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A rising temperature kinetic model to describe complex reaction kinetics of a drug: procainamide hydrochloride

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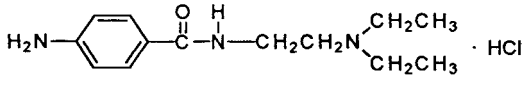
Abstract

The drug, procainamide hydrochloride ($NH_2C_6H_4CONHCH_2CH_2N(CH_2CH_3)_2HCl$), was studied using a simultaneous thermogravimetric–differential thermal analysis unit (TG–DTA) in an atmosphere of nitrogen. The study covered the range of temperature from ambient to 800°C. The DTA showed a melting point at 169°C followed by a two stage endothermic transition. The TG–DTG plots clearly showed this two-stage transition. A kinetic analysis of the two stages was attempted. The best fit appeared to be a first order mechanism for both stages. It also was noted that the values of E_{act} varied as the reaction progressed. Supportive evidence regarding the study was obtained from a range of other physio-chemical measurements. © 2000 Published by Elsevier Science B.V.

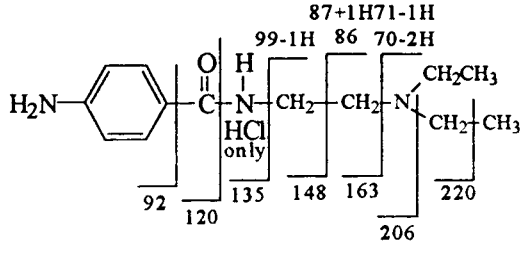
Keywords: Procainamide hydrochloride; Kinetics; Thermal analysis; TG–DTA

1. Introduction

The drug procainamide hydrochloride finds a use pharmaceutically as a cardiac depressant, especially as an antiarrhythmic. It is used in tablet form mixed with various excipients. The present study was initiated to see if thermal analysis could be used to fingerprint the presence of the material and to determine the manner of its degradation as an aid to quality control. Thermal analysis on this material has been studied by Valenti [1] using differential thermal analysis (DTA). A sharp endotherm due to melting was reported in the range of 168.4–169.2°C. Valenti also conducted a DSC study to establish the purity of procainamide hydrochloride. There appears to be no thermal analysis studies beyond the melting point region. The formula for procainamide hydrochloride is $C_{13}H_{22}N_3OCl$ and it has the structure:



Some insight into possible thermal degradation routes may be found in the reported mass spectra fragmentation pattern, which can be represented by the reported assignments [1] as shown.



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2. Materials and methods

The procainamide hydrochloride used in the present study was obtained from Sigma Chemical Company (Lot # 53H2518). It is a white microcrystalline material. Scanning electron microscopy (SEM) studies, using JOEL JSM-6100 scanning electron microscope, showed particles with round edges. This indicates possible surface diffusion or surface melting has occurred (see Fig. 1). Optical Microscopy, using a Reichert model # 355 169 connected to a Sony television and a color video printer mavigraph, reveals an aggregation of the particles (see Fig. 2).

The thermal analysis system used was a simultaneous TG–DTA unit from TA Instruments, Model # 2960, used with the Thermal Analyst 2000 work station using a TA operating system, Version 1.0B. The runs were conducted using platinum crucibles containing approximately 10 mg of the sample. An empty crucible was used as the reference. The study was carried out in an atmosphere of dry nitrogen at a flow rate of 100 ml min^{-1}, over the temperature range of ambient to 800°C at a heating rate of 10°C min^{-1}. Several runs were performed on the sample with identical results. The flow rate was regulated using an electronic flow meter from J. & W. Scientific.

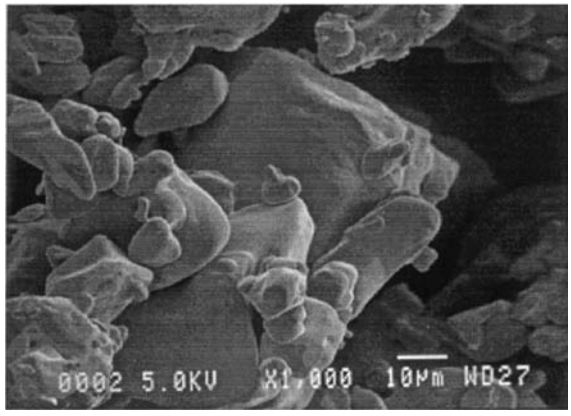


Fig. 1. SEM of procainamide hydrochloride.

