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Thermal analysis study on vaporization of some analgesics. Acetanilide and derivatives

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Abstract

The thermal behaviour of acetanilide (Ac) and two of its analogues, namely the *para*-ethoxyacetanilide (*p*-Eto Ac) and the *para*-bromoacetanilide (*p*-Br Ac), which are used as analgesics in the pharmaceutical industry was studied with a simultaneous TG/DSC unit. The examined analgesics showed two endothermic DSC peaks due to melting and vaporization. By combining the experimental TG data with the corresponding reference vapour pressure data obtained with the Antoine equation the plot of P versus v was derived. From the slope of this equation the constant k-value was determined for Ac. Then, using the same k-value the vapour pressures of *p*-Eto Ac and *p*-Br Ac were determined in the same temperature range. The vaporization enthalpies for all the studied compounds were obtained from different methods and a very good agreement was found. Vaporization follows a zero-order kinetics. The activation energy of vaporization (E_{vap}) was calculated from the dynamic TG experiments, using the Arrhenius equation.

Keywords: Vaporization; Acetanilide derivatives; Langmuir equation; Antoine equation; Clausius–Clapeyron equation; Activation energy

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1. Introduction

Acetanilide (Ac) and its investigated derivatives are active components of drugs that show analgesic activity. Analgesics are contained in numerous non-prescription preparations which relieve pain arising from organic disorders or of psychosomatic origin. Wendlandt and Collins have used thermal analysis to identify qualitatively different analgesic preparations [1]. Ibuprofen and acetylsalicylic acid, pure and in solid mixture with excipients usually present in the tablet formulations of some analgesics, were studied by thermal analysis with a particular view on the thermal decomposition processes [2–4].

However, the atmospheric accumulation of toxic compounds such as pesticides and pharmaceuticals is essential due to the use of compounds with a low vapour pressure at room temperature [5]. Therefore, the way in which these substances tend to vaporize is a phenomenon that is worth investigating. In fact, the amount of an active component in a tablet dosage form may vary due to evaporation during the tableting process, hence depleting its specific properties in the solid mixture. In addition, for a given formulation of a drug it is important to determine and quantify the evaporation characteristics of each individual component [6]. In order to determine the thermodynamic quantities (e.g. enthalpy of fusion, etc.) needed to the characterization of the formulation, the knowledge of the vapour pressure data as a function of temperature might be essential.

The Knudsen or the torsion represent the most classical methods used to measure the absolute vapour pressure. Conversely, a simultaneous TG/DSC unit provides some advantages that can be summarized as follows:

1. Small amounts of the sample are required.
2. The effective experimental time is relatively short.
3. The validation with the actual experimental results, calculated by traditional methods, is quite precise.

More pharmaceutical preparations undergo heat treatment during accelerated stability testing or in their shelf-life,

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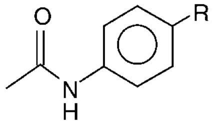

Fig. 1. Structural formulas for Ac (R=H), *p*-Eto Ac (R=OCH_2CH_3) and *p*-Br Ac (R=Br).

necessitating the accurate thermal characterization of each individual component [6].

In the present study, the thermal behaviour of acetanilide (Ac) and two of its analogues, namely the *para*-ethoxyacetanilide (*p*-Eto Ac) and the *para*-bromoacetanilide (*p*-Br Ac), has been considered using a simultaneous TG/DSC apparatus under a N_2 flowing atmosphere. In order to validate the assumption that active component such as Ac (or one of its derivative) exists in a formulation in the same physical form at elevated temperatures as they do at ambient temperature, their vaporization characteristics were obtained through the vapour pressure data. The method proposed in this study determines the vapour pressure values by modifying the Langmuir equation for the presence of the purge gas, which is introduced by the TG unit. The structural formulas of these compounds are given in Fig. 1.

2. Experimental

Ac (CAS: 103-84-4, purity of 97%, lot 25322-118), *p*-Eto Ac (CAS: 62-44-2, purity of 97%, lot 25316-111) and *p*-Br Ac (CAS: 103-88-8, purity of 98%, lot 29183-042) were supplied by Aldrich and they were used as received without further purification. The TG/DSC measurements were carried out on a Stanton-Redcroft 625 simultaneous TG/DSC connected to a 386 IBM-compatible personal computer.

