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Kinetic Study ofCyclocondensation Reaction in Acetic Acid, Yielding 3, 4 Dihydropyrimidines

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Abstract:*The kinetics of cyclocondensation of aromatic aldehydes, 1,3dicarbonyls 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 dihydropyridines has been proposed and on that basis rate expression has been derived.*

Keywords*: 3, 4 dihydropyridines, cyclocondensation reaction, kinetic study, pharmacophore.*

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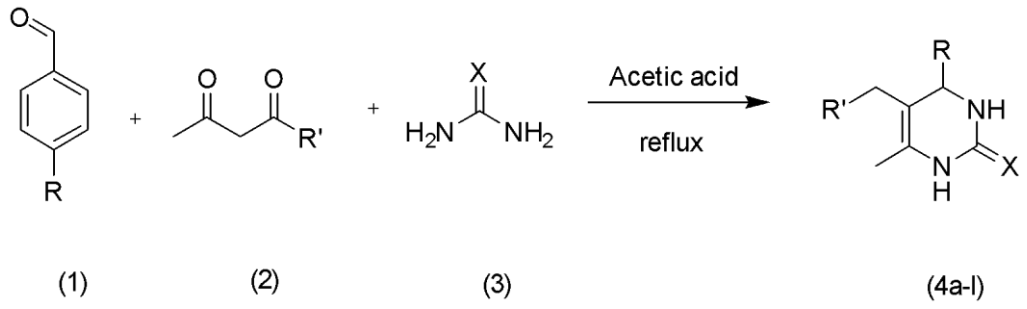
I. Introduction

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, α-1a-antagonists and neuropeptide Y (NPY) antagonist[6-9]. Dihydropyrimidinone derivatives are found as core units in many marine alkaloids like Batzalladine and Carambine, which have potent HIV-gp 120 CD4 inhibitory property[10].

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, ethylacetoacetate 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.



(1) (2) (3) (4a-l)

Scheme I

Table: 1

Physical data of 3, 4-dihydropyrimidinones

Product	R	R'	X	M.P[a] °C	Yield[b] (%)
4a	-H	$-OC_2H_5$	O	203-205	85
4b	$-OCH_3$	$-OC_2H_5$	O	201-203	89
4c	-Cl	$-OC_2H_5$	O	212-214	84
4d	$-NO_2$	$-OC_2H_5$	O	206-208	83

III. Kinetic Measurements

In the present work we have measured the extend 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 stoichemetric 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 ethylacetoacetateconstant.(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 ($k\times 10^{-3}$ $dm^3mol^{-1}sec^{-1}$)

Aldehyde	0.1M	0.0875M	0.075M	0.0625M	0.05M
Benzaldehyde	3.002	2.513	2.259	2.017	1.637
4-MeO-benzaldehyde	7.614	5.471	4.186	3.362	2.424
4-Cl-benzaldehyde.	2.351	1.721	1.518	1.238	1.107
4-NO_2-benzaldehyde	2.09	1.733	1.436	1.207	0.1075

Table 3: Rate constant at different concentrations of urea with 0.1M aldehyde and 0.1M EAA ($k\times 10^{-3}$ $dm^3mol^{-1}sec^{-1}$)

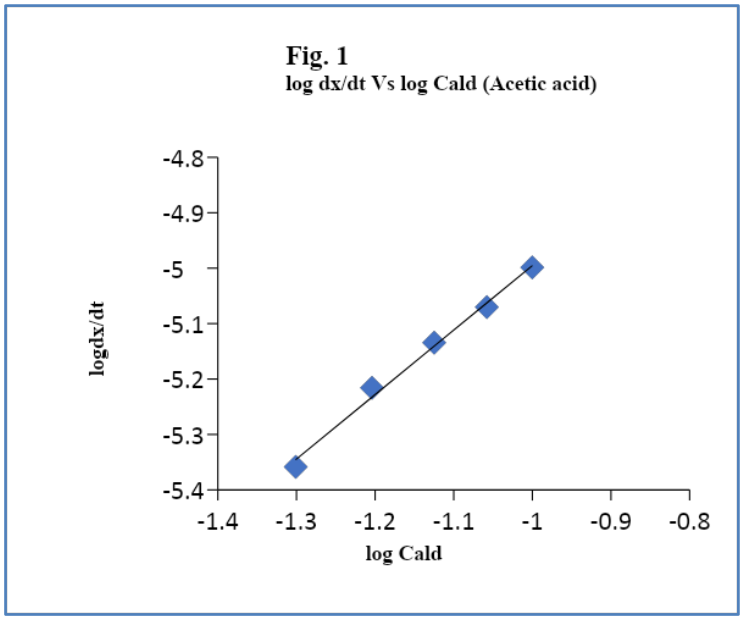
Aldehyde	0.1M	0.0875M	0.075M	0.0625M	0.05M
Benzaldehyde	3.002	2.82	2.539	2.153	1.904
4-MeO-benzaldehyde	7.614	6.418	5.349	4.59	3.39
4-Cl-benzaldehyde.	2.351	2.115	1.881	1.456	1.376
4-NO_2-benzaldehyde	2.09	1.828	1.644	1.474	1.286