The X-ray powder diffraction analysis was done using a Scintag XRD 2000 X-ray powder diffractometer (see Fig. 3 and Table 1).

3. Results and discussion

Fig. 4 shows a TG–DTG plot for the decomposition of procainamide hydrochloride. The DTG plot shows a perturbation at 169°C, the melting point of the

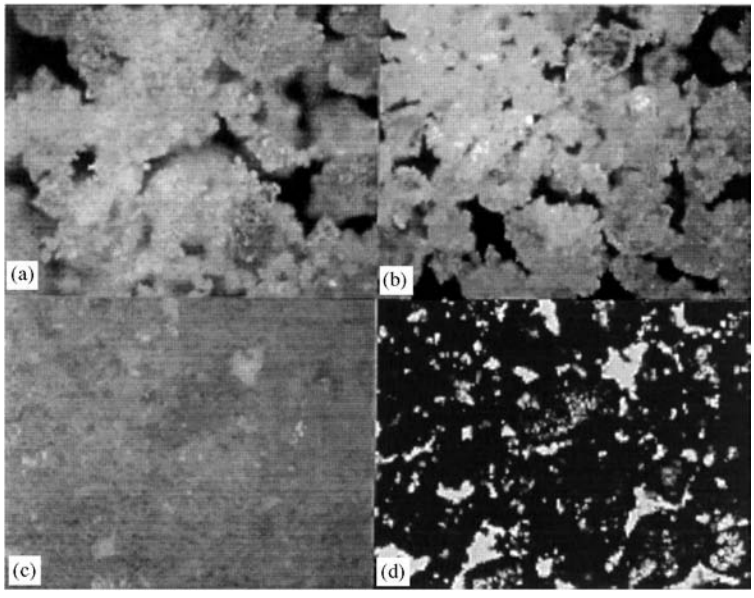


Fig. 2. Optical microscopy, using Reichert model # 355 169 of procamamide hydrochloride under: (a) oblique-reflected light; (b) polarized light; (c) bright field and (d) transmitted light.

