Conversion of Fructose to 5-Hydroxymethyl Furfural: Mathematical Solution with Experimental Validation

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Conversion of fructose to furan aldehydes is a rapidly developing concept considering the emergent scenario of the replacement of fossil-derived components to biomass-derived green precursors. 5-hydroxymethyl furfural (HMF) and levulinic acid (LA) are the two most important bio-precursors with expanded downstream utilization in modern industries. Therefore, their simulated optimization is an important tool that can help for process optimization in an economical way. In this article, we have developed a mathematical solution for fructose conversion, HMF production, and levulinic acid (LA) formation in a reactive environment. The accuracy of the developed model is further verified through experiments and found satisfactory with high accuracy. Therefore, the developed model can be used to simulate the reaction environment and product optimization under a given set of conditions.

1. Introduction

The alarming phenomena of global warming and environmental pollution have compelled individuals to shift production processes from fossil-derived to C-neutral feedstock [1–3]. Hence, this compelling problem has expounded the use of lignocellulosic biomass as an efficient and green alternative [4–6]. Lignocellulosic biomass, in this regard, is an abundantly available natural resource of carbohydrates, which is extensively available as forest residues, agricultural waste, and in the form of macro/microalgae [7, 8]. This paradigm shift explored the comprehensive dissolution and fractionation of lignocellulosic biomass to polysaccharides and monosaccharides for further conversion into different downstream expedient commodity chemicals [9–11]. Fructose is the simplest C6 sugar which is obtained by the hydrolysis of cellulose, the major constituent of lignocellulosic biomass [6, 12]. Fructose is versatile platform sugar that has extended utilization due to its biodegradability, environmentally friendly characteristics as well as abundant availability in nature [13, 14]. A long range of different biochemicals can be produced from fructose by employing multiple catalytic routes [15, 16]. Extensive experimental work has been performed on the catalytic
conversion of fructose to 5-hydroxymethyl furfural (HMF) and levulinic acid (LA) [15–17]. In our previous study, it was concluded experimentally that the reaction steps involved in the conversion of fructose are (i) dehydration of fructose to 5-hydroxymethyl furfural and (ii) rehydration of produced HMF to LA and formic acid (FA) consuming two H₂O molecules under a protonic environment, as shown in Scheme 1 [18]. However, the formation of HMF and LA/FA depends strongly on the reaction environment. The proton concentration [H⁺], in particular, plays a significant role with strong temperature dependency.

Experimental research is time-consuming and requires extensive financial support [19–21]. To address such challenges, the reaction environment can be optimized using artificial intelligence by developing a similar computational environment [22–26]. Computational analysis is an economical and efficient approach to solving many time-consuming problems [27–30]. Optimized parameters achieved during computational investigations can be used for the performance of experimental work [31, 32]. A reliable balance between computational and experimental results will help to develop a process with less energy and financial affliction [13, 33–35]. However, the computational study needs detailed kinetic data and mathematical modeling for the establishment of a reaction environment similar to experimental conditions [23, 36]. HMF and LA are the two most important bioprecursor components [37, 38]. These can be produced by the catalytic dehydration of C6 sugars under a protonic environment (Scheme 1). Although extensive experimental work has been performed for the conversion of fructose to HMF and LA/FA, however, commercial production of HMF has not been realized yet [39–41]. Mathematical modeling and kinetic data evaluation will help to establish a computational reaction environment for the conversion of fructose to HMF and LA/FA.

Based on this motivational aspect, we have developed a comprehensive kinetic model to sketch the reaction process based on our experimental work [18]. A detailed mathematical model is developed considering the established reaction sequence and reaction stoichiometry. Employing kinetic and mathematical modeling, the theoretical solution of reaction species is developed which will help to establish a real reaction environment in a computational framework. The developed model will help to optimize the dehydrated conversion of lignocellulosic biomass-derived sugar to platform chemicals. This model can be used as a base tool to develop a reaction network model for other sugars, which will ultimately help to convert lignocellulosic biomass to platform chemicals. Replacing the feedstock fructose with other sugars, the same model can be used to elaborate the reaction environment of conversion of various C5 and C6 sugars.