Instrument calibration was performed by using very pure standards (indium, gallium, lead, tin, naphthalene and benzoic acid samples were used in the present work for their well known temperatures and enthalpies of melting).

Rising temperature experiments were carried out on the sample and the readings were taken at every 1 °C to provide accurate results. For each compound almost three runs were performed in a temperature range from ambient to 300 °C. Different heating rates of 2.5, 5, 10 and 20 K min^{-1} were used during this study and at least three runs were performed for each heating rate. An open, aluminium crucible with a cross sectional area $\forall$ of $2.0 \times 10^{-5}\,\text{m}^2$, was used to contain the sample and an empty aluminium crucible of equivalent area was used as the reference. Small sample size of 4–6 mg enough to uniformly cover the base of the crucible was weighted and placed in an argon filled dry box to avoid oxidation of the sample.

The simultaneous TG/DSC system was flushed with the purge gas stream. In this way the gas evolved during the thermal decomposition experiment was continuously removed.

3. Methods

A decomposition reaction is defined as a chemical process in which a compound is degraded into simpler species. Such reactions include processes in which the crystal lattice structure is destroyed, such as melting, evaporation, sublimation, as well as chemical reactions that result in the formation of a new compound [7].

The rate of mass loss of a sample is related to its vapour pressure by the Langmuir equation [8]:

$$\frac{\mathrm{d}m}{\mathrm{d}t} = P\alpha' \left(\frac{M}{2\pi RT}\right)^{1/2} \tag{1}$$

where dm/dt is the rate of mass loss per unit of the surface area, P the pressure, T the absolute temperature, R the universal gas constant, and M the vapour molecular mass and α' the vaporization constant. Langmuir gave the value of unity under vacuum conditions [8], though he did not categorically state that it could not change under the influence of a purge gas. Moreover, in practice a value of $\alpha' = 1$ is only true for a one-component system while the experimental design utilized in this study would have a multi-component atmosphere: first, there is nitrogen as the purge gas and second, the compound being investigated is itself vaporizing and continuously adding to the partial pressure of the material.

Rearrangement of the Eq. (1) gives:

$$P = \left[(\alpha')^{-1}(2\pi R)^{1/2}\left(\frac{T}{M}\right)^{1/2}\left(\frac{\mathrm{d}m}{\mathrm{d}t}\right)\right] = k\nu \tag{2}$$

where $k = (\alpha')^{-1}(2\pi R)^{1/2}$ and $\nu = (T/M)^{1/2}(\mathrm{d}m/\mathrm{d}t)$. Plotting P versus ν, k and then the α' value would be derived. The coefficient of vaporization k is perhaps the most important parameter in the Langmuir equation that is being utilized in such studies. This parameter was considered as a constant, independent of the material being studied [8–11]. However, Eq. (2) is admittedly not perfect, as it is applicable over a finite range of temperature and pressure and the application of this equation should be made for compounds with similar chemical nature and bonding characteristics [16]. No reliable results can be obtained extrapolating the conditions of chemical structures that differ widely.

In the present study the coefficient of evaporation has been determined for Ac using Eq. (2) where the reference vapour pressures were obtained over a given temperature range by applying a non-linear regression procedure to the Antoine equation:

$$\ln P = a - \frac{b}{c + T} \tag{3}$$

where P is the vapour pressure, T the absolute temperature and $a = 2.303A$, $b = 2.303B$ and $c = C$ are the Antoine constants found in [12]. The values for Ac are $A = 10.3727$, $B = 2920.3$ and $C = -32.92$ and they are applicable only in the specific temperature range of 401–489 K.

Combination of Eq. (2) with the Clausius–Clapeyron equation:

$$\ln P = -\frac{\Delta_{\mathrm{vap}} H^{\circ}(\langle T\rangle)}{RT} + \text{constant} \tag{4}$$

where $\Delta_{\mathrm{vap}}H^{\circ}(\langle \mathrm{T}\rangle)$ is the standard molar enthalpy of vaporization at the mean of the experimental temperature range $\langle \mathrm{T}\rangle$, gives:

$$\ln v = -\frac{\Delta_{\mathrm{vap}} H^{\circ}(\langle T\rangle)}{RT} + \text{constant} \tag{5}$$

where the two constants in Eqs. (4) and (5) differ only for the constant $\ln k$. It is interesting to note that the enthalpy of vaporization can be alternatively evaluated from the slope of $\ln v$ versus $1/T$ obtained from thermogravimetric data even when the value of k is unknown.

