

A Study on Kinetic Model for the Formation of 5-methyl-4-imidazolecarboxylic Acid Ester

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5-methyl-4-imidazolecarboxylic Acid Ester 연속합성의 반응속도론 및 특성 연구

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Abstract: The chemistry of 5-methyl-4-imidazolecarboxylic acid ester synthesis involves three distinct reaction steps. Of these the rate of formation of diketone was found to be a function of oxime and HCl concentration and temperature by the batch experiment. The decomposition of diketone was found to be a slow process, whereas temperature was the only variable to affect it significantly. An empirical rate expression for the net formation of diketone fits the experimental data satisfactorily. The principal objectives of this study are to study the kinetics of the diketone formation reaction and to develop the empirical rate expression.

요 약 : Ethylacetoacetate로부터 2단계의 연속합성을 통하여 생성되는 5-methyl-4-imidazolecarboxylic acid ester의 합성반응 속도론과 중간 생성물인 α, β -dioxobutyric acid(일명 diketone)의 반응 안정성을 연구하였다. 반응속도 결정 단계는 α -acetyl- α -hydroxy iminoacetic acid(oxime)로부터 diketone으로 진행되는 과정으로서 반응속도에 영향을 미치는 주된 인자로는 Oxime, HCl의 농도와 반응온도를 확인하였고 HCl 농도 4.6~8.0M, 반응온도 8.5~20°C의 변화에 따른 diketone의 최대 반응수율 변화는 50~74%이었다. Power-law 수식모델 및 회분식 반응기 empirical data로부터 diketone 생성반응 속도식을 구하였으며 이 식이 실험 Data와 잘 일치하고 있음을 보였다. 본 연구는 5-methyl-4-imidazolecarboxylic acid ester 연속반응 공정개발의 기초단계로서 반응속도론 연구를 통하여 합성 반응의 특성을 파악하는데 중요한 의의를 두고 있다.

1. Introduction

The production of 5-methyl-4-imidazole-carboxylic acid ester from ethyl acetoacetate via the oxime

and diketone intermediates is thought to offer significant advantages over the existing processes[1-6]. The 5-methyl-4-imidazolecarboxylic acid esters are very useful as intermediates for preparing hista-

mine H₂ antagonists, for example cimetidine.

The mechanism of 5-methyl-4-imidazole-carboxylic acid ester synthesis involves three distinct reaction steps: i) The production of oxime (α -acetyl- α -hydroxy-iminoacetic acid) from the reaction of ethyl acetoacetate with sodium nitrite and acetic acid, ii) The production of diketone (α , β -dioxobutyric acid) from the reaction of oxime with formaldehyde in the presence of hydrochloric acid. iii) The production of 4(5)-etyoxycarbonyl-5(4)9-methylimidazole from the reaction of diketone with formaldehyde and ammonia.

This process is quite acceptable environmentally, that is, no extensive treatment of the effluent is needed to meet environmental requirements.

Of these, the diketone formation step is the most complicated one in the reaction sequence, and represents the greatest processing challenge because of the difficulties associated with carrying out this reaction. These are: (a) Diketone stability: The reaction product decomposes rather rapidly, especially at elevated temperatures. (b) Exothermicity: The reaction is highly exothermic; hence, unless heat is removed during the reaction, the temperature rise leads to intolerable decomposition rates. Furthermore, the heat of solution of anhydrous HCl is also high and, since the molar ratio of HCl to oxime is as high as seven, this constitutes another significant source of heat liberation. These combined heat loads require a means for continuous removal of heat from the reactor to prevent significant temperature elevations which are detrimental to diketone yield. (c) Reactor specification: The reaction kinetics dictate the use of a plug flow reactor optimum yield. This requirement increases the severity of the heat transfer problem.

The objectives of the study deal with the problems enumerated above.

They are:

1. Determine the dependence of reaction rate on oxime and CHI concentrations and determine reaction rate constants and their dependence upon temperature.

2. Study the diketone stability characteristics.

3. Identify potential problems in the continuous production of diketone.

2. Experimental

Reaction rate constants are best determined under batch conditions, and since knowledge of the kinetics assists meeting the other objectives, this study was carried out first.