2. Kinetic Modeling

It has been observed that the conversion of fructose proceeded through the dehydration of fructose to HMF followed by the rehydration to LA/FA as shown in Scheme 1 [18]. The mechanistic step took place by the removal of one water molecule in each step under a protonic environment as shown in Scheme 2.

Hence, the first step is dehydration of fructose to HMF.

\[
C_6H_{12}O_6 \xrightarrow{H^+} C_6H_6O_3 + 3H_2O \quad (1)
\]

Accordingly, this conversion of fructose to HMF does not proceed in a single step but proceeded through three elementary reactions with the removal of one water molecule in each step as follows:

\[
\begin{align*}
C_6H_{12}O_6_{(sol)} \xrightarrow{k_1^{+}} & [C_6H_{10}O_5]_{(sol)} + H_2O \\
[C_6H_{10}O_5]_{(sol)} \xrightarrow{k_2^{+}} & [C_6H_6O_4]_{(sol)} + H_2O \\
[C_6H_6O_4]_{(sol)} \xrightarrow{k_3^{+}} & [C_6H_6O_3]_{(sol)} + H_2O
\end{align*}
\]

whereas the second step is the hydration of HMF to LA and FA with the consumption of two water molecules.

\[
C_6H_6O_3_{(sol)} + 2H_2O \xrightarrow{k_4^{+}} CH_2O_2 + C_6H_4O_3 \quad (3)
\]

Again, the consumption of two water molecules for the conversion of HMF to LA/FA does not proceed in a single step as shown in Scheme 2. Instead, rehydration proceeded through the following elementary steps:

\[
\begin{align*}
C_6H_6O_3_{(sol)} + H_2O \xrightarrow{k_1^{+}} [C_6H_6O_4]^{+}_{(sol)} \\
[C_6H_6O_4]^{+}_{(sol)} + H_2O \xrightarrow{k_2^{+}} [C_6H_{10}O_5]^{++}_{(sol)} \\
[C_6H_{10}O_5]^{++}_{(sol)} \xrightarrow{k_3^{+}} CH_2O_2 + C_6H_6O_3
\end{align*}
\]

Besides this principal route, fructose degrades through some side reactions yielding unproportioned products. Similarly, the nascent HMF is also degraded sometimes through dimerization or some other nonstoichiometric reactions. All these products are summarized as humin [42, 43]. Therefore, the formation of humin from fructose and HMF can be represented as follows:

\[
C_6H_{12}O_6 \xrightarrow{k_4^{+}} HUMIN \quad (5)
\]

\[
C_6H_6O_3_{(sol)} \xrightarrow{k_4^{+}} HUMIN \quad (6)
\]

Following the principles of elementary reactions defined by Espenson and O. Levenspiel [44, 45], the mechanistic elementary reactions of fructose conversion to HMF are as shown in equation (1). HMF conversion to LA/FA is as shown in equation (3) and formation of Humin from fructose as well as from freshly produced HMF can be summarized as shown in equations (7) to (10). [40, 46].
where $C$ represents the molar concentration, $F$ is fructose, $H$ is humin, and HMF is 5-hydroxymethyl furfural. $k_1$, $k_2$, $k_3$, and $k_4$ represent the rate constants as shown in Scheme 1.