The enthalpy of vaporization was also calculated using the Trouton and Hildebrand rule [13]:

$$\Delta_{\mathrm{vap}} H = T_{\mathrm{b}}(\text{constant} + R \ln T_{\mathrm{b}}) \times 10^{-3} \tag{6}$$

where T_{b} is the temperature at the normal boiling point and the constant value is equal to 36.61 J K^{-1} mol^{-1} [14].

A further method to calculate the enthalpy of vaporization is obtained by combining the traces recorded by a simultaneous TG/DSC equipment, namely, mass loss (m in mg) and heat flow ($\mathrm{d}Q/\mathrm{d}t$ in J s^{-1}) versus $T(t)$, the former being also in the derivative form ($\mathrm{d}m/\mathrm{d}t$ in mg s^{-1}). The ratio between the DSC and DTG signals $(\mathrm{d}Q/\mathrm{d}t)/(\mathrm{d}m/\mathrm{d}t)$, represents a set of $\mathrm{d}Q/\mathrm{d}m$ infinitesimal quantities (in J mg^{-1}) as a function of temperature that can be considered a simple check of the enthalpy drop related to the mass recorded by a TG experiment [15].

Vaporization kinetics is usually not applied on solid for the negligible mass loss recorded by a thermal balance below the melting temperature in rising temperature conditions. For this reason the kinetics was examined for all the compounds on the molten. The vaporization parameters A and E_{vap} for a molten compound were determined by the temperature dependence of its rate of mass loss $\mathrm{d}m/\mathrm{d}t$ from the first derivative of a TG curve (DTG).

Moreover, vaporization kinetics is based on a constant area of reaction interface and it is possible to predict a zero-order process with a high degree of certainty [16,17]. For a zero-order rate process, the coefficient of vaporization, k_{vap}, is calculated by dividing ($\mathrm{d}m/\mathrm{d}t$) by the surface of the molten compound that practically correspond to the area of the bottom of the crucible ∀. This coefficient is linked with the kinetic parameters of vaporization A and E_{vap} by the Arrhenius equation:

$$k_{\mathrm{vap}} = A \exp\left(-\frac{E_{\mathrm{vap}}}{RT}\right) \tag{7}$$

Treating by a linear least square the $\ln k_{\mathrm{vap}}$ data versus $1/T$, from the slope of the derived equation the activation energy of vaporization was obtained, R being the gas constant.

4. Results and discussion

The TG/DSC curves of Ac (a), p-Eto Ac (b) and p-Br Ac (c) at the heating rate of 5 K min^{-1} are reported in Fig. 2 as an example. The DSC signals show two distinct endotherms on account of the melting at lower temperatures and vaporization at higher temperatures. Moreover, it can be seen that for each compound the vaporization begins to be detectable after the completion of melting.

The derivative DTG plots are presented in Fig. 3. In these plots typical shaped DTG peaks corresponding to vaporization are shown: diffuse initial temperatures and sharp final temperatures.

As Fig. 3 clearly indicates all the calculations performed in the present study were restricted to the linear portion of each vaporization peak where the sample maintains a constant liquid interface.

The melting and vaporization temperatures for Ac, p-Eto Ac and p-Br Ac determined either as onset and peak temperatures from the endothermic peaks of their DSC curves are summarized in Table 1. The onset temperatures and mass loss percentages corresponding to vaporization only as