These batch experiments were performed in jacketed stirred, one-liter and two-liter glass reactors (Fig. 1). The oxime material was prepared first, according to a specified standard procedure which included a two-hour preparation period at a temperature of 20~25°C. For the most part, the oxime preparation followed the procedure described in U. S. Patent[7].

To this oxime solution paraformaldehyde (powder) or formaldehyde solution was added first. Aqueous HCl solution was added next. The diketone reaction was initiated during the HCl addition. The HCl solution had to be added gradually, over the period of 5 to 15 minutes, in order to avoid any temperature excursions which might ignite a runaway reaction. This gradual addition causes some uncertainty in reaction time, t , since it is very diffi-

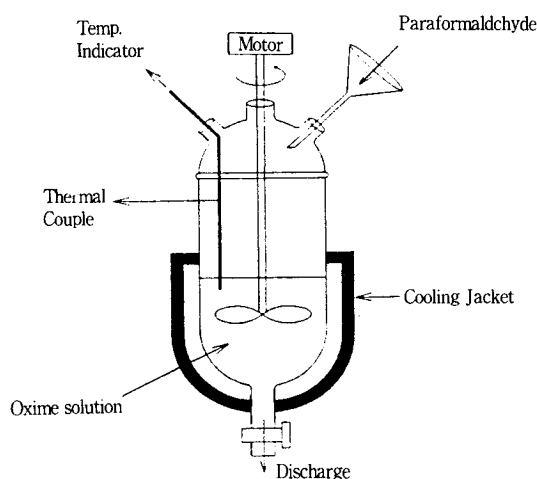


Fig. 1. Batch experiment apparatus for kinetic model developments.

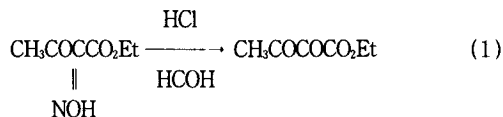
cult to pinpoint the exact starting time.

The progress of the reaction was monitored as a function of time by withdrawing 5ml samples by pipet, reacting the sample with 5ml of 27% ammonia solution, and analyzing the mixture by High Pressure Liquid Chromatography(HPLC) for oxime and 5-methyl-4-imidazolecarboxylic acid ester. It was assumed that the conversion of the diketone to 5-methyl-4-imidazolecarboxylic acid ester was 100%. In subsequent studies of this conversion of diketone to 5-methyl-4-imidazolecarboxylic acid ester in continuous reactors, it was found that the yields were 2 to 4% higher in the continuous reactors than in the analytical method described above and, therefore the conversion was not 100%. However, since the analytical method was applied in a consistent fashion and since relative yields were important in this phase of the work, the slight inaccuracy in the assumption of 100% conversion should not affect our overall conclusions. The principal independent variables and their ranges are listed in Table 1.

3. Results and Discussion

3.1. Kinetics of Diketone Formation Reaction

Oxime is converted to diketone in the presence of HCl and formaldehyde according to the following simplified scheme:



As mentioned, the kinetics of this reaction were

Table 1. Ranges of Variables: Batch Diketone Reaction Tests

Variable	Range
HCl concentration	4.6 to 8.0M
Temperature	0 to 20°C
Initial oxime concentration	1.0 to 1.8M
Paraformaldehyde concentration	1.8 to 3.5 times oxime concentration

studied in a batch reactor. The concentrations of oxime and diketone were determined as a function of time by withdrawing samples from the reactor, converting the diketone to 5-methyl-4-imidazolecarboxylic acid ester with ammonium hydroxide, and analyzing the resulting mixture using HPLC. In these analyses it was assumed that 100% of the diketone was converted to 5-methyl-4-imidazolecarboxylic acid ester.

Typical diketone concentration and yield profiled are shown of Fig. 2~4. Yield computations are based on ethylacetoacetate rather than an oxime so as to account for possible oxime yields less than 100%. Fig. 2 shows diketone concentration and yield at a reaction temperature of 8.5°C and initial oxime concentration of approximately 1.1 mole/l with the concentration of HCl as a parameter. It is seen that increasing the HCl concentration in the range 4.6~8.0M results in increased diketone yields. Maximum yields vary from 50 to approximately 74%.

