دراسة التحلل الحرارى لمادة هيدروكلوريد النورتريبتيلين

ليلى كامل

تمت دراسة التحلل الحرارى لمادة هيدروكلوريد النورتريبتيلين عن طريق التسخين بمعدل واحد (عشر درجات مئوية فى الدقيقة الواحدة) . لوحظ أن تكسير هذه المادة يتم فى خطوة واحدة ، والتى أثبتت أن التفاعل من الدرجة الأولى .

استخدمت فى هذه الدراسة سبع طرق لحساب طاقة التحلل التنشيطى (E_a) والعامل الأسى (A) ،تعتمد على معدل حرارى واحد ، وهم كوتسرد فرن (CR) ، ماككالم-تنر (MC)، هورويتس- متزجر (HM) ، فإن كرفلن (VK) ، مادهوسيودانبن- كريشنان - نيان(MKN) ، برويدو(B) ، وانجان-يون-هن-كانيكسين(WYHC).

أثبتت الدراسة توافق قيم E_a الناتجة عن استخدام الطرق الآتية CR, HM, MKN, MC ، كما توافقت قيم E_a المحسوبة بالطريقتين B ، WYHC ولكن بقيم أقل بـ ١٠-٢٠ كجول/مول ، فى حين أظهرت طريقه (VK) أقل قيمة حسابية كذلك تم حساب مفردات التحلل الديناميكى الحرارى (تغير درجة التعادل الحرارى $\Delta S^{\#}$ ، تغير المحتوى الحرارى $\Delta H^{\#}$ وتغير الطاقة الحرة $\Delta G^{\#}$) . وتم تحليل النتائج التجريبية بطريقة كريادو - مالك - أورتيجا والتى أشارت إلى أن آليات التحلل الفعلى لمادة هيدروكلوريد النورتريبتيلين من النوع D_n deceleration.

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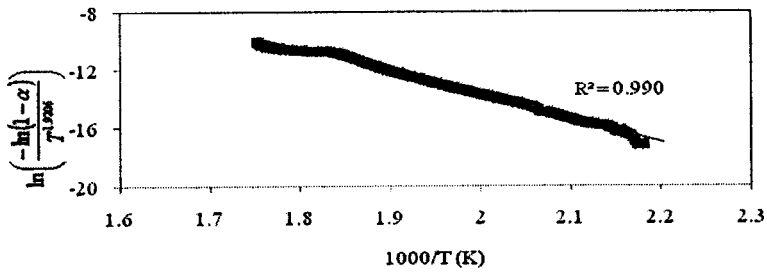
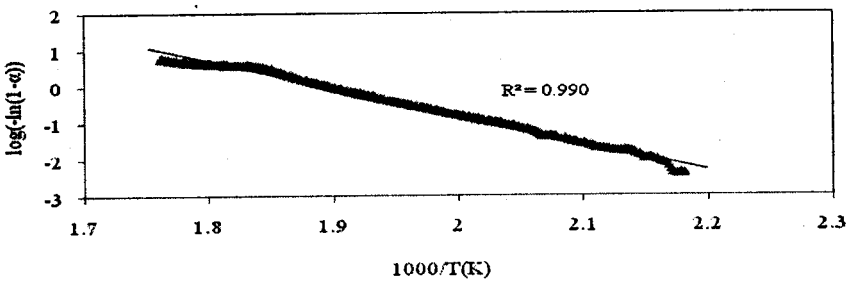


Fig(9) Madhusudanan Plot for the Non-isothermal Decomposition of NTH



Fig(10) MacCallum-Tanner Plot for the Non-isothermal Decomposition of NTH

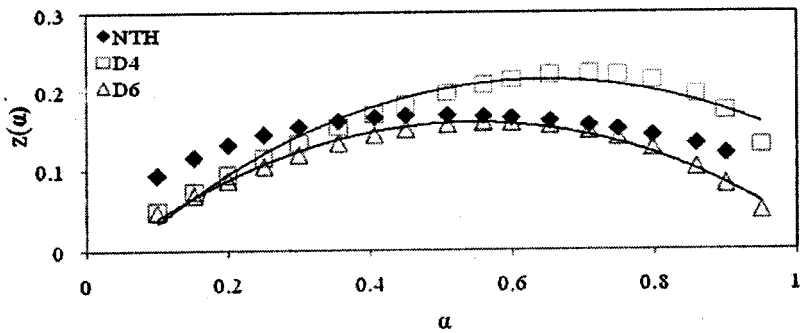
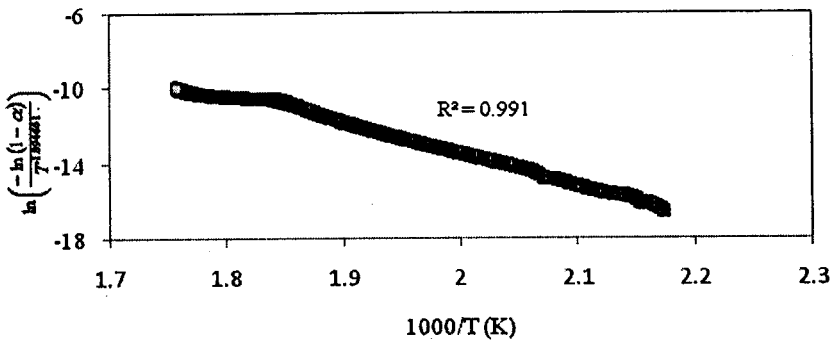


