst (sodium acetate) was undertaken using the UV–vis spectrophotometry technique. The results can be summarized as follows:

1. It was found that the overall reaction order belonged to second-order kinetics and the reaction order with respect to benzaldehyde 1, aniline 2 and acetophenone 3 were one, one and zero, respectively.
2. The rate of reaction increases at a higher temperature which is in good agreement with the Arrhenius equation.
3. Activation parameters ($\Delta H^\ddagger$, $\Delta S^\ddagger$ and $\Delta G^\ddagger$) have been calculated using the Eyring equation.
4. The rate of the overall reaction increases in solvents with higher dielectric constants, so at the RDS, the activated complex must have more charges than the reactant. Therefore, the solvent stabilizes the activated complex more than the reactant; making step1 of the reaction mechanism compatible with the solvent study.
5. Based on the experimental data, the first step of the suggested mechanism was identified as a RDS ($k_1$) and this was confirmed by the steady-state assumption, the values of the activation parameters and the experimentally determined solvent effects on the rate of the reaction.
6. Negative values of $\Delta S^\ddagger$ suggest that entropy decreases upon achieving the transition state, which often indicates an associative mechanism, making step1 an associative process.
7. Herein, the magnitude of $\Delta H^\ddagger$ is larger than $(T\Delta S^\ddagger)$; therefore, the reaction is enthalpy-controlled.
8. The reaction was preceded more easily in the presence of a non-ionic catalyst such as saccharose.

#### Acknowledgements

Authors sincerely thank Sistan and Baluchestan University for providing the support of this work.

#### Disclosure statement

No potential conflict of interest was reported by the authors.
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