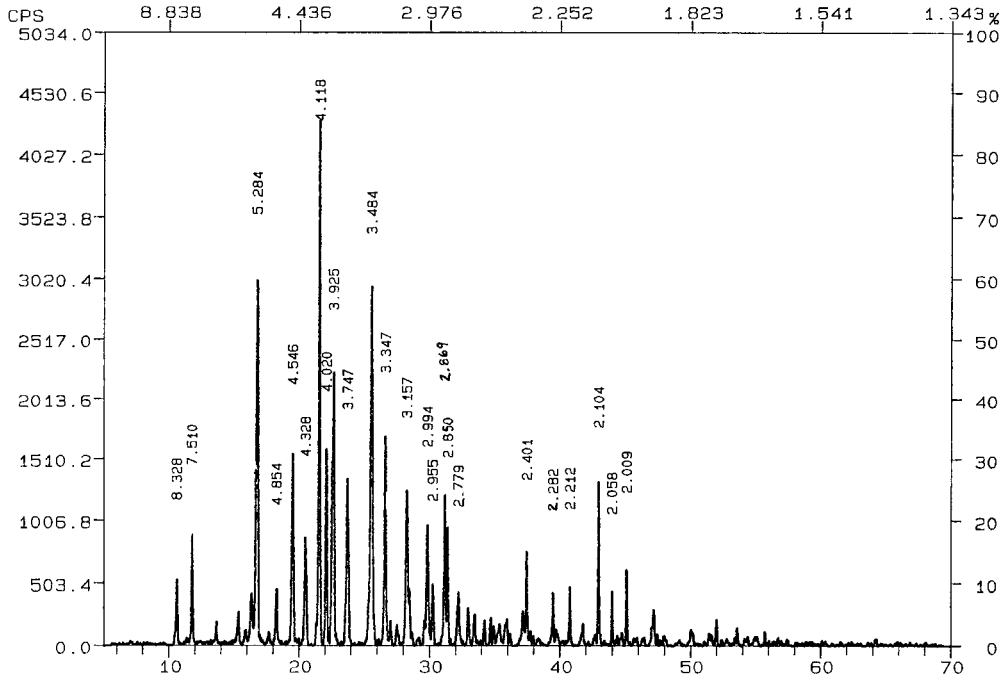


Fig. 3. X-ray powder diffraction spectra of procainamide hydrochloride.

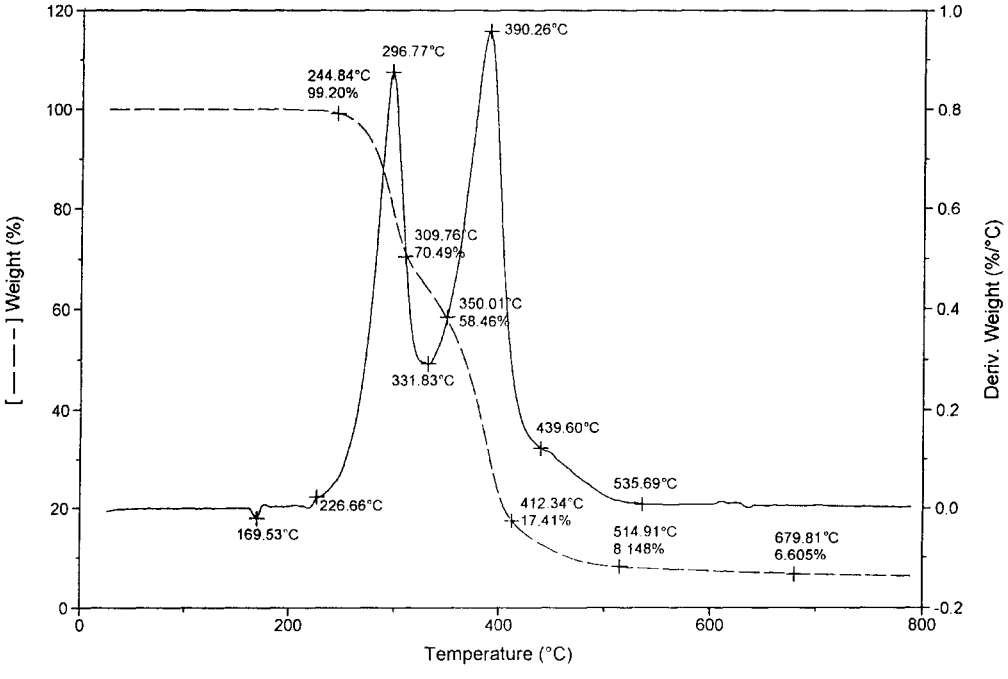


Fig. 4. A typical TG–DTG plot of percentage mass loss vs. temperature for the decomposition of procainamide hydrochloride.

Table 1
The X-ray powder diffraction analysis data for procainamide hydrochloride

2θ	D-Spacing	Intensity
10.6141	8.32822	12
11.3859	7.46530	1
13.6353	6.48893	4
16.7644	5.28415	79
18.2638	4.85359	11
19.5097	4.54634	39
20.5028	4.32831	22
21.5606	4.11829	100
22.0950	4.01988	38
22.6344	3.92529	57
23.7266	3.74701	33
25.5494	3.48366	74
26.6116	3.34698	42
28.2484	3.15664	31
29.8209	2.99367	25
30.2203	2.95501	12
31.1525	2.86868	27
31.3578	2.85037	22
32.1841	2.77905	11
37.4291	240079	17
39.4519	2.17223	10
40.7597	2.21197	10
42.9500	2.10410	29
43.9700	2.05762	9
45.0919	2.00900	14

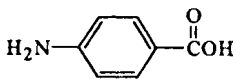
material. There is a noticeable two-stage endothermic process that shows up in all of the TG–DTG runs completed for procainamide hydrochloride in a nitrogen atmosphere.