### 3. Mathematical Modeling

Fructose concentration decreases with time as the reaction proceeds. The instantaneous concentration of fructose can be calculated with the integration of the rate equation with respect to time $t$ [44, 45, 47]. Hence, from equation (7),
\[ \frac{dC_F}{dt} = (k_1 + k_2)C_F, \]  
\[ \frac{1}{C_F} \frac{dC_F}{dt} = (k_1 + k_2). \]  

Integrating from the start of the reaction to time interval \( t \), i.e., between \( t = 0 \) to \( t = t \),

\[ \int^t_0 \frac{dC_F}{C_F} = -(k_1 + k_2) \int^t_0 dt, \]

\[ \ln \left( \frac{C_{F(t)}}{C_{F(0)}} \right) = -(k_1 + k_2)t, \]

\[ \left( \frac{C_{F(t)}}{C_{F(0)}} \right) = e^{-(k_1 + k_2)t}, \]

\[ C_{F(t)} = C_{F(0)} e^{-(k_1 + k_2)t}. \]

Hence, equation (12) represents the analytical solution of fructose concentration. The concentration of fructose at any time \( t \) can be calculated using this equation (12). Here, \( C_{F(t)} \) is the concentration of fructose at a time \( t \), \( C_{F(0)} \) is the initial fructose concentration when \( t = 0 \), \( k_1 \) and \( k_2 \) are rate constants as shown in Scheme 1, and \( n \) is the time of reaction.

Similarly, the instantaneous concentration of HMF can be calculated by the analytical solution of equation (8) implying time limits similar to the fructose equation (7). Hence, from equation (8),

\[ r(t) = k_1 CF = k_1 CF e^{-(k_1 + k_2)t}, \]

\[ \int^t_0 r(t)e^{A(t)} dt = \int^t_0 k_1 C_{F(0)} e^{-(k_1 - k_2 + k_3 + k_4)dt} \]

\[ = \frac{k_1 C_{F(0)}}{(-k_1 - k_2 + k_3 + k_4)} \left( e^{-(k_1 - k_2 + k_3 + k_4)t} - 1 \right), \]

\[ y_S = \frac{k_1 C_{F(0)}}{(-k_1 - k_2 + k_3 + k_4)} \left( e^{-(k_1 + k_2)t} - e^{-(k_1 + k_4)t} \right), \]

\[ C_{HMF(t)} = \frac{k_1 C_{F(0)}}{(-k_1 - k_2 + k_3 + k_4)} \left( e^{-(k_1 + k_2)t} - e^{-(k_1 + k_4)t} \right) + C_{HMF(0)} e^{-(k_1 + k_4)t}, \]

\[ C_{HMF(t)} = \left[ \frac{k_1 C_{F(0)}}{(-k_1 - k_2 + k_3 + k_4)} \left( e^{-(k_1 - k_2 + k_3 + k_4)t} - 1 \right) + C_{HMF(0)} \right] e^{-(k_1 + k_4)t}. \]

equation (16) represents the analytical explanation for HMF yield concentration. HMF concentration can be calculated using this equation at any time interval \( t \) during a reaction. Through equations (12) and (16), the concentration profiles of reactant (fructose) and product (HMF) can be developed through simulation. In these models, we have the following assumptions:

(a) The process is acid-catalysed and \([H^+]\) is unchanged during the time course of a reaction

(b) The reaction is assumed to proceed at a fixed temperature

(c) All the unproportioned products are summarized as humin (H)
4. Experimental Evolution

Based on these developed models, a control experiment was performed in the laboratory. Oxalic acid was selected as a weak organic acid and p-toluenesulfonic acid (pTSA) as a strong organic acid. Water was selected as a reaction solvent due to its excellent sugar solvation capacity and recognition as a universal solvent; hence, selectively adopted as a solvent in organic reactions. The reaction was proceeded for a long enough time to determine the reaction parameters with high accuracy. The experimental data were used to calculate the kinetic parameter employing developed models in MATLAB and presented here in Table 1. With the help of these predicted values, a dynamic simulation of this process was performed. Results thus obtained are then compared with experimental results in Figure 1 and Figure 2 for oxalic acid-catalysed reaction and pTSA catalysed reaction, respectively. Here, the lines are showing the simulated values and symbols are representing experimental results.

