Kinetic Study of Cyclocondensation Reaction in Acetic Acid, Yielding 3, 4 Dihydropyrimidines

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Abstract: The kinetics of cyclocondensation of aromatic aldehydes, 1,3 dicarbonyls and urea/thiourea has been investigated. The kinetic measurements have been carried using spectrophotometric technique. The reaction is found to be first order with respect to aromatic aldehyde and first order with respect to urea. Hence over all order of reaction is found to be two, which is in good agreement with rate law. The effect of substituents on the rate of the cyclocondensation and the thermodynamic parameters are also evaluated. The reaction products have been isolated and characterized. The probable mechanism of the cyclocondensation leading to 3, 4 dihydropyrimidines has been proposed and on that basis rate expression has been derived.

Keywords: 3, 4 dihydropyrimidines, cyclocondensation reaction, kinetic study, pharmacophore.

I. Introduction
Dihydropyrimidinones have been paid increasing attention due to their various therapeutic and pharmacological properties, such as antiviral\(^1\) and antibacterial\(^2\), antihypertensive\(^3\), antitumor\(^4\), antimalarial\(^5\). Most recently they have emerged as integral backbone of several calcium blockers, \(\alpha\)-1a-antagonists and neuropeptide Y (NPY) antagonist\(^6,7\). Dihydropyrimidinone derivatives are found as core units in many marine alkaloids like Batzalladine and Carambine, which have potent HIV-gp 120 CD4 inhibitory property\(^8\).

Due to the importance of multi component reactions in the combinatorial chemistry and the interesting pharmacological properties associated with dihydropyrimidinones structure, the reaction has received increasing attention and its scope has now extended considerably by variation of all three building blocks. Thus, several modified and improved procedures have been reported\(^11-13\). Literature survey revealed that considerable attention has not been paid on the kinetic study of this type of cyclocondensation. In view of the above observations and considering the synthetic utility of dihydropyrimidinones, it was therefore decided to carry out the kinetic study of dihydropyrimidinones to optimize the synthesis parameters.

II. Experimental

The dihydropyrimidinones were synthesized using reported procedure\(^14-17\) carrying one pot cyclocondensation of aromatic aldehydes, ethylacetooacetate and urea. Aldehydes used in the work were benzaldehyde, 4-methoxy benzaldehyde, 4-chloro benzaldehyde and 4-nitro benzaldehyde.(Scheme I) Solvent, catalyst and reagents were obtained from S.D fine chemicals of HPLC/AR standard and were purified further by literature procedure\(^18,19\). The products obtained were crystallized from ethanol and the melting points of these 3, 4 dihydropyrimidinones were determined and were in good agreement with those reported in the literature\(^20,21\). Table 1 gives the physical data of dihydropyrimidinones.

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III. Kinetic Measurements

In the present work we have measured the extent of the cyclocondensation by spectrophotometric method using UV-1601 SHIMADZU spectrophotometer, determining concentration of dihydropyrimidinones. A high precision thermostatic oil bath was used to carry the cyclocondensation. The accuracy of the reaction temperature was about ±0.1 °C.

Solutions of the aldehydes (20 ml) of the known molarity containing was transferred in 100ml two necked round bottom flask. The combined solution of ethylacetoacetate and urea [20 ml] of the known concentration was taken in the standard flask. Both the flasks were then allowed to stand in thermostatic oil bath to attain the required temperature. Then the content of the standard flask was completely transferred to the round bottom flask containing aldehyde solution. The obtained reaction mass was thoroughly stirred and heated in thermostatic oil bath at the required temperature. At different time intervals, fixed volume (0.4 ml) aliquot was removed from the reaction mass, and diluted with alcohol to achieve the measurable concentration. The obtained diluted solution was employed to determine optical density (absorbance) at appropriate λmax of the generated dihydropyrimidinones.

From this optical density the concentration (x) of dihydropyrimidinones formed at particular time was determined with the help of the standard/reference plot of the respective dihydropyrimidinones.