Fig. 5 shows a DTA plot of the decomposition. It is clear that the melting point is 169°C due to the sharp endothermic peak at that temperature. There are also two other endothermic peaks associated with the transition.

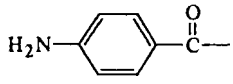
Fig. 6 shows a temperature versus time plot. They are useful plots in that they confirm the temperature regime as being between 9.8 and 9.9°C min^{-1} with some perturbations at the melting point and the two transitions. Previous studies show that the perturbation is of a kind that is associated with endothermic processes [2].

3.1. Kinetics discussion

There was a carbon char left as a residue at the end of the experiment. This was formed from liquid procainamide hydrochloride as the melting had taken place at 169°C and the two-stage decomposition was noted in the temperature range of 241–538°C. Consideration of the reported fragmentation pattern of the mass spectra would suggest several steps, such as the degradation into the fragments noted. There is a note in references for degradation from solution that



is a possible cleavage product [1] which taken together with the mass spectra data would suggest the fragment



is one of the early products. Breakdown to a carbon residue would probably be from a simpler compound. Logically this would suggest a variety of degradation steps each with its own individual activation energy. The TG data suggests two of the processes are rate controlling in a limited temperature range. It seems possible that an order type reaction might be a suitable reaction mechanism. A variation in the energy of activation could be recorded as the temperature is advanced. Accordingly, the first-order rate constants were determined in the two temperature ranges 226–298°C and 326–392°C using 2° intervals in the following manner. The expression for k is given by:

$$k = \frac{\mathrm{d}\alpha/\mathrm{d}t}{1-\alpha} \tag{1}$$

where k is the rate of decomposition and α, the fraction decomposed. By using the print out for every degree, k was calculated using every 2°. It is defined by:

$$\alpha = \frac{\%w_\mathrm{i} - \%w_t}{\%w_\mathrm{i} - \%w_\mathrm{f}} \tag{2}$$

where $\%w_\mathrm{i}$ is the initial percent weight; $\%w_t$, the percent weight at time t and $\%w_\mathrm{f}$, the final percent weight.

At any temperature, T_{n-1} of a rising temperature reaction the Arrhenius expression gives:

