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Kinetic analysis of thermal decomposition for penicillin sodium salts
Model-fitting and model-free methods

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Abstract

A kinetic study on decomposition processes of some penicillin salts was carried out. Both isothermal and dynamic thermogravimetric curves were used. As expected by their complex structures, several steps with different energies were involved in decomposition processes. Model-fitting and -free kinetic approaches were applied to nonisothermal and isothermal data. The kinetic triplet ($f(\alpha)$, A and E_a) related to model-fitting method that defines a single step reaction resulted to be at variance with the multi-step nature of salts-decomposition. The model-free approach represented by the isothermal and nonisothermal isoconversional methods, gave different dependencies of the activation energy on the extent of conversion. The complex nature of the multi-step process of the studied compounds was more easily revealed using a broader temperature range in nonisothermal isoconversional method. The failure in the model-fitting method did not allow calculating shelf life and half-life times. © 2002 Elsevier Science B.V. All rights reserved.

Keywords: Penicillin salts; Chemical reactivity; Kinetic analysis; Isothermal and nonisothermal model-fitting and model-free methods

1. Introduction

Thermal analysis is a routine method for the analysis of drugs and substances of pharmacological interest [1–4]. Some years ago, a study concerning the penicillin sodium salts was carried out by thermal analysis [3]. By using thermal analysis it was possible to evaluate by TG the sodium content of the cited compounds. The accuracy and the precision of the method were good, especially if compared with those obtained by flame photometry.

It is also well known that at high temperature the chemical reactivity of drugs active components, both pure and in the mixture, can be modified thus leading to uncontrollable reactions with consequent danger situations.

For this reason it is necessary to carry out a thermal stability study that usually requires weeks

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or months. However, kinetic analysis allows us to obtain some data more rapidly.

Although this technique cannot completely replace the classical stability program that implies long time observation, it can provide an early alert to danger problems and indicate the most favourable directions to pursue a successful formulation.

Before the application of thermal analysis the following considerations must be made: (i) the chemical analysis of the compound structure is able to supply useful expectations on its stability; (ii) the presence of an oxygen atom in the compound structure permits the decomposition process without the presence of air; (iii) the presence of a notable exothermic process at low temperature requires the knowledge of decomposition rate, the suitable mechanism and the activation energy values at various temperatures. Moreover, an attempt to find the half-life (the isothermal decomposition of half product) at a given temperature can be made by heating a sample and by quickening its decomposition process. This procedure requires a single step reaction and a severe statistical analysis [5].

In this work all the above-cited quantities were provided by means of kinetic analysis of solid-state decomposition processes of some of the penicillin sodium salts having very similar structures. To reveal the complex nature of the multi-step processes both isothermal and nonisothermal model-free together with isothermal model-fitting methods were used instead of a nonisothermal model-fitting one that uses a single TG run.

Table 1
Names, empirical formulas and molecular weights for the antibiotics studied (sodium salts)

Sample	Names	Empirical formula	Molecular weight
1	Benzylpenicillin	$C_{16}H_{17}N_2NaO_4S$	356.38
2	Ampicillin	$C_{16}H_{18}N_3NaO_4S$	371.39
3	Carbenicillin[a]	$C_{17}H_{16}N_2Na_2O_6S$	422.36

[a] Disodium salt.

TG/DSC curves of these substances allow also to obtain some information on the physical properties (melting, solid–gas phase transitions) related to the thermal decomposition processes. The compound studied were benzylpenicillin, ampicillin and carbenicillin.

2. Experimental

Penicillin sodium salts (Table 1) were supplied by the Istituto Biochimico Italiano (ampicillin) and by Farmitalia (benzylpenicillin, carbenicillin).

The measurements were carried out on a Stanton–Redcroft 625 Simultaneous TG-DSC connected to an Olivetti 250 computer.

Instrument calibration was performed with standard indium, gallium, lead, tin, zinc, naphthalene and benzoic acid samples of known temperatures and enthalpies of melting. Both the metals and organic compounds were of purity over 99.9%.

For decomposition studies, under dynamic and static conditions, samples (8–10 mg) were weighed in aluminium pans placed in a nitrogen-filled dry box. The TG-DSC system was flushed with air stream both below (flow rate 30 ml min^{-1}) and above (flow rate 50 ml min^{-1}) the open pans. In this way the gas evolved during the thermal decomposition experiment was continuously removed. The chosen heating rate was a 5 K min^{-1} (in nonisothermal experiment) and at least two runs were made for each compound. For isothermal measurements the prefixed temperature was reached using a heating rate of 8 K min^{-1}.

All the thermodynamic parameters were calculated using Stanton–Redcroft Data Acquisition System, Trace 2, Version 4. The compounds were used without purification.

The simultaneous TG-DSC system is a very useful tool for investigating organic compounds since it combines, in a single run, weight loss and heat change processes.

In this manner, the transformations that occur even with small weight changes (chemical reactions, decomposition, vaporisation, and oxidation processes) can be distinguished from those occur-

ring without weight change (melting, crystallisation, polymorphic changes).

The quantities used to characterise the compounds were, in nonisothermal measurements, the percent loss in TG technique and the corresponding onset temperatures (T_o).

In differential scanning calorimetry technique the enthalpy values related to various processes were considered together with the temperature peaks T_p that could provide valuable information in the analytical study of organic compounds. Ideally, T_p is the temperature at which the process occurs most rapidly, but it is also the temperature at which the maximum rate of the heat change between the sample and the environment takes place.