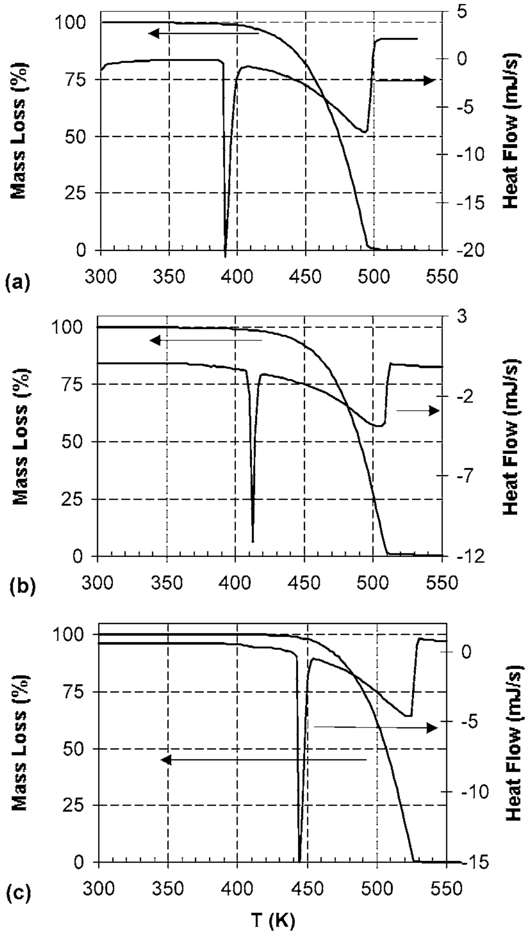

Fig. 2. Simultaneous TG/DSC curves under a stream of N_2 at 5 K min^{-1} for Ac (a), p-Eto Ac (b) and p-Br Ac (c).

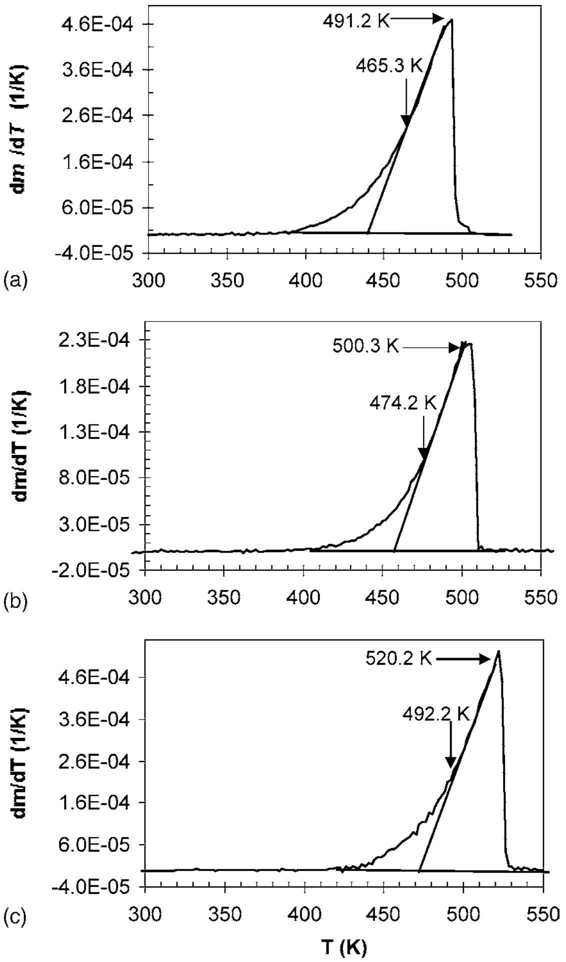

Fig. 3. DTG curves under a stream of N_2 at 5 K min^{-1} for Ac (a), *p*-Eto Ac (b) and *p*-Br Ac (c).

obtained from TG measurements are also given in Table 1. The enthalpies of fusion given in Table 2 confirm the order based on the onset temperature derived by TG curves: Ac < *p*-Eto Ac < *p*-Br Ac.

Fig. 4 is a plot of ln ν versus $1/T$ that shows a very good linear trend. From the slope of the straight lines obtained treating the data with the least square method the corresponding $\Delta_{vap}H$ values are obtained according to Eq. (5). The $\Delta_{vap}H$ values obtained from DSC curves, from Eqs. (5) and (6) and from advanced chemistry development (ACD) Software Solaris V4.67 (©1994–2003 ACD) are reported in Table 3. The comparison of all the derived $\Delta_{vap}H$ values shows an excellent agreement among the data derived from DSC, from Eq. (5) and those calculated by using the ACD software, especially for the Ac and *p*-Eto Ac. Lower enthalpy values are calculated from Eq. (6) but the difference with the other ones is poor. Based on the $\Delta_{vap}H$ values the order found is: Ac < *p*-EtoAc ≈ *p*-Br Ac.