Fig (11) Master Curves of z(α) and Experimental Data



Fig(7) Wanjun-Yuwen-Hen-Cunxin Plot for the Non -isothermal Decomposition of NTH

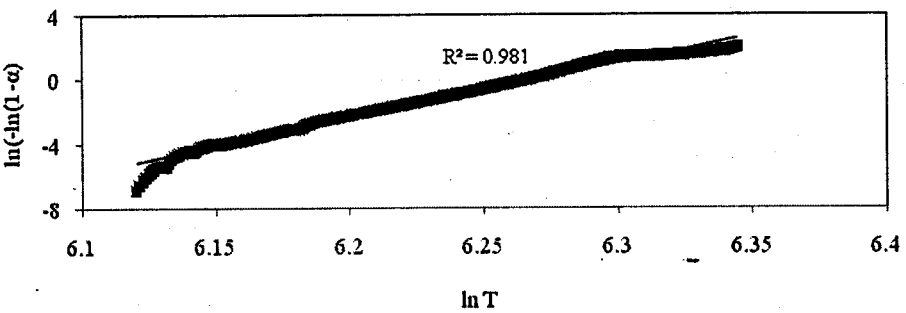
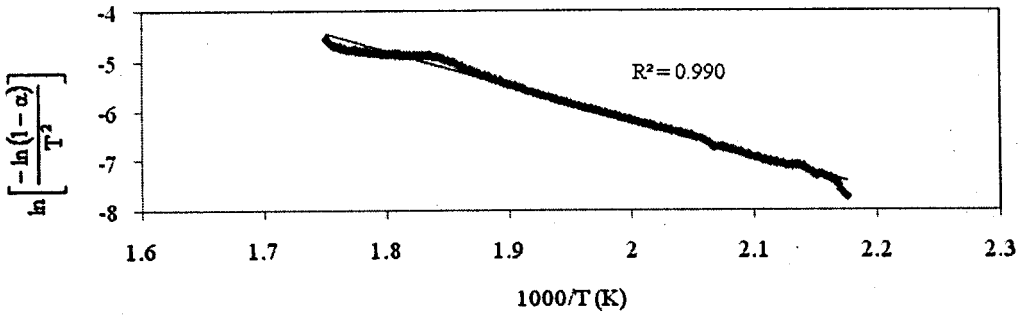
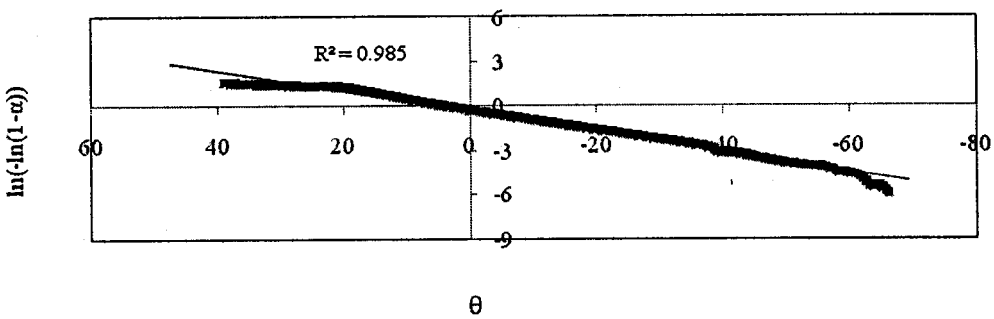