Figure 1 elucidates a good relationship between experimental results and model-predicted values. Briefly, there is a difference between model-predicted values and experimental results for fructose conversion and humin formation in the first 120 minutes. This is because of intermediate formation (as shown in Scheme 2). Here, all the unaccounted species formed through different side reactions (condensation, polymerization, and degradation) are termed as humin and calculated by mass difference [48]. Therefore, all the intermediates, whether desired or undesired, were accounted as humin which made the difference. After the first two hours, a good relationship exists for fructose conversion as well as for humin formation. However, for HMF and LA formation, a satisfactory balance can be observed in Figure 1 which proved the model’s accuracy and applicability. Additionally, the linear comparison of experimental results and modeled predicted values shows high goods of fit as all the R$^2$ values are >0.9 (Table 1). Hence, it can be validated that the developed model is appropriate for fructose conversion reactions influenced by weak acids.

It can be observed from Figure 2 that there is a high difference between the experimental value and model-predicted results during the first hour of the reaction, which rapidly decreased in the second hour. After two hours, both values coincide and show high accuracy. However, an overlap of experimental results and model values can be observed for HMF production and LA formation throughout the reaction similar to the oxalic acid-catalysed process (Figure 1). This proved the developed model accuracy for relatively strong acid (pTSA) catalysed fructose conversion reaction. Hence, it can be validated that the developed is equally applicable to both for strong acid as well as for weak acid-catalysed sugar conversion reactions. Kinetic investigation of the conversion of sucrose solution to HMF employing homogenous catalysts was performed by Abdilla-Santes et al. [49]. The hydrolysis of sucrose yields equimolar concentrations of glucose and fructose. These sugars are then dehydrated to HMF. Therefore, sucrose conversion data are logical to compare with this study because fructose is a common dehydration feedstock in both reactions. It was observed during data analysis that most of the experimental data is comparable with modeled data. The only minor exception was observed with HMF formation during the first hour of the reaction [49]. This anomaly can be explained because the employed catalyst was mineral acid (H$_2$SO$_4$) which is more reactive at a reaction temperature of 180°C during the initial phase of the reaction. Overall, the tested model was accurate which was proved with high compatibility of experimental and modeled data-based parity plot. The results presented by Guo et al. [29] are as accurate as shown in this study; however, the catalyst used was again H$_2$SO$_4$ and the use of mineral acids as catalysts has severe environmental concerns [50]. Mostly, the use of environmentally friendly catalysts is the primary choice which can be achieved either using organic acid catalysts or

Table 1: Calculated kinetic parameters of organic acid-catalysed dehydration of fructose to HMF. The initial fructose and acid-catalyst concentrations were 1.0 M. The reaction was performed in 50 ml solvent for 3 hours with continuous stirring.

<table>
<thead>
<tr>
<th>Acid catalyst</th>
<th>Solvent</th>
<th>Temp (°C)</th>
<th>$k_1$ ($\times 10^{-3}$)</th>
<th>$k_2$ ($\times 10^{-3}$)</th>
<th>$k_3$ ($\times 10^{-3}$)</th>
<th>$k_4$ ($\times 10^{-14}$)</th>
<th>Fructose HMF LA Humin</th>
<th>Goodness of fit ($R^2$)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Oxalic acid</td>
<td>Water</td>
<td>100</td>
<td>$1.1 \times 10^{-3}$</td>
<td>$9.7 \times 10^{-4}$</td>
<td>$1.5 \times 10^{-3}$</td>
<td>$4.2 \times 10^{-14}$</td>
<td>0.9525</td>
<td>0.9849</td>
</tr>
<tr>
<td>pTSA</td>
<td>Water</td>
<td>100</td>
<td>$2.1 \times 10^{-3}$</td>
<td>$1.97 \times 10^{-3}$</td>
<td>$3.7 \times 10^{-3}$</td>
<td>$4.4 \times 10^{-13}$</td>
<td>0.9576</td>
<td>0.9247</td>
</tr>
</tbody>
</table>

Figure 1: Plots of oxalic acid-catalysed conversion of fructose in water solvent. Reaction conditions: 1.0 M oxalic acid with 1.0 M fructose in 50 ml deionized water; FUR: fructose; HMF: 5-hydroxymethylfurfural; LA: levulinic acid; HUM: humin.
recoverable heterogeneous catalysts [51, 52]. Therefore, this study was aimed to use organic acids catalysts to substitute mineral acids as a homogenous catalyst.