$$\ln k_{T_{n-1}} = \ln A - \frac{E_\mathrm{act}}{RT} \tag{3}$$

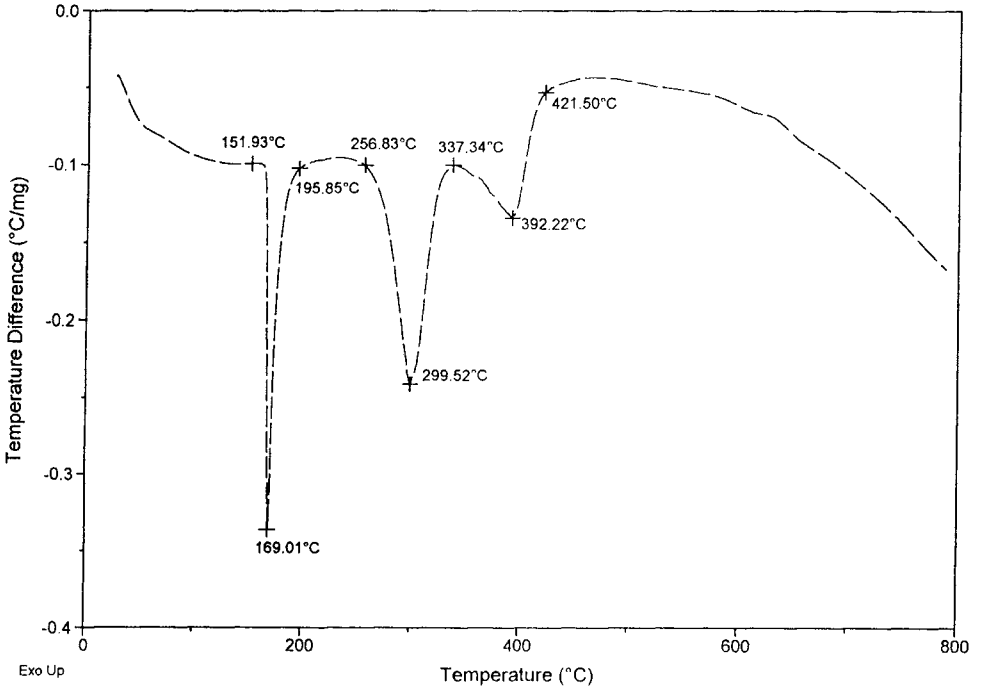


Fig. 5. A typical DTA plot of temperature difference vs. temperature for the decomposition of procainamide hydrochloride.

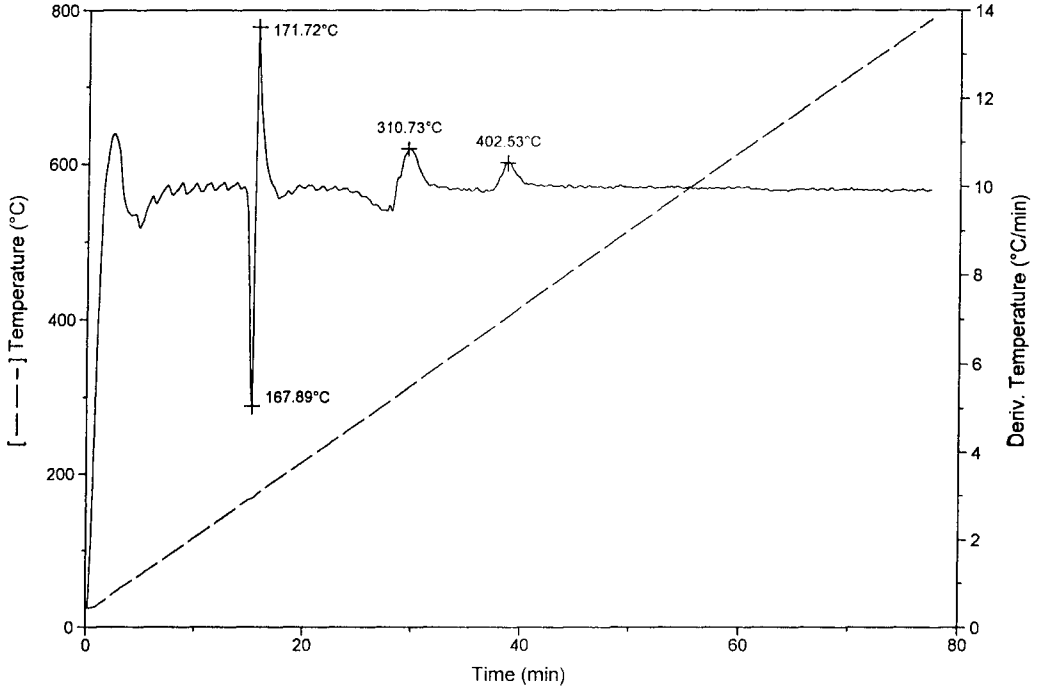


Fig. 6. Time–temperature plot and its first derivative for procainamide hydrochloride.

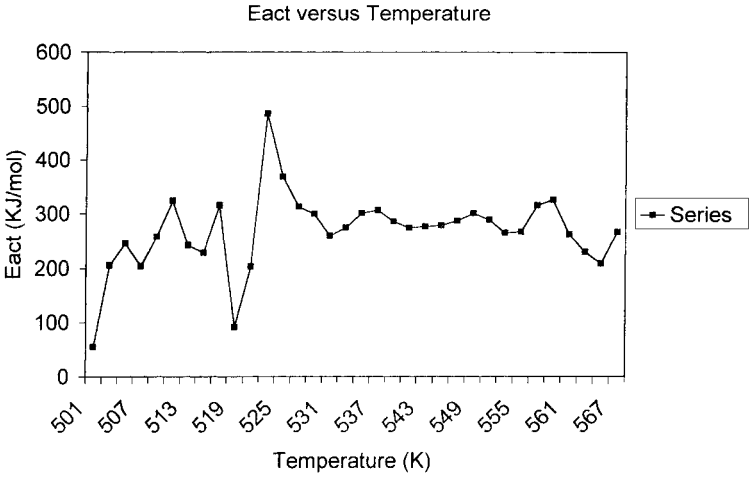


Fig. 7. A graph of the energy of activation vs. temperature for the first stage of the decomposition of procainamide hydrochloride.