The effects of temperature on reaction rate and yield are shown of Fig. 3 and 4. At low HCl concen-

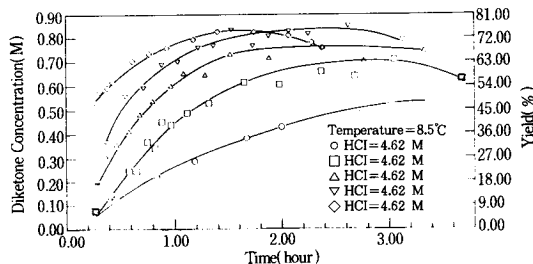


Fig. 2. Dependence of diketone concentration and yield on HCl concentration.

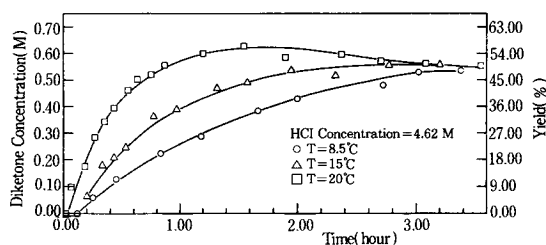


Fig. 3. Dependence of diketone concentration and yield on temperature at low HCl concentrations.

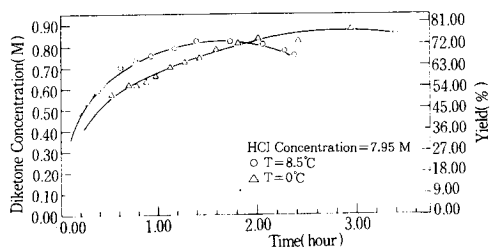


Fig. 4. Dependence of diketone concentration and yield on temperature at high HCl concentrations.

trations of 4.62 M, the yield is shown on Fig. 3 to increase with increasing temperature, in the range of 8.0~20.0°C. Low HCl concentrations were used in these runs so as to be able to follow the reaction at higher temperatures and to avoid runaway temperature conditions. The effects of temperature on yield at an HCl concentration of 7.95 M are shown of Fig. 4. The maximum yield obtained at 0°C is approximately 78% at a reaction time of 3 hours. The maximum yield obtained at 8.5°C is approximately 74% at a reaction time of 1.5 hours. These results obviously suggest that an optimum condition will require a compromise between reaction time (reactor size) and diketone yield.

3. 2. Determinations of Kinetic Parameters

The kinetic data were analyzed following both a differential and an integral approach, so as to obtain diketone formation rate expressions. The simplest overall reaction model which gives satisfactory fit to the experimental data is the following:



Assuming that the rates of these reactions can be expressed in terms of power-law formulations and the the decomposition of diketone is a function of temperature only, these rates can be written as:

$$\frac{-dC_o}{dt} = k_1 C_o^\alpha C_{\text{HCl}}^\beta \quad (3)$$

$$\frac{-dC_D}{dt} = k_2 C_o^\alpha C_{\text{HCl}}^\beta - k_2 \quad (4)$$

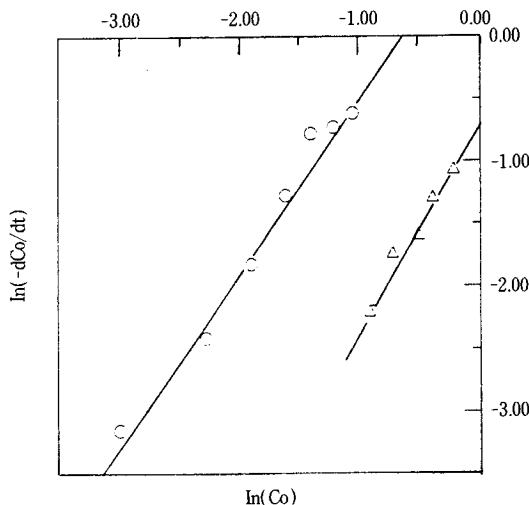


Fig. 5. Typical plots for the determination of the kinetic model following the differential method.