At this regards some α-amino acids [6], for example, were identified on the basis of T_p alone because these values are distinct and do not overlap with those of the adjacent α-amino acids on the decomposition scale.

Furthermore, thermal analysis of different series of dipeptides, by simultaneous TG-DSC measurements, was carried out. The thermal behaviour of these compounds was compared to that of independent free α-amino acids contained in the dipeptides [7,8].

3. Kinetic procedure

Kinetic analysis of decomposition process is traditionally expected to produce an adequate kinetic description of the process in terms of the reaction model and of the Arrhenius parameters using a single-step kinetic equation,

$$d\alpha/dt = k(T) f(\alpha), \quad (1)$$

where t is the time, T is the temperature, α is the extent of conversion and $f(\alpha)$ is the reaction model. The temperature dependence of the rate constant is introduced by replacing $k(T)$ with the Arrhenius equation, which gives

$$d\alpha/dt = A \exp(-E_a/RT)\ f(\alpha), \quad (2)$$

where A (the pre-exponential factor) and E (the activation energy) are the Arrhenius parameters and R is the gas constant. For nonisothermal conditions $d\alpha/dt$ in Eq. (2) is replaced with $\beta\ d\alpha/dT$ where β is the heating rate giving,

$$d\alpha/dT = (A/\beta) \exp(-E_a/RT) f(\alpha). \quad (3)$$

The three components ($f(\alpha)$, E and A) called 'kinetic triplet' define both in Eqs. (2) and (3), a single-step reaction that disagrees with the multi-step nature of decomposition that usually occurs in the solid-state.

As the studied compounds have complex structures, it can be hypothesised that several steps with different energies will be involved.

If a process involves several steps with different activation energies, the relative contributions of these steps to the overall reaction rate will vary with both temperature and extent of conversion. This means that the effective activation energy determined from the analysis of the results will also be a function of these two variables. The use of the Eqs. (2) and (3) determines reactions model that does not represent multi-step kinetics.

For this reason one cannot justify the establishing of the reaction mechanism from $f(\alpha)$ alone.

Also for a simple step of decomposition process one cannot justifiably expect that identical values of Arrhenius parameters result from isothermal and nonisothermal experiments, which are necessarily conducted in different regions of temperature.

Moreover, the application of nonisothermal model-fitting (method) approaching to single-rate data fails to achieve a clean separation between the rate temperature dependence $k(T)$ and the reaction model $f(\alpha)$, so that almost any $f(\alpha)$ can satisfactorily fit the data by virtue of the Arrhenius parameters compensation effects, thus substituting the true unknown reaction model. For this reason a single heating rate data for the determination of kinetic parameters should be avoided. The application of these models to isothermal parameters gives rise to believable values of Arrhenius parameters that, however, are likely to conceal the kinetic complexity. Anyway the complex nature of a multi-step process can be more easily detected when a broader temperature range in the nonisothermal method is used. In the narrow ranges used under isothermal conditions, the differences between different models are much less

visible and lead to a statistically acceptable description of the multi-step by one set of kinetic parameters. An alternative approach to kinetic analysis is the model-free methods that allow for evaluating Arrhenius parameters without choosing the reaction model. The isoconversional methods make up the best representation of the model-free approach.

These methods yield the variation of the effective activation energy as a function of the extent of conversion.

The knowledge of the dependence E_a on α allows detecting multi-step processes and predicting the reaction kinetics over a wide temperature range.

The isoconversional methods could also yield similar dependencies of the activation energy on the extent of conversion for isothermal and non-isothermal experiments but direct comparison between these two methods should not be made because they cover different range of temperatures.

In order to obtain the above-cited values both TG isothermal and dynamic curves have been carried out.

3.1. Isothermal methods

For the isothermal model-fitting method the following procedure was adopted.

It is well known that isothermal kinetics of solid-state reactions can be represented by the equation,

$$g(\alpha) = kt, \tag{4}$$

where k is the specific constant rate and $g(\alpha)$ is an integral mathematical expression related to a mechanisms of solid phase reactions.

Three groups of mathematical expressions (D_1, D_2, D_3, D_4), (R_2, R_3, F_1) and (A_2, A_3, A_4) describe, respectively, diffusion, chemical reaction and nucleation mechanisms.

Degree of conversion α (fraction of compound decomposed) is given by the expression,

$$\alpha(t) = [(\%m_i - \%m_t)]/[(\%m_i - \%m_f)], \tag{5}$$

where $\%m_i$ is the initial percent mass; $\%m_t$, the percent mass at time t; and $\%m_f$, the final percent mass, as they are collected from an isothermal TG experiment.

The degree of conversion (α)–time plots $\alpha = f(t)$ were constructed using experimental percentage mass data taken from TG isothermal curves performed at different constant temperatures, lying in the temperature range where decomposition processes of the studied compounds occur.

Generalised reduced time plots, in which α values for each curve are reported as a function of the ratio $t/t_{0.5}$ ($t_{0.5}$ is the experimental time corresponding to $\alpha = 0.5$), have subsequently been constructed.