Then at temperature T_{n+1}:

$$\ln k_{T_{n+1}} = \ln A - \frac{E_{act}}{RT} \tag{4}$$

Based on these assumptions, we obtain the expression:

$$\ln\left(\frac{k_{T_{n-1}}}{k_{T_{n-1}}}\right) = -\frac{E_{act}}{RT_{n-1}} + \frac{E_{act}}{RT_{n-1}} = \frac{E_{act}}{R}\left(\frac{1}{T_{n+1}} - \frac{1}{T_{n-1}}\right) \tag{5}$$

Simplifying this then gives:

$$\ln\left(\frac{k_{T_{n-1}}}{k_{T_{n+1}}}\right) = -\frac{2E_{act}}{RT_{n+1}T_{n-1}} \tag{6}$$

It can then be assumed that:

$$T_n^2 = T_{n+1}T_{n-1} \tag{7}$$

Which then gives:

$$\ln\left(\frac{k_{T_{n-1}}}{k_{T_{n+1}}}\right) = -\frac{2E_{act}}{RT_n^2} \tag{8}$$

This then allows us to calculate the activation energy for the two stages using the expression:

$$E_{act} = -\frac{1}{2}\ln\left(\frac{k_{T_{n-1}}}{k_{T_{n+1}}}\right)RT_n^2 \tag{9}$$

It was found that E_{act} varied throughout the two stages.

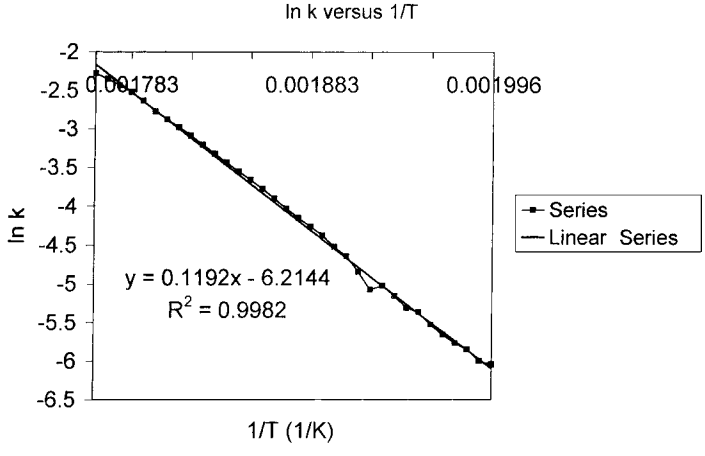


Fig. 8. A graph of the $\ln k$ vs. T^{-1} for the first stage of the decomposition of procainamide hydrochloride.

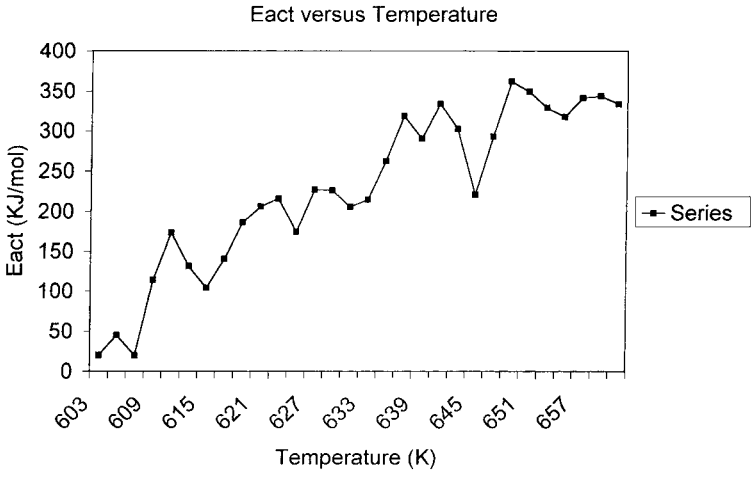


Fig. 9. A graph of the energy of activation versus temperature for the second stage of the decomposition of procainamide hydrochloride.