where C_o , C_{HCl} and C_D are the oxime, HCl and diketone concentrations, respectively, and k_1 and k_2 are reaction rate constants which are assumed to follow the Arrhenius temperature dependence:

$$k_1 = k_{10} \exp\left(\frac{-E_1}{RT}\right) \quad (5)$$

$$k_2 = k_{20} \exp\left(\frac{-E_2}{RT}\right) \quad (6)$$

E_1 and E_2 are the activation energies for the diketone formation and decomposition reaction, respectively.

From the differential method of analysis, oxime decomposition and diketone formation rates can be obtained from concentration versus time curves [8]. Then, from Equation 3,

$$\ln\left(-\frac{dC_o}{dt}\right) = \ln k_1 + \beta \ln C_{\text{HCl}} + \alpha \ln C_o \quad (7)$$

and Equation 4 at low temperature where $k_2=0$,

$$\ln\left(-\frac{dC_D}{dt}\right) = \ln k_1 + \beta \ln C_{\text{HCl}} + \alpha \ln C_o \quad (8)$$

The values of α , β and k_1 are obtained from plots of $\ln(-dC/dt)$ or $\ln(dC_D/dt)$ versus $\ln C_c$ at constant C_{HCl} or $\ln(C_{\text{HCl}})$ at constant C_c . Typical such

Table 2. Average Kinetic Parameters(Differential Analysis)

Kinetic Parameter	From Oxime Data	From Diketone Data	Overall Average
α	1.55	1.54	1.54
β	5.55	5.46	5.51
k_1	2.2×10^{15}	—	2.2×10^{15}
E_1	24,900	—	24,900
k_2	—	4.82	4.82
E_2	—	1,290	1,290

plots are shown on Fig. 5. The activation energies E_1 and E_2 are obtained from plots of $\ln k_1$ or $\ln k_2$ versus $1/T$ according to Equations 5 and 6. The average values of the kinetic parameters which were obtained from the differential analysis of the data are shown on Table 2.

In order to refine further the values of the kinetic parameters obtained from the differential method, the integral method of analysis was used. This method consists of integrating the rates expressions so as to generate concentration versus time curve which can be compared with the experimental concentration versus time curves. The values of the kinetic parameters are adjusted so as to obtain the best fit to the experimental data.

It can be shown that Equations 3 to 4 can be integrated to the following forms.

$$C_o = \left[C_{o,i}^{1-\alpha} - (1-\alpha)k_1 C_{HCl}^\beta \cdot t \right]^{\frac{1}{1-\alpha}} \quad (9)$$

$$C_D = C_{o,i}^{1-\alpha} - \left[C_{o,i}^{1-\alpha} - (1-\alpha)k_1 C_{HCl}^\beta \cdot t \right]^{\frac{1}{1-\alpha}} - k_2 \cdot t \quad (10)$$

where $C_{o,i}$ is the initial concentration of oxime. Equations 9 and 10 describe the oxime and diketone concentrations as a function of time. These concentrations were compared to the experimental ones and the values of the kinetic parameters were adjusted as necessary so as to obtain the best possible fit to the experimental data.

The values of the kinetic parameters which were found to be most consistent with the experimental data are the following:

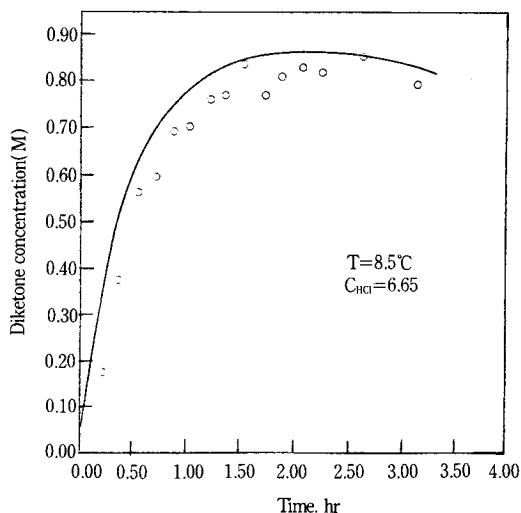


Fig. 6. Comparison of diketone concentration profile obtained from the kinetic model(-) with the experimental profile(-o-).