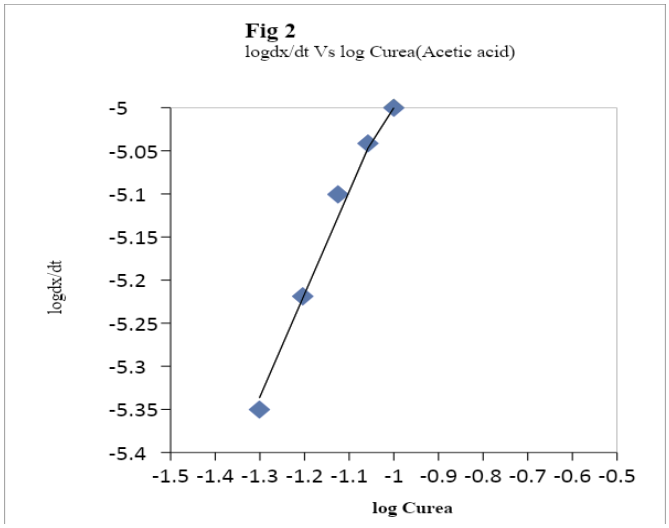
Table 4: Rate constants of the reaction at different temperatures. (solvent Acetic acid)

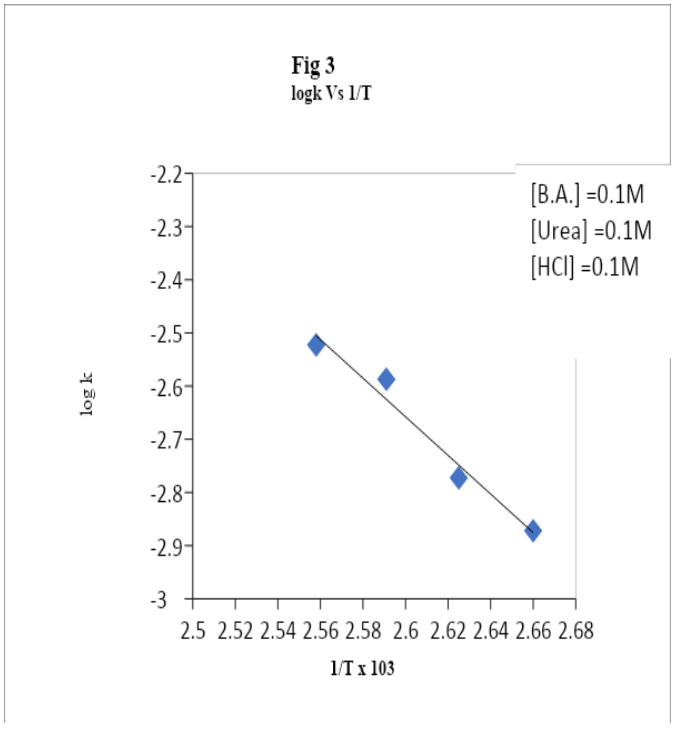
Name of aldehyde	$k \times 10^{-3}$ at 391K $dm^3mol^{-1}sec^{-1}$	$k \times 10^{-3}$ at 386K $dm^3mol^{-1}sec^{-1}$	$k \times 10^{-3}$ at 381K $dm^3mol^{-1}sec^{-1}$	$k \times 10^{-3}$ at 376K $dm^3mol^{-1}sec^{-1}$
B.A.	3.002	2.587	1.688	1.343
4-MeO-B.A.	7.614	5.419	3.016	2.096
4-Cl-B.A.	2.351	1.969	1.391	1.098
4-NO_2-B.A.	2.09	1.64	1.2	1.02