The curves $\alpha = f(t/t_{0.5})$ were compared with the theoretical ones reported in literature [9,10] to individuate the most probable mechanisms. The mathematical expressions $g(\alpha)$ describing the possible decomposition mechanisms, together with the experimental α and t values corresponding to a fixed temperature, were inserted in Eq. (4). The values of kinetic constant rate k were determined at different temperatures from the slope of the straight line obtained by plotting $g(\alpha)$ against time (least-square method). These values were subsequently inserted in the Arrhenius equation together with the corresponding temperature values T:

$$\ln k = \ln A - E_a/RT, \tag{6}$$

supplying E_a activation energy and pre-exponential factor values from the slope and intercept of regression straight-line.

If no expression was found to describe the kinetic complexity, an alternative procedure, the isothermal isoconversional method, was used to verify the energy value variation related to the multi-step in the experimental temperature range.

From isothermal TG curves a set of temperature T and t values were obtained for fixed values of α. Substituting $k = A \exp(-E_a/RT)$ in Eq. (4) one obtains,

$$g(\alpha) = A \exp(-E_a/RT)\, t, \tag{7}$$

where the obtained t and T are the time and temperature values which make constant the function $g(\alpha)$. By using the logarithmic form of Eq. (7):

$$\ln g(\alpha) = \ln A - E_a/RT + \ln t, \quad (8)$$

and rearranging it, one obtains

$$\ln t = -\ln A + \ln g(\alpha) + E_a/RT. \quad (9)$$

By plotting $\ln t$ against $1/T$ according to Eq. (9), the activation energies were found at any given α values from the slope of a regression straight line.

It must be taken into account that in the isothermal mode the reactions are very slow at the lowest temperatures, so that the experiments will be limited by long times to completion and by low detection limits, while for high temperatures, the reaction will be too fast.

These restrictions imply that the experimental isothermal domain of temperature available is limited, hence the possible separation of several reactions with isothermal isoconversional method will depend on this.

Furthermore, the complexity of the process could be concealed if different processes have similar activation energy.

3.2. Nonisothermal methods

To avoid this fact nonisothemal model-fitting at various heating rates can be applied.

In order to study chemical and physical properties variation related to nonisothermal processes it has become usual to associate mathematical relationship with a particular model of mechanism, but there are several models giving the same mathematical expression and the same model giving two, three or more alternative expressions.

Dollimore et al. [11–14] have carried out a computer program that plots theoretical $d\alpha/dT$ curve by using Eq. (3) when the hypothesised mechanism $f(\alpha)$ and the suitable values of both A and E_a are introduced.

This approach may be considered as the reverse of the Arrhenius nonisothermal kinetics in which A and E_a are calculated both from the α–T plots and a proper mechanism. The shape of the theoretical curve obtained in this way results to be only a function of the mechanism and allows determining the following parameters:

(i) Initial (T_i) and final (T_f) temperature of TG curve as diffuse (d) or sharp (s).
(ii) The half width defined as the peak width on the differential plot of $d\alpha/dT$ against T measured at half height.
(iii) the value of α_{max} at the maximum rate of the process (at T_p) in the α–T plot.

The comparison of these characteristic quantities (half width, α_{max}, T_i, and T_f) for experimental curves with those reported in literature [10,11] shows more than one possible mechanism for each compound.

In order to select the appropriate mechanism for each compound and to determine the kinetic parameters A and E_a, the following method can be used.

The α values, calculated from TG curves as a function of the temperature, together with those of $d\alpha/dT$ (the reverse of DTG), are inserted in the mathematical expressions of $f(\alpha)$ and used in the Arrhenius differential equation.

$$\ln[(\beta\ d\alpha/dT)/f(\alpha)] = \ln k = \ln A - E_a/RT. \quad (10)$$

The α values are also inserted in the mathematical integral expression $g(\alpha)$ and used, together with β in the Satava integral equation,

$$\log[g(\alpha)] = -0.4567\,(E_a/RT) - 2.3115 + \log(AE_a/R\beta), \quad (11)$$

where Doyle's approximation is valid in a temperature range of 100 K [15].

The Arrhenius parameters can be calculated by means of the following linear relationships,

$$\ln[(\beta\ d\alpha/dT)/f(\alpha)] = \text{vs. } 1/T, \quad (12)$$

$$\log[g(\alpha)] \text{ vs. } 1/T, \quad (13)$$

where $f(\alpha)$ and $g(\alpha)$ are the mathematical expressions related to the mechanisms according to the two methods.

From the coefficient and the intercept of the regressions straight lines, the E and parameters can be calculated.

Finally the values of A, E and related mechanisms represented by $f(\alpha)$ were inserted in Eq. (3) and the theoretical DTG curves are reconstructed and compared to the experimental ones.