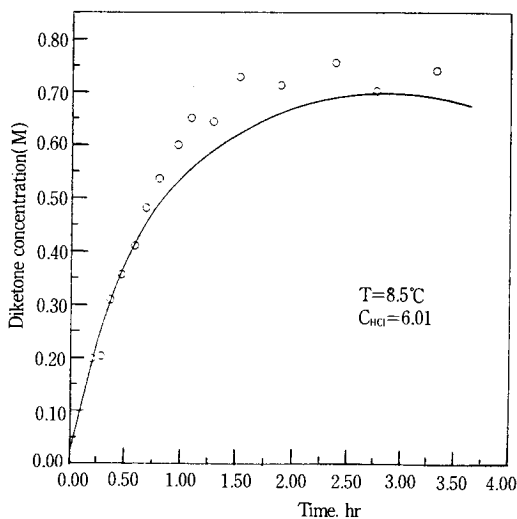


Fig. 7. Comparison of diketone concentration profile obtained from the kinetic model(-) with the experimental profile(-o-).

$$\begin{aligned} \alpha &= 1.5 \\ \beta &= 5.5 \\ k_{10} &= 2.2 \times 10^{15} \\ k_{20} &= 10.5 \\ E_1 &= 25,150 \\ E_2 &= 2,750 \end{aligned}$$

Fig. 6, 7 and 8 show typical theoretical and ex-

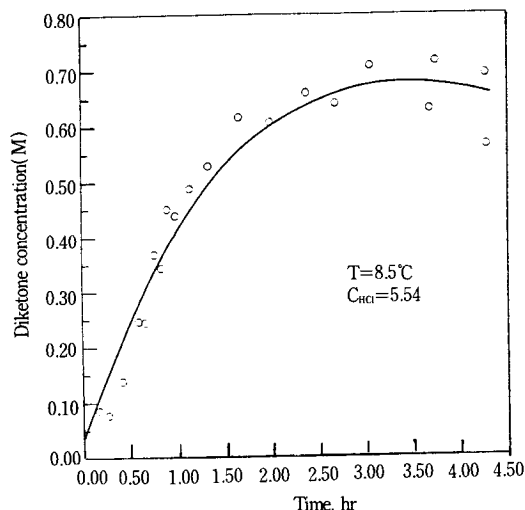


Fig. 8. Comparison of diketone concentration profile obtained from the kinetic model(-) with the experimental profile(-o-).

perimental diketone versus time curves.

Based on these results, the rate of the diketone formation can be written as:

$$r_D = 2.2 \times 10^{15} \exp\left(\frac{-25,150}{RT}\right) C_o^{1.5} \times C_{HCl}^{5.5} - 10.5 \exp\left(\frac{-2,750}{RT}\right) \quad (11)$$

in units of mol/l · hr.

4. Conclusion

The rate of formation of diketone from the oxime via the reaction sequence(oxime→diketone→5-methyl-4-imidazolecarboxylic acid ester) was found to be a function of oxime and HCl concentration and reaction temperature. It was shown that in the range of temperature 8.5~20°C and HCl concentra-

tion 4.6~8.0M maximum reaction yield vary from 50 to 74%.

The maximum yield, however, obtained at lower temperature, 0°C, was approximately 78% at a reaction time of 3 hours. It means that optimal design conditions for the reactor require a compromise between reaction time(reactor size) and diketone yield. In the subsequent study, therefore, the effects of reactor specifications on reaction yield should be studied to develop a continuous reactor specifications on reaction yield should be studied to develop a continuous reactor scheme and determine its performance in terms of diketone yield and heat transfer characteristics.

The empirical rate expression of the diketone formation reaction was developed from the analysis of kinetic parameters following the differential method. It shows that the values of kinetic parameters are found to be consistent with the experimental data.

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