Table 1
Onset temperatures and mass loss percentage obtained from TG data and onset peak melting temperatures obtained from DSC data at $\beta = 5\ K\ min^{-1}$ under a stream of argon

Compounds	From TG measurements		From DSC measurements	
	T_{onset} (K)	Δm (%)	T_{onset} (K)	T_{peak} (K)
Ac	459.0	100.0	389.3 (436.8)	391.2 (493.2)
p-Eto Ac	490.8	99.0	410.0 (467.1)	411.6 (522.0)
p-Br Ac	492.1	99.1	443.5 (474.6)	444.5 (523.0)

Vaporization temperatures are also given in brackets.

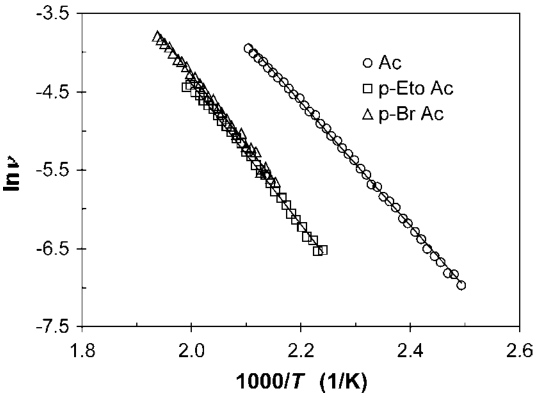

Fig. 4. ln ν vs. $1/T$ plot.

In Fig. 5 the vapour pressures calculated using Eq. (5) in a given temperature range were plotted against the v values, according to Eq. (2) for Ac. The equation of the linear regression and the square of the correlation coefficient are also given in Fig. 5. The slope of the obtained straight line was taken to be k. According to Eq. (2) this value was taken to estimate the vapour pressure for the vaporization processes of the other two analogues. The corresponding Clausius–Clapeyron plots for these analgesics are shown in Fig. 6 together with their regression equations.

A further method to evaluate the enthalpy of vaporization needs to compare DSC and DTG vaporization peaks after their corrections for the baseline. The comparison of the two peaks before and after this manipulation is shown in Fig. 7. From the plot (b) in Fig. 7 it is evident that the

Table 2
Enthalpies of melting with estimated errors obtained from DSC curves

Compounds	$\Delta_{fus}H$ (kJ mol^{-1})
Ac	18.3 ± 0.8
p-Eto Ac	21.4 ± 0.9
p-Br Ac	25.8 ± 0.9

Table 3
Enthalpies of vaporization with estimated errors obtained from DSC curves

Compounds	$\Delta_{vap}H$ (kJ mol^{-1})			
	From DSC	From ln ν vs. $1/T$	From Eq. (6)	From ACD software
Ac	53.4 ± 3.0	54.1 ± 2.4	51.7 ± 2.0	54.5 ± 3.0
p-Eto Ac	60.1 ± 3.0	60.1 ± 2.9	56.7 ± 2.2	60.0 ± 3.0
p-Br Ac	59.4 ± 3.0	62.0 ± 2.8	56.5 ± 3.1	59.8 ± 3.0

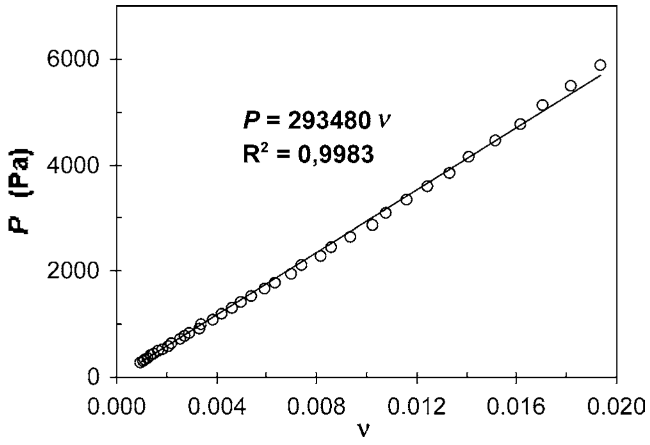

Fig. 5. Langmuir plot (5 K $\min^{-1}$, 50 ml $\min^{-1}$). The *k*-value is determined from Eq. (2) by a linear regression, treating the data with the least square method.