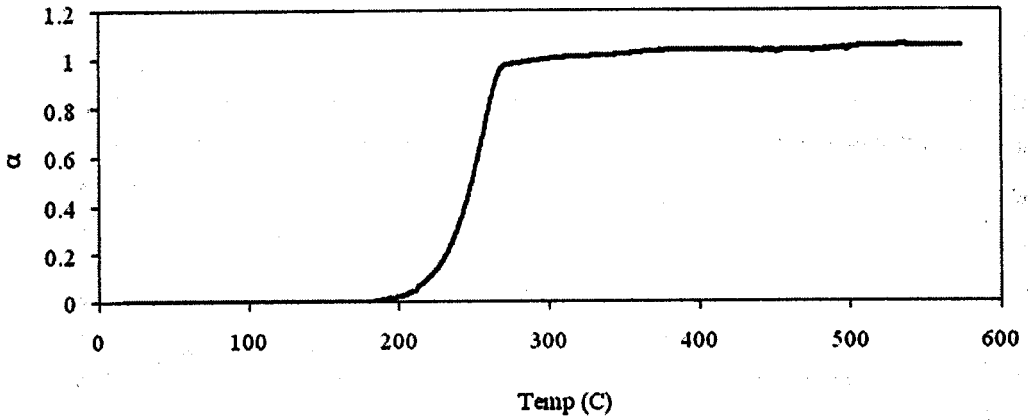
Fig (8) Van Krevelen Plot for the Non-isothermal Decomposition of NTH



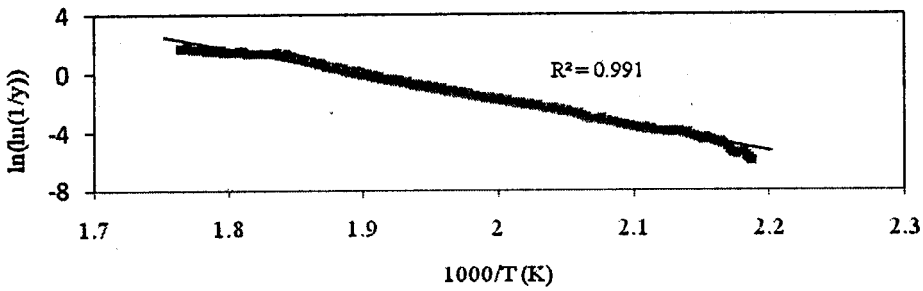
Fig(5) Coats- Redfern Plot for the Non-isothermal Decomposition of NTH



