



# Synthesis of diketopiperazine: A kinetic study by means of thermoanalytical methods

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## ABSTRACT

The enalapril maleate (EM) decomposition to diketopiperazine was monitored in helium flow by thermogravimetry at different heating rates between 0.2 and 5 °C min<sup>-1</sup>. The activation energy value was obtained (198 kJ mol<sup>-1</sup>) from the Kissinger–Akahira–Sunose isoconversional method. Isothermal experiments were simulated (125, 130, 135 and 155 °C) using the model-free method, employing only the activation energy value. The reaction model of the process was studied by means of the master-plot method. The reaction mechanism depends on the temperature; for experiments below 235 °C, the probable mechanism is nucleation. Instead, when the temperature overcomes the EM melting point, the reaction occurs in liquid state and its kinetics is better described by first order reaction. To avoid the complexity of model changes, experimental results are fitted using the model-free method.

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## 1. Introduction

Enalapril maleate (EM) is a salt of enalapril and maleic acid. The EM is a prodrug used for the treatment of hypertension and, as such, it is not manifested by a direct biological activity. After oral administration, EM is converted into Enalaprilat, the real active compound that acts through the inhibition of the angiotensin converting enzyme [1].

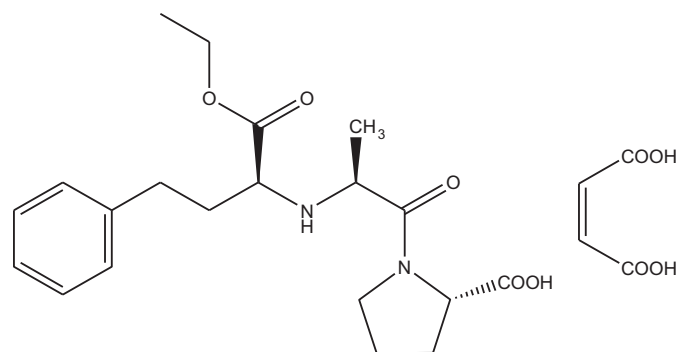
On the other hand, EM degradation in solid-state occurs and the degradation rate increases with heating temperature and time. Additionally, it has been shown that the rate and pathways of EM degradation in solutions are pH-dependant [2]. At pH below 5, the major degradation product is diketopiperazine derivative (DKP), and at pH above 5, the major degradation product is enalaprilat.

In other words, Enalapril has two major degradation ways in solid state: hydrolysis of ethylic ester to enalaprilat and intermolecular cyclization to a diketopiperazine derivative [3]. The degradation pathway recognized for the formation of enalapril diketopiperazine (DKP) involves two neighboring amino acids via intramolecular cyclization [4–7].

In this investigation we are interested in the preparation of DKP, since it is used as standard for the quality controls of EM in the

pharmaceutical industry. To obtain DKP, the synthetic methods reported in literature involve the EM heating under its melting point to promote the intramolecular reaction described before [8]. In our experiment, this method is not efficient, because we obtained DKP in low yields (14%) and several subproducts were produced.

To gain insight in the process involved in the preparation of DKP as a degradation product, in this investigation we studied the kinetics of EM. To this end, a set of thermo analytical experiments were performed.



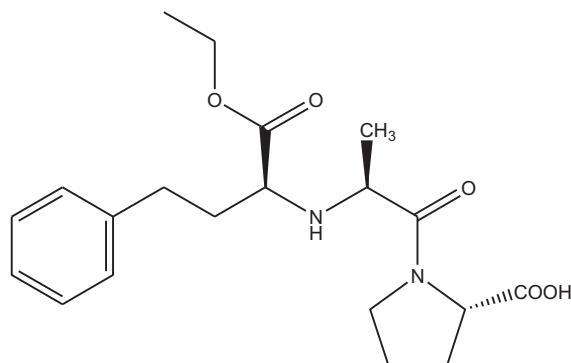
Enalapril maleate (MW 492.5)