3.2. Kinetics results

Fig. 7 shows that from 522 to 568 K the E_{act} calculated in this way varied from 125.69 kJ mol^{-1} at 522 K to 134.799 kJ mol^{-1} at 568 K. This kind of variation accounts for the systematic variation from the least straight line shown in the plot of ln k versus T^{-1} for this stage (Fig. 8). The calculation of E_{act} by this 'general chemistry' method for the second stage showed a continuous variation from 24.99 kJ mol^{-1} at 600 K to 108.38 kJ mol^{-1} at 664 K (Fig. 9). This variation is relatively larger than for the first stage and then is reflected in a larger but similar systematic variation from the 'best' linear plot of ln k versus T^{-1} shown for this second stage (Fig. 10). It would seem that this 'general chemistry' method of calculating E_{act} over very small temperature increments is very sensitive and demonstrates variations in E_{act} which can only be suspected from the plots of ln k against T^{-1} [3]. The intermediate period between the two regions where the kinetic analysis was attempted corresponds to the overlapping of the peaks shown in Fig. 4. In a complicated series of reaction mechanisms that must occur in the degradation of procainamide hydrochloride to a carbon residue, it would be expected that in some temperature regions, one reac-

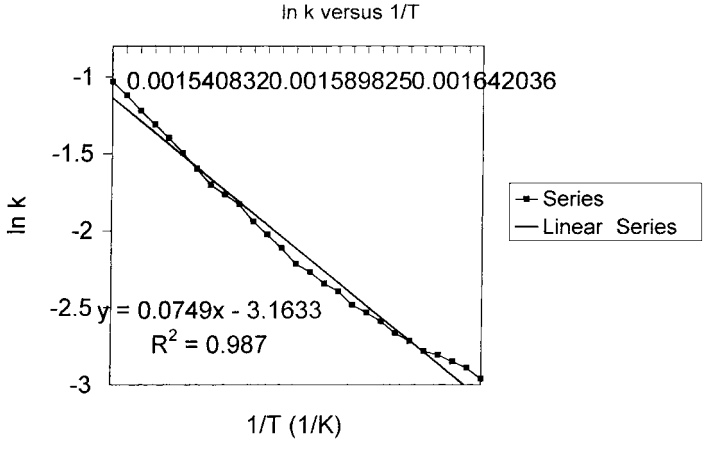


Fig. 10. A graph of the ln k vs. T^{-1} for the second stage of the decomposition of procainamide hydrochloride.

tion mechanism is rate controlling while in another temperature region a different reaction mechanism is rate controlling.

4. Conclusion

It is concluded that in a system where a material is degrading by a series of reaction mechanisms, the rate controlling mechanism varies in different temperature regions. The difference methods provided in most general chemistry textbooks, when taken over small temperature increments, is sufficiently precise to demonstrate the allocation in the energy of activation as the reaction proceeds. This contention is illustrated by detailed analysis on procainamide hydrochloride. It is further shown that the use of plots of ln k versus T^{-1} over wide ranges of temperature show small systematic variations from the 'best' straight line which can be explained by the basis of this 'general chemistry' approach.

References

[1] Raymond B. Poet, Harold Radin, in: Klaus Florey (Ed.), Analytical Profiles of Drug Substances, Vol. 4, Academic Press, New York, 1975.
[2] S. Lerdkanchanaporn, D. Dollimore, K.S. Alexander, J. Thermal Anal. 49 (1997) 887–896.
[3] Kenneth W. Whitten, Raymond E. Davis, M. Larry Peck, General Chemistry with Qualitative Analysis, 5th Edition, Saunders College Publishing, New York, 1996, pp. 623–629.