IV. Result and Discussion

The stoichiometric study indicates that when a mixture of one mole of aldehyde, one mole of urea and one mole of ethylacetoacetate allowed to react gave 1 mol of product (Dihydropyrimidinones). The reaction rates were determined at different concentrations of aldehyde by keeping concentration of urea and ethylacetoacetate constant. (Table 2) The plot of dx/ dt against log C_{ald} [Fig: 1] found to be linear and slope of plot is nearly one. Similarly rates were determined at different concentrations of urea keeping concentrations of aldehydes and ethylacetoacetate constant. (Table 3) The plot of dx/dt against log C_{urea} [Fig: 2] found to be also linear and slope of plot is nearly one. The order of reaction was also determined with respect to aldehydes and urea by using Van’t Hoff’s differential method. Kinetic measurements were carried out at equal concentration of the reactants at four different temperatures in acetic acid, Table 4. The activation energy (Ea) is determined from the slope of Arrhenius plot of log k Vs 1/T [Fig:3] and other thermodynamic parameters are computed in Table 5.

Table 2: Rate constant at different concentrations of aldehydes with 0.1M urea and 0.1M EAA (k×10^{-3} dm^3 mol^{-1} sec^{-1})

<table>
<thead>
<tr>
<th>Aldehyde</th>
<th>0.1M</th>
<th>0.0875M</th>
<th>0.075M</th>
<th>0.0625M</th>
<th>0.05M</th>
</tr>
</thead>
<tbody>
<tr>
<td>Benzaldehyde</td>
<td>3.002</td>
<td>2.513</td>
<td>2.259</td>
<td>2.017</td>
<td>1.637</td>
</tr>
<tr>
<td>4-MeO-benzaldehyde</td>
<td>7.614</td>
<td>5.471</td>
<td>4.186</td>
<td>3.362</td>
<td>2.424</td>
</tr>
<tr>
<td>4-Cl-benzaldehyde</td>
<td>2.351</td>
<td>1.721</td>
<td>1.518</td>
<td>1.238</td>
<td>1.107</td>
</tr>
<tr>
<td>4-NO_2-benzaldehyde</td>
<td>2.09</td>
<td>1.733</td>
<td>1.436</td>
<td>1.207</td>
<td>0.1075</td>
</tr>
</tbody>
</table>
Table 3: Rate constant at different concentrations of urea with 0.1M aldehyde and 0.1M EAA (k×10^{-3} dm^3 mol^{-1} sec^{-1})

<table>
<thead>
<tr>
<th>Aldehyde</th>
<th>0.1M</th>
<th>0.0875M</th>
<th>0.075M</th>
<th>0.0625M</th>
<th>0.05M</th>
</tr>
</thead>
<tbody>
<tr>
<td>Benzaldehyde</td>
<td>3.002</td>
<td>2.82</td>
<td>2.539</td>
<td>2.153</td>
<td>1.904</td>
</tr>
<tr>
<td>4-MeO-benzaldehyde</td>
<td>7.614</td>
<td>6.418</td>
<td>5.349</td>
<td>4.59</td>
<td>3.39</td>
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<tr>
<td>4-Cl-benzaldehyde</td>
<td>2.351</td>
<td>2.115</td>
<td>1.881</td>
<td>1.456</td>
<td>1.376</td>
</tr>
<tr>
<td>4-NO_2-benzaldehyde</td>
<td>2.09</td>
<td>1.828</td>
<td>1.644</td>
<td>1.474</td>
<td>1.286</td>
</tr>
</tbody>
</table>

Table 4: Rate constants of the reaction at different temperatures. (solvent Acetic acid)