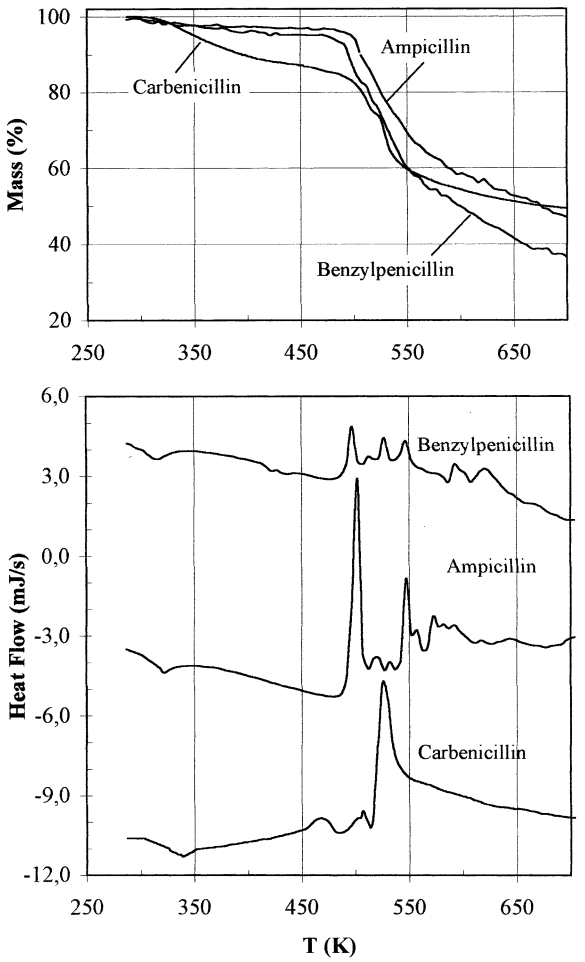

Fig. 1. Simultaneous TG (a) and DSC (b) curves of penicillin sodium salts examined.

Values of triplets obtained in this way can be used in nonisothermal model-fitting method (Eq. (10)).

To obtain the E_a values related to isoconversional nonisothermal method Ozawa–Flynn–Wall equation,

$$\log \beta = -0.4567\,(E_a/RT) - 2.3115 + \log(AE_a/R) - \log[g(\alpha)], \quad (14)$$

was applied to nonisothermal TG curves.

Finally some importance was given to the parameters determining the stability times of the drugs: half-life time (isothermal decomposition of half product) values at various temperatures were obtained by the expression,

$$t_\alpha = g(\alpha)/A\,\exp(-E_a/RT), \quad (15)$$

by using the mathematical expressions $g(\alpha)$ describing the possible decomposition mechanisms and, respectively, $\alpha = 0.5$ or small values (0.05, 0.10).

If triplet kinetic ($g(\alpha)$, A and E_a obtained from isothermal model-fitting method) fails in the description in kinetic complexity, the values of these quantities extrapolated to room temperature are not acceptable.

4. Results and discussion

4.1. Features of the thermal processes

Trends of thermal behaviour at $\beta = 5$ K min^{-1} for the examined compounds are shown in Fig. 1. The values of the thermodynamic quantities relating to TG/DSC curves are reported in Tables 2 and 3.

TG and DSC curves of benzylpenicillin show two steps of weight loss in which exothermic processes occur. A dehydration process was also found (endothermic process).

The first and second decomposition steps contain, respectively three and two exothermic processes so that it can be hypothesised that they happen through a series of superimposed reactions.

For ampicillin there are two decomposition steps, with three exothermic processes, while at low temperatures a dehydration process occurs.

Carbenicillin shows a dehydration process and three steps of decomposition with a sharp exothermic process in the third one.

4.2. Kinetics

The $\alpha = f(t)$ isothermal experimental curves of penicillin salts for the two steps of the decomposition processes, chosen at different temperatures (lying in the experimental temperature range), are given in Fig. 2a and b. The t values, that in curves at different temperatures are related to same α, were divided by the corresponding $t_{0.5}$. This quantity depends on temperature only so that the curves were normalised.

The generalised reduced time plots derived from the isoconversional curves have been compared with the generalised reduced theoretical ones reported by literature [9,10].

Theoretical curves were constructed in the following way: by substituting $k = A \exp(-E_a/RT)$ in the expressions $d\alpha = k f(\alpha)\, dt$ one obtains,

$$d\alpha = A \exp(-E_a/RT) f(\alpha)\, dt,$$

where the hypothesised mechanism $f(\alpha)$ and the suitable values of both A and E are introduced. The shape of the theoretical curves obtained in this way proves to be only a function of the mechanisms and the temperatures. These curves were normalised in the same manner as the experimental ones.

In the first and second step of decomposition the experimental normalised curves at various temperatures (Fig. 3a and b) for benzylpenicillin do not completely overlap with the theoretical one related to various mechanism. This result allows concluding that a superimposed series of reactions occur.

Table 2
Onset temperatures (T_e) and mass loss percentage obtained from TG measurements for the penicillin derivatives studied (sodium salts)

Compounds	Dehydration step		Decomposition steps	
	T_e (K)	Mass loss (%)	T_e (K)	Mass loss (%)
Benzylpenicillin	287.8	4.0	480.5	37.8
			553.8	26.9
Ampicillin	294.2	2.3	502.0	38.2
			572.8	16.3
Carbenicillin[a]	299.2	12.6	450.3	2.3
			501.8	9.1
			524.4	24.6

[a] Disodium salt.

Table 3
Onset, peak temperatures (T_e and T_p, respectively) and enthalpy changes calculated from DSC measurements for the penicillin derivatives studied (sodium salts)

Compounds	Dehydration step			Decomposition steps		
	T_e (K)	T_p (K)	ΔH (kJ mol^{-1})	T_e (K)	T_p (K)	ΔH (kJ mol^{-1})
Benzylpenicillin	286.3	303.6	19.3	492.6	497.7	−18.6
				518.6	525.7	−9.9
				541.3	543.4	−12.9
				589.2	591.3	−6.6
				613.1	618.3	−13.7
Ampicillin	286.1	296.2	21.4	494.4	501.5	−72.4
				537.1	545.5	−43.8
				570.7	572.6	−29.5
Carbenicillin[a]	318.3	313.8	29.1	452.4	467.2	−17.3
				489.1	506.9	−13.3
				517.4	525.7	−127.8

[a] Disodium salt.