Fig(6) Horowitz-Metzger Plot for the Non-isothermal Decomposition of NTH



Fig(3) The Variation of the Fraction Decomposed (α) with Temperature



Fig(4) Broido Plot for the Non-isothermal Decomposition of HTH

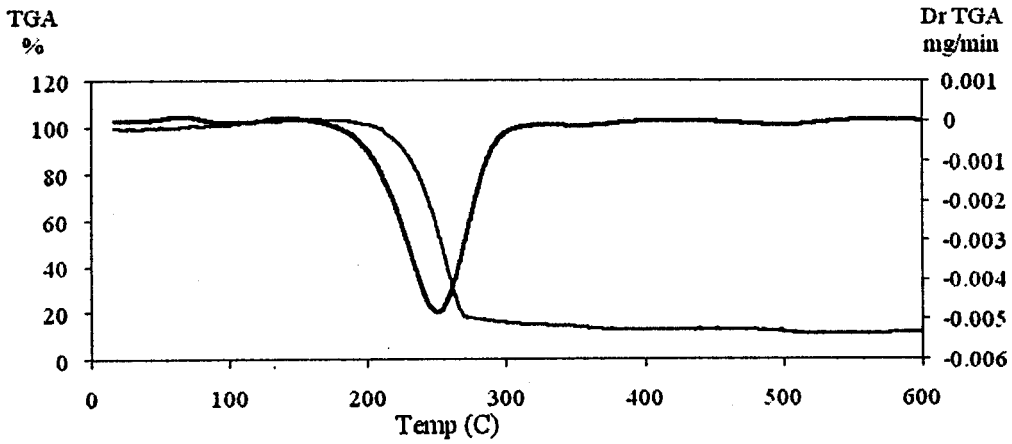


Fig (1) TGA and DTG Curves of NTH

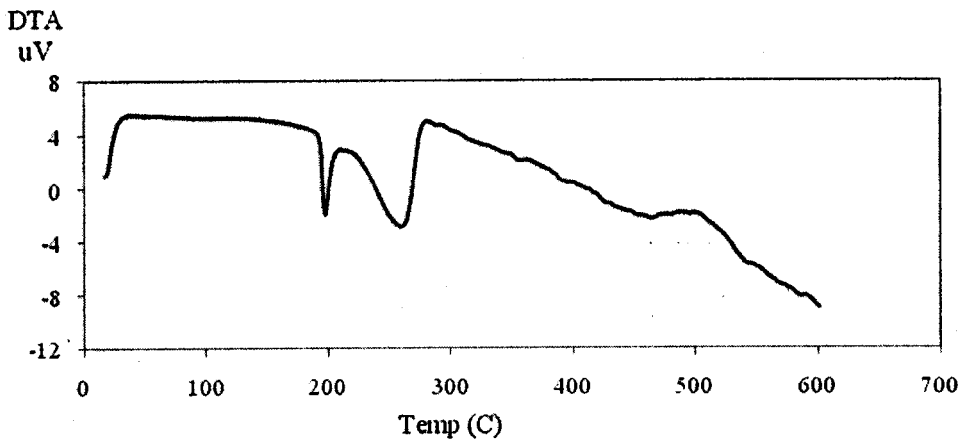


Fig (2) DTA Curve of NTH

Table (3) Kinetic Parameters of NTH

Method	$\Delta S^{\#}$ (J mol^{-1} K^{-1})	$\Delta H^{\#}$ (kJ mol^{-1}) $\times 10^2$	$\Delta G^{\#}$ (kJ mol^{-1}) $\times 10^3$
B	-73	41.82	42.63
CR	-45	41.75	27.70
HM	-58	41.71	26.10
MKN	-195	41.72	106.12
VK	-209	50.95	136.51
MC	-86	41.59	48.87
WYHC	-144	41.88	78.92

Table (2)

Kinetic Parameters of the Thermal Decomposition of NTH

Method	$E_a(kJmol^{-1})$	ln A (s^{-1})	r^2
B	145	15.0×10^8	0.991
CR	153	47.3×10^9	0.990
HM	156	40.3×10^8	0.985
MKN	156	60.6×10^4	0.991
VK	130	2.9×10^3	0.981
MC	157	3.5×10^8	0.990

Table (1)

Algebric Expression for the Most Frequently Used Mechanisms of Solid State Process

No	Mechanism	Symbol	Differential form $f(x)$	Integral form $g(x)$
Sigmoidal curves (Nucleation and nuclei growth (Avrami-Erofeev equ.)				
1	N and G (n=1)	A_1	$(1-\alpha)$	$[-\ln(1-\alpha)]$
2	N and G (n=1.5)	$A_{1.5}$	$(3/2)(1-\alpha)[-\ln(1-\alpha)]^{1/3}$	$[-\ln(1-\alpha)]^{2/3}$
3	N and G (n=2)	A_2	$2(1-\alpha)[-\ln(1-\alpha)]^{1/2}$	$[-\ln(1-\alpha)]^{1/2}$
4	N and G (n=3)	A_3	$3(1-\alpha)[-\ln(1-\alpha)]^{2/3}$	$[-\ln(1-\alpha)]^{1/3}$
5	N and G (n=4)	A_4	$4(1-\alpha)[-\ln(1-\alpha)]^{3/4}$	$[-\ln(1-\alpha)^{1/4}$
Deceleration curves				
6	Uni-dimensional diffusion (parabolic law)	D_1	$1/(2\alpha)$	α^2
7	Two- dimensional diffusion	D_2	$1/-(\ln(1-\alpha))$	$(1-\alpha)\ln(1-\alpha)+\alpha$
8	Three- dimensional diffusion (jander eq.)	D_3	$1.5[(1-\alpha)^{-1/3}-1]$	$(1-2\alpha/3)-(1-\alpha)^{2/3}$
9	Three-dimensional diffusion (Ginstling--Brounshtein)	D_4	$[1.5(1-\alpha)^{2/3}][1-(1-\alpha)^{1/3}]^{-1}$	$[1-(1-\alpha)^{1/3}]^2$
10	Three-dimensional diffusion	D_5	$(3/2)(1+\alpha)^{2/3}[(1+\alpha)^{1/3}-1]^{-1}$	$[(1+\alpha)^{1/3}-1]^2$
11	Three-dimensional diffusion	D_6	$(3/2)(1+\alpha)^{4/3}[1/(1+\alpha)^{1/3}-1]^{-1}$	$[1/(1+\alpha)^{1/3}-1]^2$

Gibbs free energy, $\Delta G^{\#}$, were calculated from the following relations respectively.

$$\Delta G^{\#} = \Delta H^{\#} - T_s \Delta S^{\#}$$

Table (3) summarizes the thermodynamic and kinetic parameters (enthalpy $\Delta H^{\#}$, activation entropy $\Delta S^{\#}$ and the free energy of activation $\Delta G^{\#}$) of NTH which were obtained by the different methods examined in this study. Results go along with the fact that the values of $\Delta H^{\#}$ and $\Delta G^{\#}$ depend on the type (strength) of the bond being stretched to arrive at the activated complex (compound just prior to decomposition). The negative value of $\Delta S^{\#}$ means that the activated compound, the reactant at the transition state, is more ordered and the degrees of freedom of rotation as well as of vibration are less than they are in the non activated compound (at the beginning of the thermal decomposition).