<table>
<thead>
<tr>
<th>Name of aldehyde</th>
<th>k × 10^{-3} at 391K dm^3 mol^{-1} sec^{-1}</th>
<th>k × 10^{-3} at 386K dm^3 mol^{-1} sec^{-1}</th>
<th>k × 10^{-3} at 381K dm^3 mol^{-1} sec^{-1}</th>
<th>k × 10^{-3} at 376K dm^3 mol^{-1} sec^{-1}</th>
</tr>
</thead>
<tbody>
<tr>
<td>B.A.</td>
<td>3.002</td>
<td>2.587</td>
<td>1.688</td>
<td>1.343</td>
</tr>
<tr>
<td>4-MeO-B.A.</td>
<td>7.614</td>
<td>5.419</td>
<td>3.016</td>
<td>2.096</td>
</tr>
<tr>
<td>4-Cl-B.A.</td>
<td>2.351</td>
<td>1.969</td>
<td>1.391</td>
<td>1.098</td>
</tr>
<tr>
<td>4-NO_2-B.A.</td>
<td>2.09</td>
<td>1.64</td>
<td>1.2</td>
<td>1.02</td>
</tr>
</tbody>
</table>

Table–5 Thermodynamic parameters of the reaction. (Solvent - acetic acid)

<table>
<thead>
<tr>
<th>Name of aldehyde</th>
<th>Frequency Factor(A) Sec^{-1}</th>
<th>Energy of Activation (Ea) KJmol^{-1}</th>
<th>Enthalpy of activation (ΔH) KJmol^{-1}</th>
<th>Entropy of activation (ΔS) Jmol^{-1}</th>
<th>Free energy of activation (ΔG) KJmol^{-1}</th>
</tr>
</thead>
<tbody>
<tr>
<td>4-MeO-B.A.</td>
<td>2.570E+12</td>
<td>25.894</td>
<td>22.685</td>
<td>-231.726</td>
<td>112.1314</td>
</tr>
<tr>
<td>4-Cl-B.A.</td>
<td>9.638E+5</td>
<td>15.331</td>
<td>12.122</td>
<td>-267.51</td>
<td>115.381</td>
</tr>
<tr>
<td>4-NO_2-B.A.</td>
<td>2.168E+5</td>
<td>14.297</td>
<td>11.087</td>
<td>-271.711</td>
<td>115.9678</td>
</tr>
</tbody>
</table>

Fig. 1

\[
\text{log } \frac{dx}{dt} \text{ Vs log } \text{Cal} (\text{Acetic acid})
\]
The entropies of activation $\Delta S^\#$ for the cyclocondensation are all negative suggesting rigid nature of transition state and also support the conversion of non-cyclic reactants to cyclic products. The high values of entropy of activation indicate that activated complex is less probable. The high negative values of entropy of activation suggest that the reaction may occur between charge ions and neutral molecule and may generate rigid intermediate transition state resulting in slow rate of reaction. The low magnitude of $\Delta H^\#$ and high magnitude of $\Delta S^\#$ indicates that the reaction is entropy controlled. The low values of $\Delta H^\#$ also points out that in the rate determining activated complex the bond breaking and bond formation are of almost equal magnitude. Almost equal values of free energies $\Delta G^\#$ for all aldehydes indicates that probably a similar mechanism prevails in all cases.

When the rate constants for reactions are compared, Fig. 3: log $k$ Vs $1/T$ the relative order of substituted aldehydes used in the cyclocondensation is found to be:

$4$-methoxy-benzaldehyde $>$ benzaldehyde $>$ $4$-chloro-benzaldehyde $>$ $4$-nitro-benzaldehyde

This has also been reflected in Hammette plot where substituents in aldehydes have shown linear relationship. The withdrawing groups in the aldehydes would have been retarding the protonation of hydroxyl group of the intermediate of the first step making the rate of formation of the iminium intermediate slower. Therefore, in the case of nitro group in aldehydes the rate of reaction is found to be slower. When electron donating groups are present the rate of the formation of the iminium intermediate are faster as observed in case...
of 4-methoxy benzaldehyde. This may be because of resonance, the protonation of hydroxy of the intermediate of first step and successive elimination of water molecule would have been faster. This is also reflected in Hammette linear plot. The negative sign of ρ value indicates the development of the positive charge at reaction centre during formation of transition state in the rate limiting step of overall reaction. Consistent with above facts the following plausible mechanism has been proposed for the reaction. (Scheme I)