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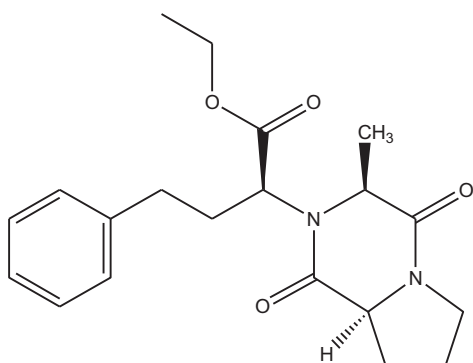
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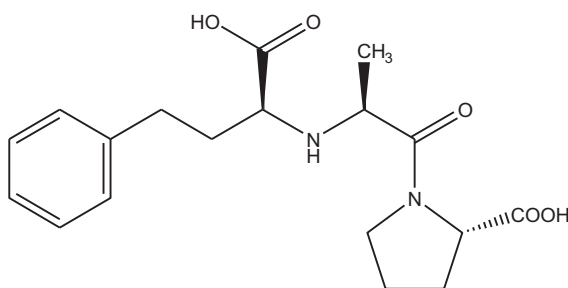
Enalapril (MW 476.4)



Enalapril (MW 476.4)



Enalapril diketopiperazine (MW 358.4)



Enalaprilat (MW 348.4)

Enalapril diketopiperazine (MW 358.4) Enalaprilat (MW 348.4)

The reaction can be kinetically evaluated by means of thermoanalytical methods mainly, thermogravimetry. A wide range of calculation techniques has been proposed for deriving the Arrhenius parameters and extrapolated to other temperatures.

In this work isoconversional, model-fitting and master-plot methods from non isothermal thermogravimetric data are used. The model-free method is used to simulate the isothermal experiments. An available enalapril maleate (provided by UPM, "Facultad de Ciencias Exactas") was used for the experiments.

As stated before, the purpose of this study is to perform an analysis of enalapril maleate degradation to obtain a representation of reaction data. The information obtained will help us to determine the optimal conditions to prepare DKP.

## 2. Experimental

### 2.1. Thermo degradation of enalapril maleate

The thermo degradation of enalapril maleate was investigated by means of dynamic thermogravimetry (TGA) using a Shimadzu TGA-50 equipment under atmospheric pressure. The method of multiple heating rate programs (multiple temperature programs) was used as recommended by the ICTAC Kinetics Committee [9]. Studies were carried out at constant heating rates between 0.2 and 5 °C min<sup>-1</sup> in He stream (50 cm<sup>3</sup> min<sup>-1</sup>) flowing onto the cylindrical sample holder. In all experiments we employed the method of multiple heating rate programs, the first stage is a heating at 20 °C min<sup>-1</sup> up to 105 °C and the second stage is at the selected heating rate. Isothermal experiments were carried out at 125, 130, 135 and 155 °C. In isothermal experiments, the heating rate between room temperature and the selected  $T$  is 20 °C min<sup>-1</sup> and the mass is 10 mg.

## 3. Kinetic analysis

Experimental data for the kinetic analysis of solid reactions can be obtained by means of dynamic thermogravimetry at constant heating rate. Under such conditions, the reaction rate is usually expressed by the general equation:

$$\frac{d\alpha}{dt} = Af(\alpha) \exp\left(-\frac{E_a}{RT}\right) \quad (1)$$

where  $\alpha$  is the conversion,  $A$  is the pre-exponential factor,  $E_a$  is the activation energy,  $f(\alpha)$  is the differential conversion function, and  $R$  is the gas constant.

If experiments are performed at constant heating rate ( $dT = \beta dt$ ), Eq. (1) can be expressed like a derivative as a function of the temperature

$$\frac{d\alpha}{dT} = \left(\frac{A}{\beta}\right) f(\alpha) \exp\left(-\frac{E_a}{RT}\right) \quad (2)$$

Introduction of the explicit value of the heating rate reduces the applicability of Eq. (1) to processes in which the sample temperature does not deviate significantly from the reference temperature.

Integration of kinetic equation (Eq. (2)) leads to the following equation

$$g(\alpha) = \int \frac{d\alpha}{f(\alpha)} = \frac{A}{\beta} \int \exp\left(-\frac{E_a}{RT}\right) dT = \left(\frac{AE_a}{R\beta}\right) \int \exp\left(\frac{-x}{x^2}\right) dx = \left(\frac{AE_a}{R\beta}\right) p(x) \quad (3)$$

where  $g(\alpha)$  is the integral form of the reaction model, and  $p(x)$  is the temperature integral, for  $x = E_a/RT$ .