Conclusion

A study on the thermal decomposition of NTH was carried out with several kinetic methods. The kinetics of thermal decomposition was investigated by thermogravimetric analysis obtained at a single heating rate 10°C/min. One main step was observed in the thermal decomposition reaction of NTH which proved to be first order reaction. The activation energy of thermal decomposition was determined using CR, MC, HM , VK, B, MKN and WYHC were 153, 157, 156, 130, 145, 156, 140 kJ mol^{-1} respectively. Thermal degradation mechanism for NTH is a decelerated D_n type, which indicates a solid state process based on n-dimensional diffusion. The thermodynamic functions of activation: $\Delta S^{\#}$, $\Delta H^{\#}$, $\Delta G^{\#}$ were also calculated. Negative values of $\Delta S^{\#}$ indicates a highly ordered activated complex and the degrees of freedom of rotation as well as of vibration are less than they are in the non-activated complex.

molecule, at the time of decomposition, is taken as a function of the active positions of the various atoms of the molecule. There will be a configuration of the atoms of minimum potential energy, related to the activation energy, through which or near which the system (molecule) is expected to pass while going to the products. This region of configuration space is the transition state and the system in the transition state is the activated complex.

The transition state theory treats the activated complex formally as a molecule (species) in spite of its ill-defined nature and transitory existence. In this work, the geometry of the decomposing molecule is a decisive factor in the rate and mechanism of decomposition. The application of the activated complex theory to calculate the thermodynamic functions of activation during the thermal decomposition of NTH is quite adequate.

Application of the theory of activated complex to the thermal decomposition of NTH means that one assumes that the compound arrives to a transition state just before decomposition. The relation between the pre-exponential factor, A, and the entropy of activation is[15]

$$A = e^{n}\left(c^{0}\right)^{1-n}\left(\frac{RT}{N_A h}\right)e^{\Delta S^{\#}/R} \qquad (15)$$

Where n is the order of the reaction, h Plank's constant and N_A is the Avogadro's number. The term c^0 is the standard state concentration (1 mol/l at a pressure of 1 bar and temperature of 298.15K) and is added in case of bimolecular reactions and is unity in case of unimolecular reactions. For a first-order reaction eq. (15) is arranged to

$$\Delta S^{\#} = R\ln\left(\frac{Ah}{k_B T_s}\right)$$

Where k is the Boltzmann constant, h is the Plank's constant and T_s is the DTG peak temperature.

The activation energy related to the enthalpy activation, $\Delta H^{\#}$, can be calculated by [16]

$$E_a = \Delta H^{\#} - nRT_s$$

Thermal data obtained at a single heating rate 10°C/min were evaluated with the CR, MC, HM, VK, B, MKN and WYHC. The Criado-Malek-Ortega method was used for kinetic analysis. In all these methods the decomposition activation energy was calculated at $0.05 < \alpha < 0.90$. In all methods, the thermal degradation process is considered to be of first-order and the calculations are done accordingly. The linearization curves of NTH obtained using the methods mentioned above and presented in Figs. 4–11.

Moreover, Table (2) summarizes the values of activation energies, E_a, the pre-exponential factors, A, and correlation coefficient, r^2, which were obtained by the different methods examined in this study. The E_a values obtained with the CR, HM, MKN, MC were 153, 156, 156, 157 kJ/mol respectively. The results show that these methods are in good agreement with each other while the E_a obtained by B and WYHC were 145 , 140 kJ/mole which shows that they are 10-20 kJ/mol less, while VK method showed the least E_a value 130 kJ/mol. As shown, the values of r^2 for the linearization curves of NTH were approximately 1.00.

In reaction kinetics, the frequency factor (A) indicates the collision fraction between the molecules that present enough energy to lead to a decomposition reaction. Differences between the values of the frequency factor (A) obtained by the different methods used in this study may be due to the different approximations used by each method.

Theoretical master curves were used to determine the reaction mechanism which according to Criado et al, a master plot that is a characteristic curve independent of the condition of the measurement. Master curve plots of $z(\alpha)$ versus α for different mechanisms are illustrated in Fig.(11). The experimental data of $z(\alpha)$ for NTH agrees very well with the deceleration D_6 master curve.