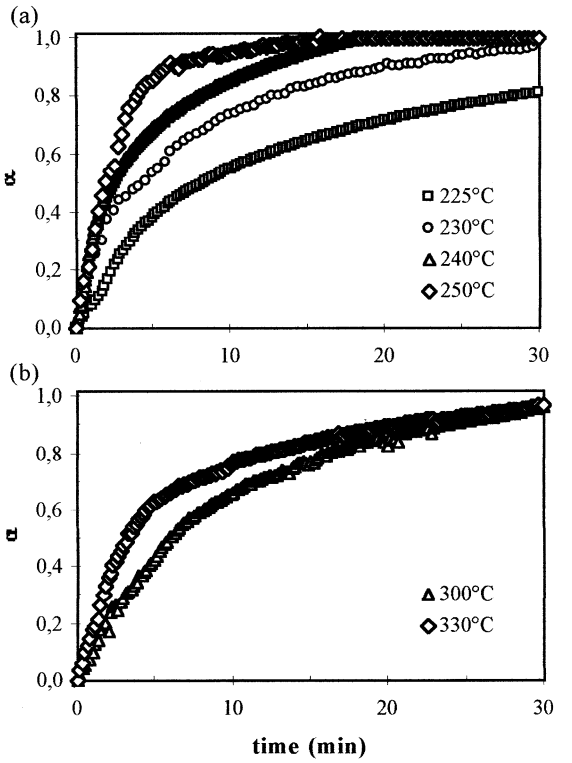

Fig. 2. $\alpha(t)$ isothermal plots for the first (a) and the second (b) decomposition step of benzylpenicillin at different fixed temperatures.

In order to apply the model-fitting method, the above cited mathematical integral expressions $g(\alpha)$ together with the experimental α and t values (corresponding to a fixed temperature), were inserted in Eq. (4). The values of kinetic constant rate k were determined at different temperatures from slope of the straight line obtained by plotting $g(\alpha)$ against time (least-square method). These values were subsequently inserted in the Arrhenius equation together with the corresponding temperature values T supplying E_a activation energy and pre-exponential factor values from the slope and intercept of regression straight-line (Table 4).

The values of activation energies, for the first step of decomposition, vary from 79.1 to 117.9 while for the second one some negative values were found, thus confirming that the model-fitting model disagrees with the multi-step nature of the decomposition process.

The Dollimore's computer program used in nonisothermal method cannot be applied to our experimental curves due to the complexity of decomposition process (as it can be seen in Fig. 4).

The change in E_a values in the isoconventional methods were obtained by using Eqs. (9) and (14).

For isoconversional isothermal method (Fig. 5) related to the first decomposition step (498–523 K) of the benzylpenicillin, the activation energy values decreases from 27 to 15 kJ mol^{-1} in the 0.1–0.2 range extent of conversion, increases from 15 to 29 kJ mol^{-1} in the 0.2–0.8 range and decreases from 29 to 15 kJ mol^{-1} in the 0.8–1 range.

For the second decomposition step (573–603 K) (Fig. 5) the activation energy decreases from 19 to 12 kJ mol^{-1} in 0.1–0.2 range extent, increases from 12 to 17 kJ mol^{-1} in the range from

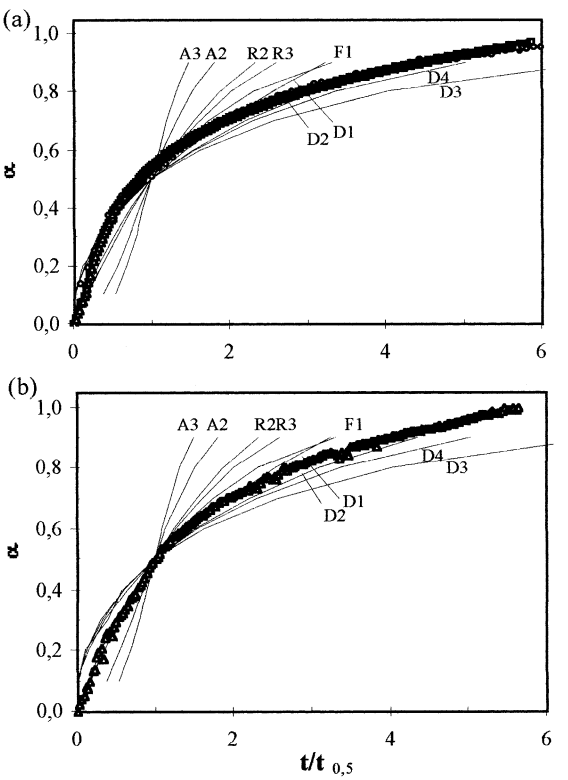

Fig. 3. Comparison between isothermal reduced time plots $\alpha(t/t_{0.5})$ for the first (a) and the second (b) decomposition step of benzylpenicillin at different fixed temperatures with those reported in literature for each kinetic model function.