### 3.1. Isoconversional methods

Isoconversional methods permit the effective activation energy of a process to be estimated as a function of the conversion without the assumption of the reaction model  $f(\alpha)$ . All isoconversional methods take their origin in the isoconversional principle that states that the reaction rate at constant conversion is only a function of temperature [9]. Such kinetic analysis requires a series of thermoanalytical curves, recorded at several constant heating rates.

For the commonly used constant heating rate program, there is a number of integral isoconversional methods that differ in approximations of the temperature integral. Many of these approximations give rise to linear equations with the general form

$$\ln\left(\frac{\beta}{T^B}\right) = \ln\left(\frac{AR}{E_a g(\alpha)}\right) - C\left(\frac{E_a}{RT}\right) \quad (4)$$

where  $B$  and  $C$  are the parameters.

In the Kissinger–Akahira–Sunose method [10,11], parameters are  $B=2$  and  $C=1$  and Eq. (4) takes the following form

$$\ln\left(\frac{\beta}{T^2}\right) = \ln\left(\frac{AR}{E_a g(\alpha)}\right) - \left(\frac{E_a}{RT}\right) \quad (5)$$

Thus, for a certain conversion ( $\alpha$ ), the plot of  $\ln(\beta/T^2)$  versus  $1/T$  obtained from thermogravimetric curves and recorded at different heating rates should be a straight line whose slope can be used to evaluate the activation energy.

### 3.2. Coats–Redfern (CR) model-fitting method

Unlike isoconversional methods, the so-called Coats–Redfern (CR) model-fitting method is applied in order to obtain all kinetic parameters from thermogravimetric data from a single heating-rate experiment. This method uses Eq. (6) obtained by rearrangement of Eq. (5)

$$\ln\left(\frac{g(\alpha)}{T^2}\right) = \ln\left(\frac{AR}{E_a \beta}\right) - \left(\frac{E_a}{RT}\right) \quad (6)$$

The most commonly used reaction models for solid-state processes were cited by Vlaev [12] and Vyazovkin [13].

### 3.3. Master-plot method

The physicochemical conversion model ( $g(\alpha)$ ) of solid-state reactions can be determined by using the so-called master-plot method.

The master-plot method is based on the comparison of theoretical master plots, which are obtained for a wide range of ideal kinetic models, with the experimental master plot. This comparison obviously requires the previous transformation of experimental data into the corresponding master plot. The application of this method usually leads to the selection of the appropriate conversion model for the solid-state reaction investigated. Mathematically, the use of this master-plot method for kinetic data recorded under non isothermal conditions is described as follows.

By using a reference at point  $\alpha=0.5$  and according to Eq. (3), the following equation is obtained:

$$g(0.5) = \left(\frac{AE_a}{\beta R}\right) p(x_{0.5}) \quad (7)$$

where  $x_{0.5} = E/RT_{0.5}$ , and  $T_{0.5}$  is the temperature required to attain 50% conversion. When Eq. (3) is divided by Eq. (7), Eq. (8) is deduced:

$$\frac{g(\alpha)}{g(0.5)} = \frac{p(x)}{p(x_{0.5})} \quad (8)$$

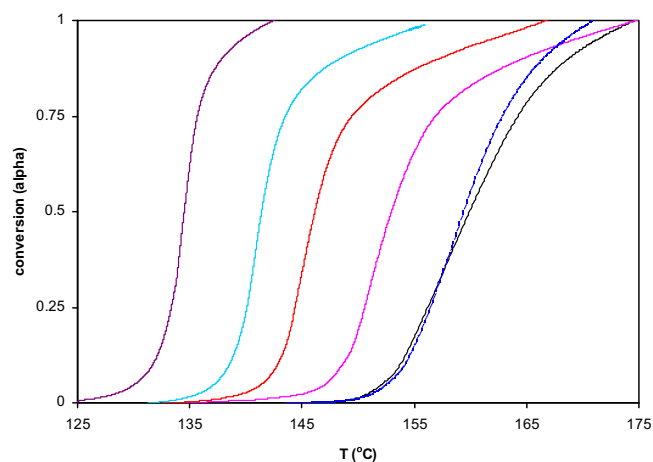


Fig. 1. Thermoanalytical curves and 5 °C min<sup>-1</sup>, 2 °C min<sup>-1</sup>, 1 °C min<sup>-1</sup>, 0.5 °C min<sup>-1</sup>, 0.2 °C min<sup>-1</sup>.