Activation complex theory gives a rate equation which although simple, provides a frame work in terms of which even quite complicated reactions can be understood in a qualitative way and wherein various assumptions and approximations are involved[14]. The theory takes in consideration, at least in principle, all the internal motions of the reacting molecule. The potential energy of the

case, the fourth rational expression of Senum and Yang[13] has been used. Combining eq. (2) and (13), we obtain the following

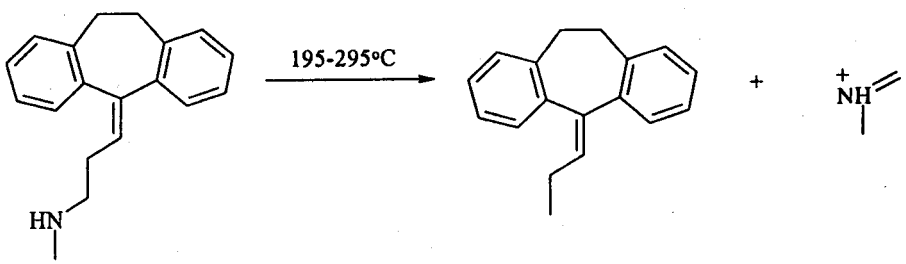
$$z(\alpha) = f(\alpha)F(\alpha) \qquad (14)$$

Where $F(\alpha)$ is a function dependence on the real reaction mechanism.

Then the master curves of different models listed in Table (1) can be obtained following this function. Comparing the plots of $z(\alpha)$ calculated by eq. (13) using the experimental data with the master curves, the mechanism of a solid –state process can be determined.

In the equations above α, g(α), β, T_s, E_a , A , R are degree of reaction, integral function of conversion, heating rate, DTG peak temperature, activation energy (kJ mol^{-1}), pre-exponential factor (s^{-1}) and gas constant (8.314 J mol^{-1} K^{-1}) respectively.

NTH was studied by thermogravimetric analysis from room temperature to 600°C in nitrogen atmosphere to examine the degradation processes and kinetic parameters. Typical TG, DTG and DTA curves are shown in Fig. (1) and Fig. (2) respectively. Fig. (3) shows the relation between the fraction decomposed ,α, and the temperature, which indicates one main region of thermal decomposition. As shown, from TG curve, that the drug showed one weight loss stage in the range 195-295°C. The stoichiometry of a possible decomposition mechanism of NTH is shown in scheme 1.



Scheme 1 A mechamism for the thermal decomposition of NTH

Madhusudanan-Krishnan-Ninan method

An integral method where the activation energy can be calculated from the following equation:

$$\ln\left[\frac{g(\alpha)}{T^{1.9206}}\right] = \ln\left(\frac{AE_a}{\beta R}\right) + 3.7678 - 1.9206\ln E - 0.12040\left(\frac{E}{T}\right) \qquad (11)$$

The plot of $\ln\left[\frac{g(\alpha)}{T^{1.9206}}\right]$ versus the reciprocal of the absolute temperature gives linear curves. E_a and A can be calculated from the slope and intercept, respectively.

Wanjun-Yuwen-Hen-Cunxin method

An approximate method from which the activation energy can

$$\ln\left(\frac{g(\alpha)}{T^{1.894661}}\right) = \left[\ln\frac{AE_a}{\beta R} + 3.63504095 - 1.89466100\ln E\right] - 1.00145033\frac{E_a}{RT} \qquad (12)$$

Plotting $ln\frac{g(\alpha)}{T^{1.894661}}$ versus 1/T, the activation energy E_a is obtained from the slope and the pre-exponential factor A can be calculated by inserting E_a and heating rate β into the interception,

$$\left[\ln\frac{AE_a}{\beta R} + 3.63504095 - 1.894661\ln E_a\right] \; g(\alpha)$$

Determination of the kinetic model by Criado-Malek-Ortega method

If the value of the activation energy is known, the kinetic model of the process can be determined by this method Criado *et al.* define the function

$$z(\alpha) = \frac{(d\alpha/dt)}{\beta}\pi(x)T \qquad (13)$$

where $x = E/RT$, and $\pi(x)$ is an approximation of the temperature integral which cannot be expressed in a simple analytical form. In this

If the reaction order ,n, is unknown, T_s is defined for the maximum heating rate. $\ln g(\alpha)$ is plotted versus θ, resulting in a straight line whose slope is E_a/RT of which E_a was calculated. The pre-exponential factor , A, was calculated from the equation:

$$\frac{E_a}{RT_s^2} = \frac{A}{\left[\beta exp\left(-\frac{E_a}{RT_s}\right)\right]}$$

Van Krevelen method

A method based on approximate integration of the rate equation.

$$lng(\alpha) = ln\left[\frac{A(0.368/T_s)^{\frac{E_a}{RT_s}}}{\beta\left(\frac{E_a}{RT_s}+1\right)}\right] + \left(\frac{E_a}{RT_s}+1\right)lnT \qquad (9)$$

The plot of $\ln g(\alpha)$ against lnT gives a straight line can for a correctly chosen value of n. Activation energy, E_a , and the pre-exponential factor ,A, can be determined from the slope and the intercept of the line respectively.