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

Name of aldehyde	Frequency Factor(A) Sec^{-1}	Energy of Activation $(Ea)^{\#}KJmol^{-1}$	Enthalpy of activation $(\Delta H)^{\#}KJmol^{-1}$	Entropy of activation $(\Delta S)^{\#}Jmol^{-1}$	Free energy of activation $(\Delta G)^{\#}KJmol^{-1}$
B.A.	6.012E+06	16.549	13.339	-262.086	114.505
4-MeO-B.A.	2.570E+12	25.894	22.685	-231.726	112.1314
4-Cl-B.A.	9.638E+5	15.331	12.122	-267.51	115.381
4-NO_2-B.A.	2.168E+5	14.297	11.087	-271.711	115.9678







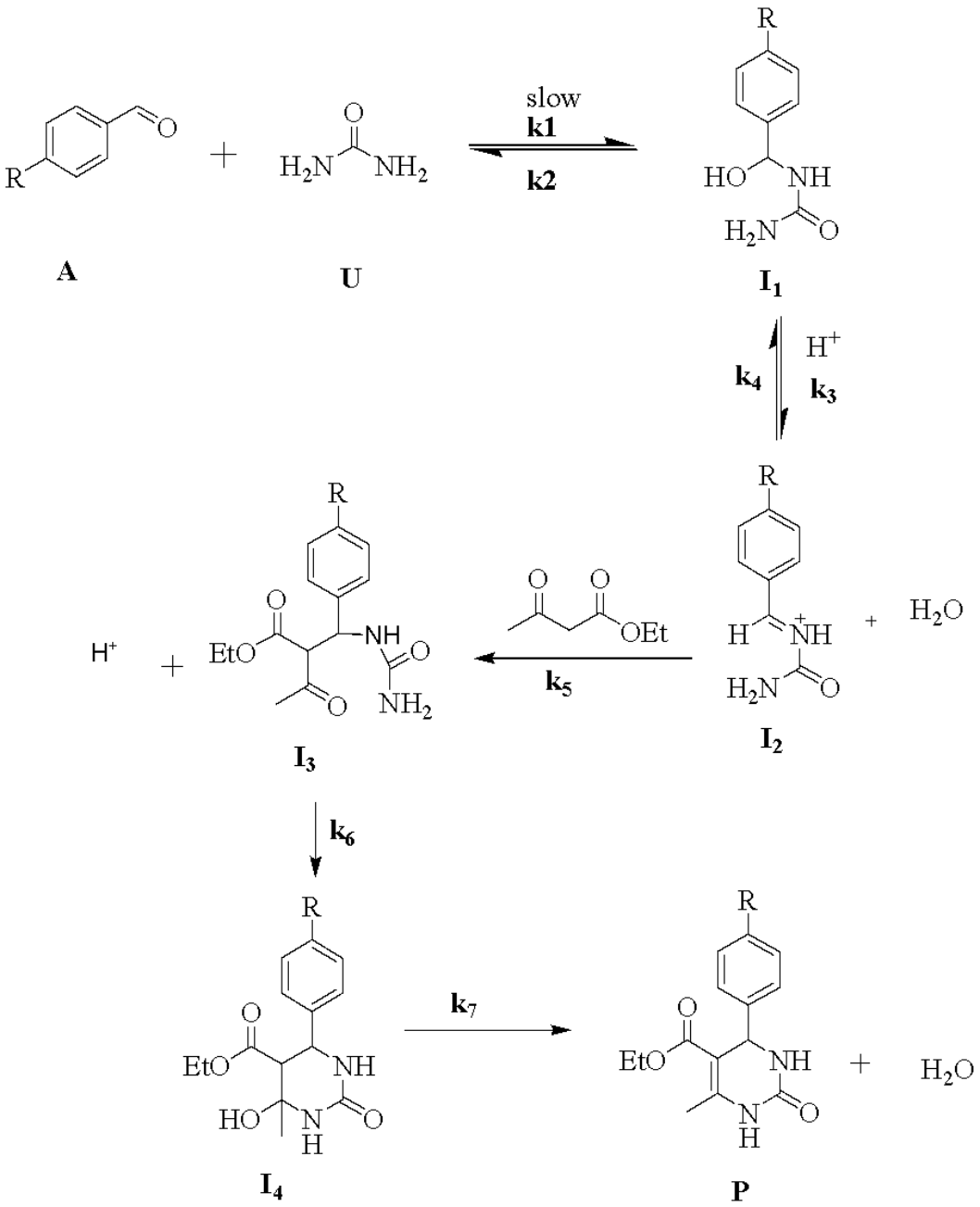
The entropies of activation ΔS# for the cyclocondensation are all negative suggesting rigid nature of transition state and also support the conversion of non-cyclic reactants to cyclic products. The high values of entropy of activation indicate that activated complex is less probable. The high negative 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 ΔH# and high magnitude of ΔS# indicates that the reaction is entropy controlled. The low values of ΔH# 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 ΔG# 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