The ratio  $g(\alpha)/g(0.5)$  is calculated and plotted as a function of “ $\alpha$ ” for all functions  $g(\alpha)$ . Both the conversion–temperature profile ( $\alpha$ – $T$ ) and the value of  $E_a$  for the process should be known in advance to draw the experimental master plots of  $p(x)/p(x_{0.5})$  versus “ $\alpha$ ” from experimental data obtained at a given heating rate. Thus, Eq. (8) indicates that, for a given  $\alpha$ , the experimental value of  $p(x)/p(x_{0.5})$  and theoretically calculated values of  $g(\alpha)/g(0.5)$  are equivalent when an appropriate conversion model is used.

## 4. Results and discussion

### 4.1. Kinetic analysis

#### 4.1.1. Isoconversional method

The thermoanalytical curves (weight loss versus temperature) obtained at constant heating rate were transformed into conversion–temperature curves.

In order to calculate the conversion, it is supposed that in the EM degradation, the principal product is diketopiperazine (DKP). The weight loss in EM degradation (molecular weight: 492.5 g/mol) to DKP (molecular weight: 358.4) is 27.2%. The conversion is calculated as

$$\alpha = \frac{W_t - W_i}{0.272 W_i} \quad (9)$$

where  $W_t$  represents the sample weight at time  $t$  (or temperature  $T$ ), whereas  $W_i$  is the sample weight at the beginning and  $0.272 W_i$  the sample weight at end of the weight loss process if the EM degrades only to DKP.

Conversion–temperature curves obtained for EM samples recorded at constant heating rate are shown in Fig. 1. The conversion is calculated taking as final weight the one that should have the sample if only degrades to enalapril DKP. As EM degradation at higher temperature can continue (enalapril DKP), the conversion exceeds the unit value.

The conversion versus temperature curves showed a noticeable dependence on the heating rate. The conversion versus temperature curves were shifted to higher temperatures at higher heating rates.

The EM and the DKP have melting point at 144 °C and 106 °C respectively. The experiment with heating rate 0.2 °C min<sup>-1</sup> occurs between 130 and 140 °C. The mixture can be molten because the product (DKP) presents a lower melting temperature. The experiment performed with a heating rate of 5 °C min<sup>-1</sup> occurs from

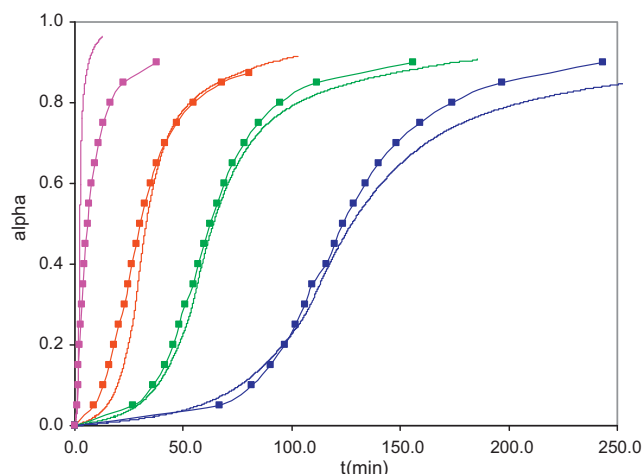
**Table 1**  
Activation energy as a function of conversion for EM degradation.

| $\alpha$ | $E_a$ (KJ/mol) | $r^2$  |
|----------|----------------|--------|
| 0.1      | 206.6 ± 7.5    | 0.9960 |
| 0.2      | 205.1 ± 6.3    | 0.9972 |
| 0.3      | 200.0 ± 5.1    | 0.9981 |
| 0.4      | 192.2 ± 2.9    | 0.9993 |
| 0.5      | 184.2 ± 2.1    | 0.9996 |
| 0.6      | 175.0 ± 1.9    | 0.9996 |
| 0.7      | 167.7 ± 1.1    | 0.9999 |
| 0.8      | 157.4 ± 5.5    | 0.9963 |