Broido's method

An approximation method where the activation energy can be calculated from the following equation:

$$ln\left[\left(ln\frac{1}{y}\right)\right] = -\frac{E_a}{R}\cdot\frac{1}{T_s} + ln\left(\frac{R}{E_a}\cdot\frac{A}{\beta}T_s^2\right) \qquad (10)$$

Plots of ln(ln1/y) versus 1/T , gives a straight line where y is the fraction of number of initial molecules not yet decomposed $y = (W_t - W_\infty)/(W_0 - W_\infty)$ where E_a can be calculated from the slope. While the pre-exponential factor (lnA) can be calculated from the relation

$$-\ln\left(\ln\frac{1}{y}\right) = \frac{E_a}{R}\times T_s - \ln A\times\frac{R}{E_a}$$

The kinetic parameters (the activation energy E_a and the pre-exponential factor A) were calculated by applying all the following methods to TG/DTG data, assuming the different reaction orders. The order related to the most appropriate mechanism is presumed to lead to the linear plot, using the following different methods.

Coats-Redfern method

Using an asymptotic approximation for the resolution of eq. (3) we can obtain the following equation:

$$\ln\left[\frac{g(\alpha)}{T^2}\right] = \ln\left[\frac{AR}{\beta E_a}\left(1-\frac{2RT}{E_a}\right)\right] - \frac{E_a}{RT} \qquad (6)$$

A plot of $\ln\left[\frac{g(\alpha)}{T^2}\right]$ against 1/T results a straight line with slope ($-E_a/R$) where E_a (activation energy) and intercept of $\ln(AR/\beta E_a)$ where A (pre-exponential factor) is calculated.

MacCallum-Tanner method

An approximate method of the rate of degradation as a function of temperature expressed by :

$$log g(\alpha) = log\frac{AE}{\beta R} - 0.4828E_a^{0.4351} - \frac{(0.449+0.217E_a)\times 10^5}{T_s} \qquad (7)$$

A plot of $log g(\alpha)$ against 1/T, gives a straight line. E_a and A can then be calculated from the slope and the intercept of the line, respectively.

Horowtiz-Metzger method

An approximate integration method of the rate equation. In this method Horowtiz-Metzger introduced a characteristic temperature, T_s and a parameter θ such that $\theta = T - T_s$. If n, the reaction order, is 1, T_s is defined as the temperature at which $(1-\alpha)_s = 1/e = 0.368$, and the final expression is:

$$ln\, g(\alpha) = \frac{E_a}{RT_s^2} \qquad (8)$$

Results and Discussion

Non-isothermal methods have been extensively used for the study of the kinetics and mechanism of condensed phase reactions. In general, most methods of kinetic analysis of thermoanalytical data begin with the well known Arrhenius equation eq. (1) and the rate expression eq.(2)

$$k = Aexp\left(-\frac{E}{RT}\right) \qquad (1)$$

$$\frac{d\alpha}{dt} = kf(\alpha) \qquad (2)$$

Where k is a specific rate constant, A is the pre-exponential factor(min^{-1}), E is the activation energy (kJ/mol), R is the gas constant ($8.314 Jmol^{-1}K^{-1}$) and T is the temperature. $f(\alpha)$ is a so called kinetic function that depends on the reaction mechanism, and α represents the fractional conversion (increasing from 0 to 1) in the solid reactant during the course of the reaction. If $f(\alpha)= (1-\alpha)^n$ (where n is the reaction order) and, with a constant temperature increase, $dT/dt=\beta$ [where β is the heating rate ($^oCmin^{-1}$)], the integration of eq. (2) leads to

$$g(\alpha)= \int_0^{\alpha}\left[\frac{1}{(1-\alpha)^n}\right]d\alpha = \frac{A}{\beta}\int_{T_0}^{T}\exp\left(\frac{-E_a}{RT}\right)dT \qquad (3)$$

where g(α) is the integral function of the conversion and T_0 is the initial temperature. For the special case of n = 1

$$\int_0^{\alpha}\left[\frac{1}{(1-\alpha)^n}\right]d\alpha = -\ln(1-\alpha) \qquad (4)$$

For n not equal to zero or unity

$$\int_0^{\alpha}\left[\frac{1}{(1-\alpha)^n}\right]d\alpha = \frac{1-(1-\alpha)^{1-n}}{1-n} \qquad (5)$$

The evaluation of drug stability in the solid state is mostly made by analyzing their decomposition under non-isothermal conditions.

The non-isothermal thermogravimetry (TG) with a linear temperature growth is a method frequently used to characterize materials from their thermal behavior standpoint. In addition it enables to determine apparent kinetic parameters of heterogeneous reactions (the activation energy E_a and the frequency factor A). Considerable attention is paid to the kinetic parameters calculation from TG curves.