Table 4
E_a and ln A values obtained by a linear regression analysis on Arrhenius equation according to the isothermal model-fitting method

Kinetic parameters	Step	Kinetic models								
		D_1	D_2	D_3	D_4	F_1	R_2	R_3	A_2	A_3
Benzylpenicillin										
E_a (kJ mol^{-1})	I	79.1	116.0	101.9	89.7	117.9	83.1	73.7	113.9	112.6
ln A (s^{-1})		11.7	20.5	16.7	13.0	22.1	12.5	9.2	20.5	19.9
E_a (kJ mol^{-1})	II	−5.8	5.2	4.3	−0.8	6.0	−4.5	−9.4	2.5	1.1
ln A (s^{-1})		−8.7	−6.5	−7.1	−8.9	−5.1	−8.7	−10.7	−6.6	−7.2
Ampicillin										
E_a (kJ mol^{-1})	I	275.5	275.4	275.2	275.3	275.3	275.5	275.6	275.4	275.5
ln A (s^{-1})		58.2	58.0	57.2	56.8	59.2	57.9	57.0	58.5	58.2
E_a (kJ mol^{-1})	II	38.3	39.8	42.2	40.6	40.7	38.3	36.5	38.6	37.8
ln A (s^{-1})		−0.2	0.0	−0.3	−1.1	1.4	−0.4	−1.7	0.2	−0.3
Carbenicillin										
E_a (kJ mol^{-1})	I	70.0	70.6	71.6	71.0	71.0	69.9	69.0	69.9	69.5
ln A (s^{-1})		9.2	9.2	8.6	8.0	10.5	8.9	7.7	9.5	9.0
E_a (kJ mol^{-1})	II	25.8	23.5	19.8	22.3	21.9	25.5	28.2	25.0	26.0
ln A (s^{-1})		−2.4	−3.1	−4.6	−4.6	−2.2	−2.8	−3.1	−2.3	−2.4

0.2 to 0.4 and decreases from 17 to 3 kJ mol^{-1} in the 0.4–0.9 range.

By applying Eq. (14) the E_a values decrease (Fig. 5) from 25 to 21 kJ mol^{-1} in the 0.05–0.1 range, increase from 21 to 29.4 kJ mol^{-1} in the 0.1–0.8 range, while in the 0.8–0.95 range decrease from 31 to 27 kJ mol^{-1}.

In the 0.25–0.85 range of conversion degree for the first decomposition process, the E_a dependencies are very close for isothermal and nonisothermal experiments while they are completely different near the beginning and the end of the reaction.

However, direct comparison between these two methods should not be made because nonisothermal method experiments cover a much wide range of temperatures (312–700 K) than those of isothermal method experiments (498–523 K).

This behaviour allows to hypothesise that more than one reaction occurs in the decomposition process.

The normalised curves of the first and second decomposition step of ampicillin overlap with those of benzylpenicillin so that partially overlap with the theoretical ones related to various mechanisms. This result allows concluding that a superimposed series of reactions occurs.

However, the values of activation energies, calculated with isothermal-fitting model (Table 4) in the first step of decomposition for all the $g(\alpha)$ are constant (275.5 kJ mol^{-1}) while in the second one (Table 4) vary from 36.5 to 42.2.

In the narrowed temperature range used under isothermal conditions, the differences between the different models are much less visible and, in the first decomposition step, lead to a statistically acceptable description (Table 4) of the multi-step process by one set of kinetic parameters.

To test the significance of the regression parameters related to Arrhenius equation for the various mechanisms the procedure mentioned as degree of significance was presented (Table 5).

σ_a and σ_b values in the regression equation representing the standard deviations of parameters allows to determine the confidence intervals (CI) $a \pm \sigma_a t_{CL,v}$, $b \pm \sigma_b t_{CL,v}$ where the probability that the true parameter values lie is given by (100 CL)% (Table 5).

$t_{CL,v}$ was chosen from proper tables [16] at a CL (confidence level) equal to 0.995 and for two degrees of freedom, providing significative intervals of regression parameter values.

Significative intervals does not indicate, for example, that b parameter is significant but that in the considered interval there is a probability of 99.5% to find the true value of b. It is clear that more the CL is close to 1, the more b could be discussed by statistical point of view in physical terms. From the above cited values it can be noted that for the three compounds the probability to find the true values of a and b are statistically equivalent for all the mechanisms proposed.

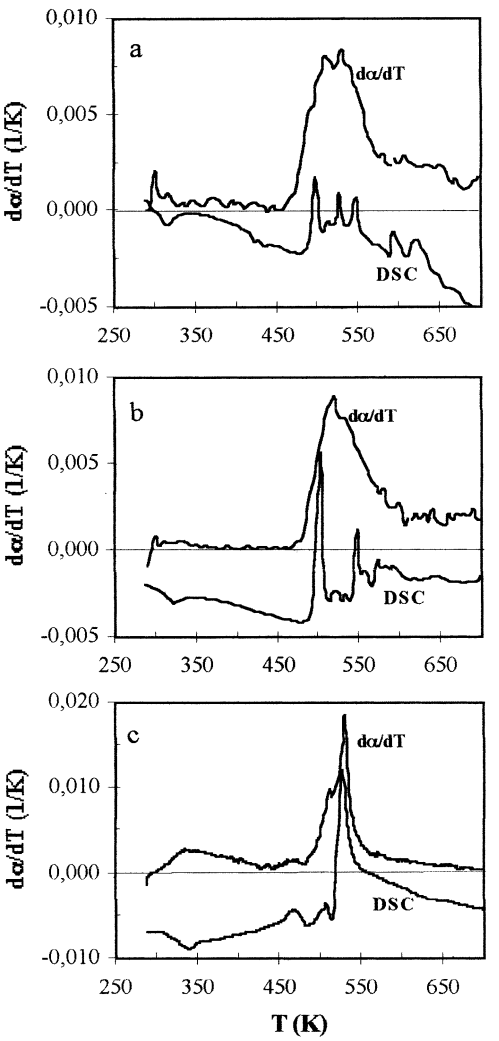

Fig. 4. Comparison between $d\alpha/dT$ and DSC curves for benzylpenicillin (a), ampicillin (b) and carbenicillin (c).