It can be observed that most of the model-predicted data are in satisfactory equilibrium with experimental data (Figures 1 and 2). Furthermore, the linear comparison between experimental concentrations with model-predicted values gives very high accuracy as all the $R^2$ values are $>0.9$. Hence, a good relationship with high $R^2$ proved the accuracy of this model. For that reason, this model can be used to predict the experimental outcomes with relatively high accuracy both for strong acids as well as for weak acids catalysed reactions.

5. Conclusions

Conversion of fructose can be optimized using a mathematical model prior to the experimental study. In this paper, an analytical solution for the instantaneous concentration of reacting fructose and products HMF has been developed using kinetic and mathematical modeling. These developed relationships can be used to determine the extent of reaction in a protonic [H$^+$] environment at any time ($t$) and for the development of concentration profiles in a computational environment. The developed models were further verified with a detailed experiment employing oxalic acid and $p$TSA as catalysts. The results are elucidated.

(i) The instantaneous concentration of reactant fructose can be calculated theoretically using $C_{F(t)} = C_{F(0)}e^{-(k_1+k_2)t}$.

(ii) The instantaneous concentration of product HMF can be calculated theoretically using $C_{HMF(t)} = (k_1C_{F(0)} / (-k_1 - k_2 + k_3 + k_4))(e^{-(k_1-k_2+k_3+k_4)t} - 1) + C_{HMF(0)}e^{-(k_1+k_4)t}$.

(iii) The comparison analyses of experimental data with modeled predicted values elucidated that the developed model is accurate to predict the concentrations because all the values of $R^2$ are $>0.9$. Hence, it can be validated that the developed solutions are a good tool to predict the reaction outcomes.

(iv) This model can be used to demonstrate the actual computational environment and reaction behavior during fructose conversion schemes.

(v) This model can be used as a baseline to develop the new specific models for the elaboration of lignocellulosic biomass-derived sugars (C5 and C6) and their derivatives to useful platform chemicals. Further extension of these models will help to demonstrate the computational environment of biomass-derived disaccharides and polysaccharides. Additionally, the model can be extended to elaborate the effect of reaction temperature on concentration profiles of reactants, intermediates, and products.

Data Availability

The required data are included in the manuscript.

Conflicts of Interest

The authors declare that they have no conflicts of interest to report regarding the present study.

Authors’ Contributions

Muhammad Sajid, Apu Chowdhury, and Riaz Ahmad conceptualized the study. Muhammad Sajid, Ghulam Bary, and Ilyas Khan developed methodology. Muhammad Sajid, Yin Guoliang, and Riaz Ahmad were responsible for formal analysis. Muhammad Sajid, Waqar Ahmed, and Apu Chowdhury investigated the study. Muhammad Sajid, Yin Guoliang, and Ghulam Bary were responsible for data curation. Muhammad Sajid, Riaz Ahmad, and Muhammad Farooq Saleem Khan prepared the original draft. Muhammad Sajid, Aisha M. Alqahtani, and Md. Nur Alam reviewed and edited the manuscript. Md. Nur Alam, Muhammad Farooq Saleem Khan, and Ilyas Khan supervised the study. Aisha M. Alqahtani and Ilyas Khan were responsible for project administration. Md. Nur Alam and Aisha M. Alqahtani were responsible for funding acquisition. All authors have read and agreed to the published version of the manuscript.

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