The aim of this work is to describe the thermal behavior, kinetic and thermodynamic parameters of NTH and calculate the values of activation energy. In this study, the NTH drug was investigated by means of thermal analysis (TG-DTG). The results allowed us to acquire information concerning this drug in the solid state, including their thermal stability and thermal decomposition. Also, this study seeks for determination of kinetic parameters of non-isothermal decomposition of the compounds. To the best our knowledge, there is no previous report on the thermal behavior of this drug.

In this work, we have selected the following methods, representative of different categories and applied several equations to describe the thermal behaviors of NTH to determine the kinetic parameters of the thermal decomposition by means of Caots-Redfern[5] (CR), MacCallum-Tanner[6](MC), Horowitz-Metzger[7](HM), Van Krevelen[8](VK), Broido[9](B), Madhusudanan-Krishnan-Ninan[10](MKN), Wanjun-Yuwen-Hen-Cunxin[11](WYHC) and Criado-Malek-Ortega[12] methods.

Experimental

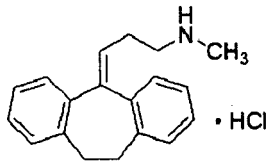
Material

NTH were supplied by Sigma (St. Louis, MO).

Physical Measurements

The DTA,TG and DTG curves were obtained with Shimadzu TGA-50 thermobalance. The measurements were performed with dynamic nitrogen furnace atmosphere at a flow rate of 20 ml min^{-1} up to 600^0C. The heating rate was 10^oC min^{-1} and the sample was of mass 1.848 mg for NTH which was contained in an alumina crucible.

1950s, tricyclic antidepressants remain a widely prescribed class of antidepressants. Nortriptyline hydrochloride (NTH) (3-(10,11dihydro5Hdibenzo[*a*,*d*]cyclohepten-5-ylidene)-*N*-methylpropylamine hydrochloride), is a tricyclic antidepressant widely used in the treatment of unipolar depression. Besides that, there is growing evidence of its efficacy for smoking cessation pharmacological therapy[1].



Nortriptyline Hydrochloride

Thermal analytical techniques can provide important information regarding storage and stability of pharmaceuticals. Also, kinetic parameters obtained from thermoanalytical data are highly useful for making predictions of performance parameters of drugs, for example, ''shelf life.''

On the other hand, understanding the response of drugs and their formulations to thermal stresses is an integral part of the development of stable medicinal products. Thermal analytical methods have thus become important tools for the development of modern medicines [2]. These are precise and accurate techniques with low sample requirements, and can provide detailed information about new chemical entities even at the very earliest stages of discovery and development of the new compositions and drugs [3]. One main purpose for the kinetic analysis of solid decomposition is to determine the reaction mechanism(s) and to calculate the Arrhenius parameters [4].

Great significance of NTH in the medicine and pharmacy is the reason for studies of the physico-chemical and the thermal properties, where thermal methods of analysis are widely used in the study of stability and thermal decomposition of substances used as medicine.

NON-ISOTHERMAL KINETIC STUDY OF THE THERMAL DECOMPOSITION OF NORTRIPTYLINE HYDROCHLORIDE

Laila T. Kamel*

Thermogravimetric study of nortriptyline hydrochloride (NTH) was investigated by thermal analysis. Thermal data obtained at a single heating rate 10°C/min. One main step was observed, which proved to be first order reaction. Seven single rate kinetic methods (Caots-Redfern (CR), MacCallum-Tanner (MC), Horowitz-Metzger (HM), Van Krevelen (VK), Broido (B), Madhusudanan-Krishnan-Ninan (MKN), Wanjun-Yuwen-Hen-Cunxin (WYHC) were used to investigate the thermal decomposition and to calculate the activation energies of thermal decomposition E_a and pre-exponential factor A. The E_a values obtained with the CR, HM, MKN, MC methods were in good agreement with each other while the E_a obtained by B and WYHC are in good agreement with each other but shows that they are 10-20 kJ/mol less, while VK method showed the least E_a value. Thermodynamic parameters (entropy change $\Delta S^{\#}$, enthalpy change $\Delta H^{\#}$, free energy change $\Delta G^{\#}$) were also calculated. Analyses of the experimental results were studied by Criado-Malek-Ortega master plot method which suggested that the actual decomposition mechanisms of NTH were a D_n deceleration type.

Introduction

Tricyclic antidepressants are a class of drugs commonly used to treat patients with major depressive disorder, panic disorder, social phobia, narcolepsy, and chronic pain syndromes. Though the options for pharmaceutical treatment of these psychological disorders have increased since the introduction of tricyclic antidepressants in the late

* Expert, Narcotic Research Department, National Center for Social and Criminological Research.

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