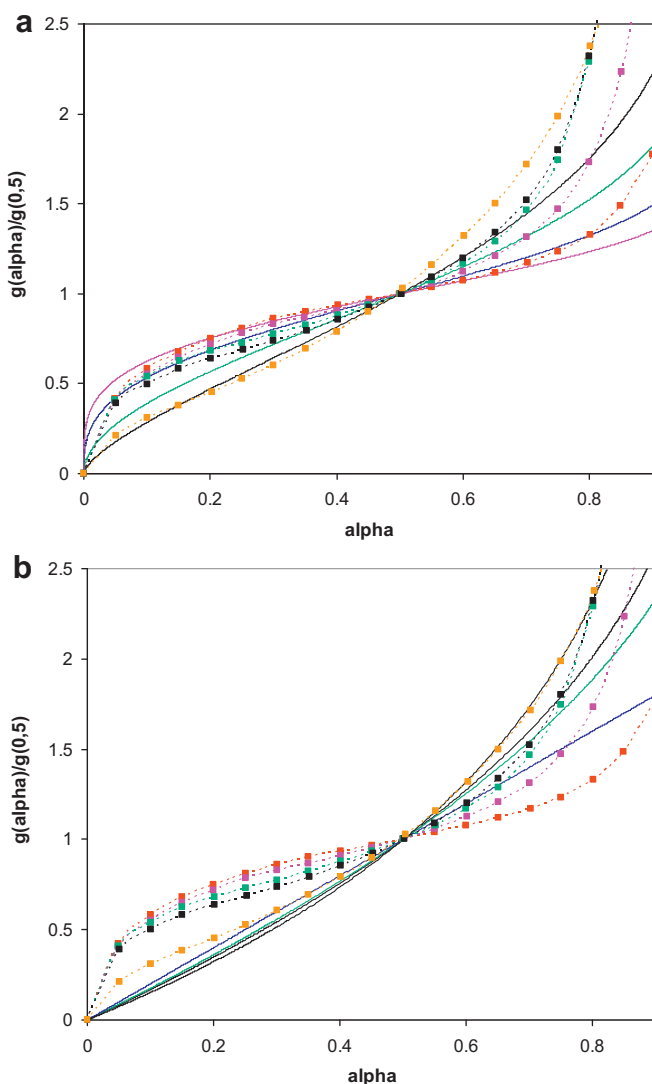
150 °C, therefore, the reagent (EM) is already found in liquid state from the initial time.

According to the KAS method, the activation energy was obtained from the slope of the resulting linear adjustment after plotting  $\ln(\beta/T^2)$  versus  $1/T$  at several constant conversion  $\alpha$ .

Results derived from KAS method in terms of the activation energy as function of the conversion are listed in Table 1.



**Fig. 3.** Isothermal experiment at 125, 130, 135 and 155 °C. Model-free method. Theoretical: — 155 °C, — 135 °C, — 130 °C, — 125 °C. Experimental: ■ 155 °C, ■ 135 °C, ■ 130 °C, ■ 125 °C.



**Fig. 2.** (a) Master plots of theoretical  $g(\alpha)/g(0.5)$  vs.  $\alpha$  for the conversion models. ■ 5 °C min<sup>-1</sup>, ■ 2 °C min<sup>-1</sup>, ■ 1 °C min<sup>-1</sup>, ■ 0.5 °C min<sup>-1</sup>, ■ 0.2 °C min<sup>-1</sup>, — A1.5,  $(-\ln(1-a))^{1/1.5}$ , — A2,  $(-\ln(1-a))^{1/2}$ , — A3,  $(-\ln(1-a))^{1/3}$ , — A4,  $(-\ln(1-a))^{1/4}$ . (b) Master plots of theoretical  $g(\alpha)/g(0.5)$  vs.  $\alpha$  for the conversion models. ■ 5 °C min<sup>-1</sup>, ■ 2 °C min<sup>-1</sup>, ■ 1 °C min<sup>-1</sup>, ■ 0.5 °C min<sup>-1</sup>, ■ 0.2 °C min<sup>-1</sup>, — P1,  $(a)$  — P2,  $(1-(1-a))^{1/2}$  — P3,  $(1-(1-a))^{1/3}$  — R1,  $(-\ln(1-a))$ .