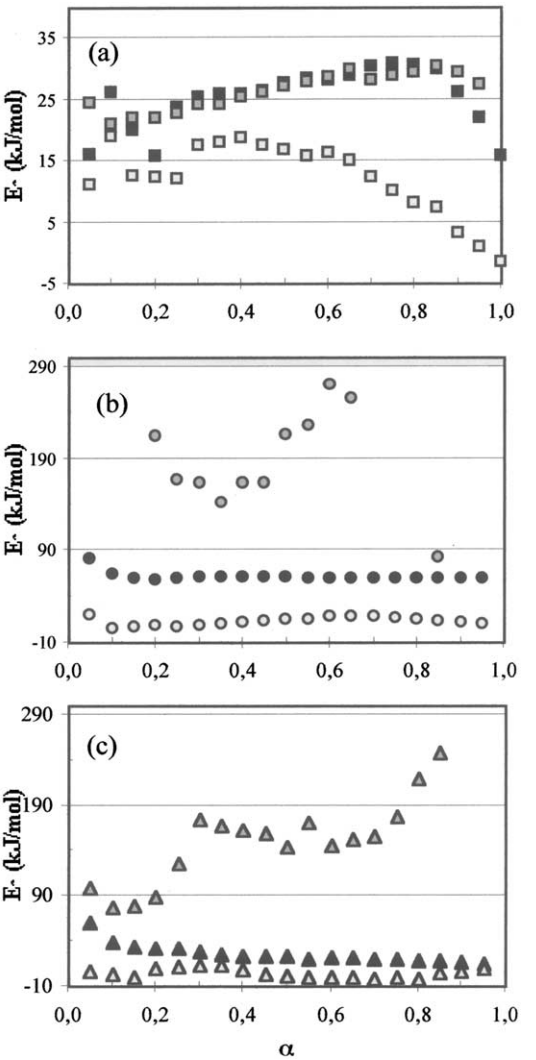

Fig. 5. E_a vs. α plots according to model-free methods related to the decomposition of benzylpenicillin (a), ampicillin (b) and carbenicillin (c) displayed as follows: the grey symbols for the nonisothermal procedure while the black and white symbols for the first and the second isothermal steps, respectively.

For isoconversional isothermal method related to the first decomposition step (498–523 K) of the ampicillin the activation energy (Fig. 5) with the exception of 0.0–0.1 range extent, results to be constant at about 60 kJ mol^{-1}. In the second (Fig. 5) decomposition step (573–603 K) the acti-

Table 5
Linear regression parameters obtained from Arrhenius equation according to the isothermal model-fitting method for the first decomposition step (498–523 K)

Regression parameters[a]	Kinetic models								
	D_1	D_2	D_3	D_4	F_1	R_2	R_3	A_2	A_3
Benzylpenicillin									
a	12 ± 205	20 ± 119	17 ± 132	13 ± 171	22 ± 114	13 ± 195	9 ± 225	21 ± 130	20 ± 136
b	-10 ± 104	-14 ± 60	-12 ± 67	-11 ± 87	-14 ± 58	-10 ± 99	-9 ± 114	-14 ± 66	-14 ± 69
$\sigma_{y:x}$	0.8	0.4	0.5	0.6	0.4	0.7	0.8	0.5	0.5
r^2	0.2909	0.7244	0.6210	0.4303	0.7452	0.3334	0.2277	0.6781	0.6547
F	2	10	6	3	12	2	1	8	7
Ampicillin									
a	58 ± 18	58 ± 18	57 ± 19	57 ± 19	59 ± 19	58 ± 18	57 ± 18	59 ± 19	58 ± 19
b	-33 ± 9	-33 ± 9	-33 ± 10	-33 ± 10	-33 ± 10	-33 ± 9	-33 ± 9	-33 ± 9	-33 ± 9
$\sigma_{y:x}$	0.07	0.07	0.07	0.07	0.07	0.07	0.07	0.07	0.07
r^2	0.9985	0.9984	0.9982	0.9983	0.9983	0.9984	0.9985	0.9983	0.9984
F	2585	2457	2235	2383	2300	2489	2602	2408	2427
Carbenicillin									
a	9 ± 1	9 ± 1	9 ± 1	8 ± 1	10 ± 1	9 ± 1	8 ± 1	9 ± 1	9 ± 1
b	-8 ± 1	-8 ± 1	-9 ± 1	-9 ± 1	-9 ± 1	-8 ± 1	-8 ± 1	-8 ± 1	-8 ± 1
$\sigma_{y:x}$	0.004	0.004	0.004	0.004	0.004	0.004	0.005	0.005	0.005
r^2	0.9999	0.9999	0.9999	0.9999	0.9999	0.9999	0.9999	0.9999	0.9999
F	44 596	45 818	46 139	46 039	43 290	40 365	36 344	37 665	34 890

[a] The regression equation is $y = a + bx$.