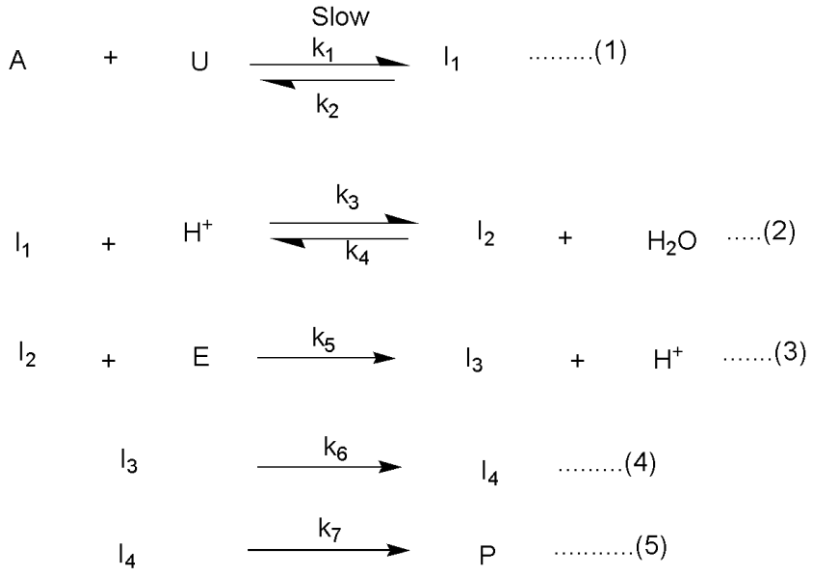
4-methoxy-benzaldehyde >benzaldehyde.> 4-chloro-benzaldehyde> 4-nitro- benzaldehyde

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 state22 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, dx/dt of the cyclocondensation is directly proportional to the concentration of I_4.

$\therefore \frac{dx}{dt} \alpha [I_4]$ or $\frac{dx}{dt} = k_7[I_4]$……(6)

It is difficult to determine the concentration of intermediate I_4.

∴ 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_4

$$k_6[I_3] = k_7[I_4]$$
$$[I_4] = \frac{k_6}{k_7}[I_3]$$

Substituting the value of I_4 in equation (6)

$\frac{dx}{dt} = k_6[I_3]$ …….(7)

Being difficulty in determining the concentration of intermediate I_3

hence the steady state condensation is applied for I_3 which is formed in step-3 and removed in step-4

i.e. Rate of formation of I_3 = Rate of removal of I_3

$$k_5[I_2][E] = k_6[I_3]$$
$$[I_3] = \frac{k_5}{k_6}[I_2][E]$$

Substituting the value of I_3 in equation (7)

$\frac{dx}{dt} = k_5[I_2]$[E] (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_2

$$k_3[I_1][H^+] = k_5[I_2][E] + k_4[I_2][H_2O]$$
$$[I_2] = \frac{k_3[I_1][H^+]}{k_5[E] + k_4[H_2O]}$$

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 $k_5[E]$ 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

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

$$[I_1] = \frac{k_1[A][U]}{k_3[H^+] + k_2}$$

Substituting the value of I_1 in equation (9)

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

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 $\frac{dx}{dt} \alpha [A]^1[U]^1$

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……..k_7& k'.

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