On the basis of the mechanism shown above the rate law expression has been derived as below
The product is formed in step 5. Hence the rate, \( \frac{dx}{dt} \) of the cyclocondensation is directly proportional to the concentration of \( I_4 \).

\[
\frac{dx}{dt} \propto [I_4] \quad \text{or} \quad \frac{dx}{dt} = k_7[I_4] \quad \ldots \ldots \quad (6)
\]

It is difficult to determine the concentration of intermediate \( I_4 \).

\[
\because \quad \text{It should be expressed in terms of measurable quantities.}
\]

Hence applying steady state condensation to \( I_4 \) which is formed in step-4 and removed in step-5

i.e. Rate of formation of \( I_4 = \) Rate of removal of \( I_3 \)

\[
k_6[I_3] = k_7[I_4]
\]

Substituting the value of \( I_4 \) in equation (6)

\[
\frac{dx}{dt} = k_6[I_3] \quad \ldots \ldots \quad (7)
\]

Being difficulty in determining the concentration of intermediate \( I_3 \), hence the steady state condensation is applied for \( I_4 \) which is formed in step-3 and removed in step-4

i.e. Rate of formation of \( I_3 = \) Rate of removal of \( I_1 \)

\[
k_5[I_2][E] = k_6[I_3]
\]

Substituting the value of \( I_3 \) in equation (7)

\[
\frac{dx}{dt} = k_5[I_2][E] \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad (8)
\]

Intermediate \( I_2 \) is not isolated and its concentration is determined by applying steady state condensation.

i.e. Rate of formation of \( I_2 = \) Rate of removal of \( I_1 \)

\[
k_5[I_1][H^+] = k_5[I_2][E] + k_4[I_2][H_2O]
\]

\[
[I_2] = \frac{k_5[E] + k_4[H_2O]}{k_5[I_1][H^+]} \]
Substituting the value of $I_2$ in equation (8)

$$\frac{dx}{dt} = k_5[E] \times \frac{k_3[I_1][H^+]}{k_5[E] + k_4[H_2O]}$$

Dividing the numerator and the denominator by $k_4[E]$ we get

$$\frac{dx}{dt} = \frac{k_3[I_1][H^+]}{1 + \frac{k_4[H_2O]}{k_5[E]}}$$

As \(\frac{k_4[H_2O]}{k_5[E]}<<1\)

Hence can be neglected

\[ \therefore \frac{dx}{dt} = k_3[I_1][H^+] \] (9)

It is difficult to determine the concentration of intermediate $I_1$

Hence applying steady state condensation to $I_1$ which is formed in step-1 and removed in step-2 i.e. Rate of formation of $I_1 = $ Rate of removal of $I_1$

\[ k_1[A][U] = k_3[I_1][H^+] + k_2[I_1] \]

\[ [I_1] = \frac{k_3[A][U]}{k_3[H^+] + k_2} \]

Substituting the value of $I_1$ in equation (9)

$$\frac{dx}{dt} = k_5[H^+] \times \frac{k_3[A][U]}{k_5[H^+] + [k_2]}$$

Dividing the numerator and the denominator by $k_3[H^+]$ we get

$$\frac{dx}{dt} = \frac{k_1[A][U]}{1 + \frac{k_2}{k_3[H^+]}}$$

$[H^+]$ is constant during the progress of the reaction.

Hence the term \(1 + \frac{k_2}{k_3[H^+]} = \) constant = $k'$

\[ \therefore \frac{dx}{dt} = \frac{k_1[A][U]}{k'} \]

Thus \(\frac{dx}{dt} \propto [A][U]^1\)

This indicates that the cyclocondensation is first order with respect to aldehydes $[A]$, and with respect to urea $[U]$. Thus over all order of condensation is second.

Hence theoretically derived rate law expression on the basis of proposed mechanism is in good agreement with the experimental results.

Abbreviations used in mechanism and rate expression are

| Aldehyde = A | Urea = U |
| Ethylacetoacetate = E | Dihydropyrimidine (product) = P |
| Intermediates = $I_1, I_2, I_3, I_4$ | Constants = $k_1, k_2, \ldots, k_7, k'$ |

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