Table 6
Storage time values (years) at 25 °C for a conversion of 5, 10 or 50% (half-life) for the first decomposition step (498–523 K)

Conversion (%)	Storage time (years)								
	D_1	D_2	D_3	D_4	F_1	R_2	R_3	A_2	A_3
Benzylpenicillin									
5	0.05	10.91	0.37	0.11	182.58	1.06	16.74	797.56	1522.34
10	0.18	44.42	1.52	0.44	375.03	2.16	17.15	1143.07	1935.16
50	4.50	1316.72	54.38	13.92	2467.25	12.30	20.41	2931.89	3626.05
Ampicillin[a]									
5	7.54	4.35	2.06	3.41	51.71	100.04	7042.21	48.16	1171.31
10	30.2	17.7	8.5	14.0	106.1	202.6	7207.2	689.8	1487.1
50	754.3	525.4	305.6	440.8	698.2	1156.5	8580.2	1768.9	2786.4
Carbenicillin									
5	0.02	0.01	0.01	0.01	0.12	0.20	11.84	0.96	2.16
10	0.06	0.04	0.02	0.03	0.26	0.40	12.13	1.37	2.75
50	1.51	1.19	0.83	1.06	1.69	2.29	14.44	3.52	5.15

[a] Storage time values $\times 10^{12}$.

Table 7
Prediction of the storage temperature (K) for a given storage time values at 5% of conversion for the first decomposition step (498–523 K)

Storage time (h)	Storage temperature (K)								
	D_1	D_2	D_3	D_4	F_1	R_2	R_3	A_2	A_3
Benzylpenicillin									
10 000	0.271	0.313	0.290	0.280	0.334	0.298	0.328	0.348	0.354
20 000	0.265	0.308	0.285	0.275	0.328	0.292	0.320	0.342	0.348
30 000	0.263	0.306	0.283	0.272	0.325	0.288	0.315	0.338	0.344
Ampicillin									
10 000	0.406	0.403	0.400	0.402	0.416	0.419	0.443	0.428	0.433
20 000	0.403	0.400	0.396	0.399	0.412	0.416	0.439	0.424	0.429
30 000	0.401	0.398	0.395	0.397	0.410	0.414	0.437	0.422	0.427
Carbenicillin									
10 000	0.259	0.256	0.252	0.254	0.277	0.281	0.325	0.296	0.305
20 000	0.253	0.250	0.247	0.249	0.271	0.274	0.317	0.289	0.298
30 000	0.250	0.247	0.244	0.246	0.267	0.271	0.312	0.285	0.293

vation energy, in the 0.1–1 range, varies from 5 to 18 kJ mol^{-1}.

In the nonisothermal isoconversional method the E_a values assume, in the range of degree of conversion 0.2–0.6, high values varying from 142 to 270 kJ mol^{-1} while in isothermal isoconversional method the above cited temperature restrictions limit the separation of superimposed reactions. From these results it can be seen that the complex nature of a multistep process can be more easily detected when using a broader temperature range.

For carbenicillin the normalised curves of first and second step of decomposition overlap with those of benzylpenicillin so that they do not completely overlap with the theoretical ones related to various mechanism.

The isothermal model-fitting shows, in the two steps, practically constant (Table 4) values, thus confirming the statistically acceptable description (Table 4) of the multi-step by one set of kinetic parameters.

In the isothermal isoconversional method, in the first step (Fig. 5), the activation energy values decrease (in the 0.5–0.95 range of degree of conversion) from 60 to16 kJ mol^{-1}. For the second step E values are contained in the range $-1 \leq E_a \leq 12$ kJ mol^{-1}. For the nonisothermal isoconversional method the activation energy values (Fig. 5) are very high. These values increase from 0.1 (77 kJ mol^{-1}) to 0.3 (177 kJ mol^{-1}), decrease up to 0.5 (143.49 kJ mol^{-1}) and subsequently sharply increase up to 0.85 (247 kJ mol^{-1}) degree of conversion.

This confirms the fact that for this compound a complex system of decomposition occurs and that the isoconversional nonisothermal method is the most reliable one.

Finally the half-life times and the storage temperatures for penicillin salts were calculated by inserting in Eq. (15) the triplet kinetic values obtained by isothermal fitting model (Tables 6 and 7).

Scattered values displayed by the compounds in the different mechanisms clearly indicate that the failure in the model-fitting method makes unsuitable half times extrapolated at room temperatures.

5. Conclusion

The application of the model-fitting method to a multi-step decomposition process results to be unsuitable for the nonisothermal data. For the isothermal data this method gives rise to appar-

ently reliable results that however are likely to conceal the kinetic complexity. A viable alternative to the model-fitting method is the model-free isoconversional method.

By this method both isothermal and non-isothermal data can be analysed and the E_a vs. α plots can reveal complexities in reaction kinetics. Due to the wide temperature range covered non-isothermal method gives a more complete picture of the decomposition process.

By applying the commonly known model-fitting methods only, misleading kinetic values for complex decomposition processes can be found. On the contrary the combination of model-fitting and -free methods is able to reveal the complex nature and the change in activation energies for all decomposition processes.

Using this procedure one can avoid to calculate misleading shelf and half values for compounds showing complex decomposition processes.

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