#### 4.1.2. Coats–Redfern (CR) model-fitting method

The CR analysis of thermogravimetric data recorded at a single heating rate was carried out by inserting  $g(\alpha)$  into Eq. (6). A set of Arrhenius parameters determined from the plot  $\ln[g(\alpha)/T^2]$  against  $1/T$  was attained.

Results of the application of the Coats–Redfern method for various kinetic models to the experimental kinetic data recorded at 0.2, 0.5, 1.0, 2.0 and 5 °C min<sup>-1</sup> gives a series of  $E_a$ ,  $\ln A$  and  $r^2$ . The values of the Arrhenius parameters depended on the kinetic model as well as on the heating rate. Each TG curve could be equally well described by several kinetic models resulting in correlation coefficients close to the unit.

The obtained pairs of Arrhenius parameter values ( $E_a$  and  $A$ ) can be correlated by the so-called compensation effect, mathematically described by Eq. (10).

$$\ln A = a + bE_a \quad (10)$$

The pairs of activation energy and pre-exponential factor were fitted according to a linear relationship defined by the compensation effect. Estimated values of  $a$  and  $b$  are (−9.33 and 0.0003) respectively. We used the value of the activation energy obtained by the KAS method ( $E_a = 197.6$  KJ/mol) as proposed by Vyazovkin [14] to estimate  $\ln A$ .

#### 4.1.3. Determination of the conversion model

The knowledge of  $\alpha$  as a function of temperature and the value of the activation energy are essential in order to calculate the experimental master plot of  $p(x)/p(x_{0.5})$  against  $\alpha$  from experimental data obtained under a linear heating rate.

Fig. 2a and b shows the theoretical master plots corresponding to the  $g(\alpha)/g(0.5)$  functions and experimental master plot for all heating rates (0.2–5 °C min<sup>-1</sup>).

The comparison of experimental master plots with the theoretical ones revealed that the kinetic process for EM degradation was most probably described by the Am (Avrami–Erofeev) model, with the 43 for the experiment with a heating rate 0.2 °C min<sup>-1</sup> (Fig. 2a). When the heating increases (5 °C min<sup>-1</sup>) experimental master plots are described by the first-order model.

The heating rate reaction of 0.2 °C min<sup>-1</sup> occurs below the EM melting point, while the reaction at 5 °C min<sup>-1</sup> occurs above the EM melting temperature.

## 4.2. Simulation of isothermal experiments

As the  $E_a$  estimated by the isoconversional method varies with  $\alpha$ , a better option to simulate isothermal experiments is to use a method that does not require the value of the pre exponential factor  $A$ .

### 4.2.1. Model-free method

A variation of  $E_a$  with  $\alpha$  is often overcome by averaging  $E_a$  over  $\alpha$ . The difficulties of extrapolation to other temperatures can be overcome without averaging  $E_a$  and even without evaluating both absent components pre-exponential factor and reaction model.

Isothermal experiment performed at 125, 130, 135 and 155 °C were simulated using the model-free method proposed by Vyazovkin [14] and results of this simulation are shown in Fig. 3.

## 5. Conclusions

The kinetics of EM degradation was accurately determined from a series of thermoanalytical experiments at different constant heating rates. The activation energy was calculated by the integral isoconversional KAS method. The activation energy was found to slightly depend on conversion. This suggests that the EM degradation changes its reaction mechanism for higher conversions.

Kinetic experiments were simulated by using the model-free method. Experimental results are fitted to the theoretical values for experiments carried out below 135 °C. For temperatures higher than the EM melting point, experimental results are not fitted with the theoretical model, possibly because the reaction occurs since initial time in liquid state.

These results open the possibility to investigate the EM degradation to DKP for temperatures lower than the ones cited in the bibliography, so opening the possibility of increasing the conversion to the desired product DKP.

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