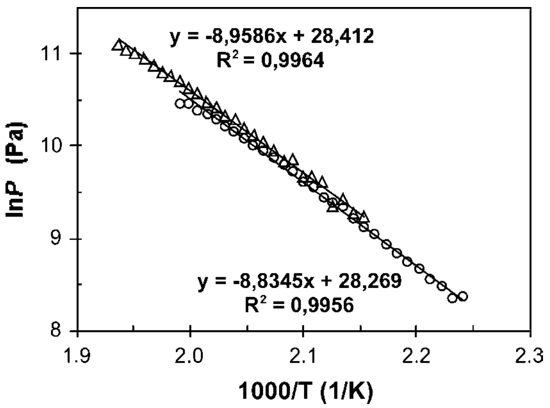

Fig. 6. Clausius–Clapeyron plot for the vaporization process of *p*-Eto Ac (○) and *p*-Br Ac (△).

two signals agrees quite well. Thus, the time constant of the simultaneous TG/DSC instrument used in the present work does not influence the obtained results. From the ratio between the areas of the DSC and DTG peaks an mean estimate of the enthalpy of vaporization (in J mg^{-1}) is obtained. It was obtained the value of 61 ± 3 kJ mol^{-1} that agrees within the experimental error with the literature value of 64 kJ mol^{-1}found in literature [18].

Arrhenius parameters calculated by Eq. (7) are reported in Table 4. As expected in the case of physical processes (e.g. vaporization) where perturbations in the enthalpy does not occur [19], $\Delta_{\mathrm{vap}}H \approx E_{\mathrm{vap}}$.

Table 4
Arrhenius parameters of vaporization with their estimated errors

Compounds	$\ln A$ (s^{-1})	E_{vap} (kJ mol^{-1})
Ac	9.5 ± 0.4	53.2 ± 2.0
p-Eto Ac	10.2 ± 0.5	60.6 ± 2.1
p-Br Ac	10.4 ± 0.5	59.9 ± 1.8

It is assumed as a zero-order process.

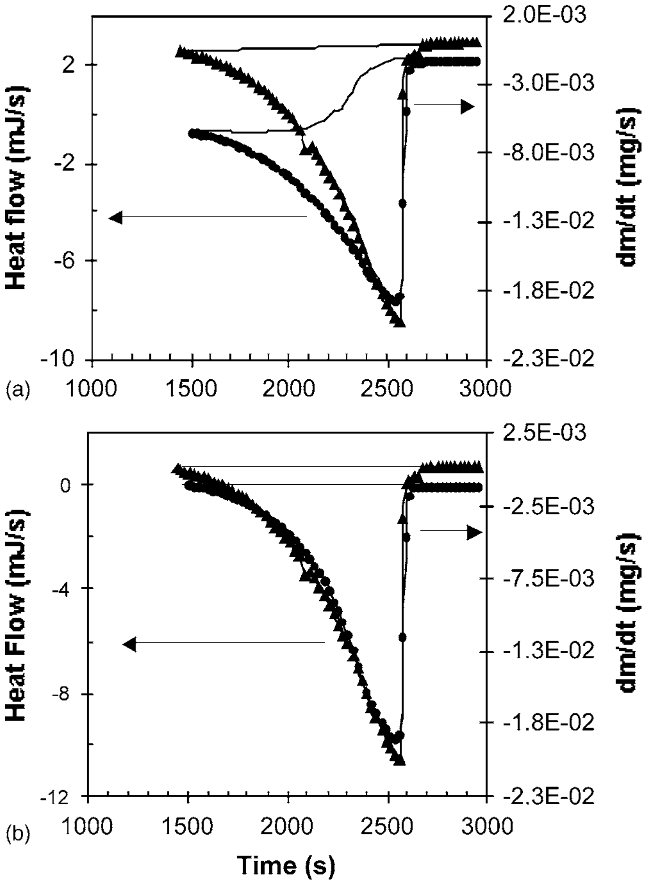

Fig. 7. DTG (▲) and DSC (●) vaporization peaks for Ac at 5 K $\min^{-1}$ as a function of time before (a) and after (b) the corrections for the baselines.

For the investigated compounds it can be concluded that Ac derivatives seem to show a higher stability with respect to Ac, the decomposition onset temperature shifts towards higher values and the decomposition occurs at a slightly lower rate. No significant contribution to the stability is due to the different substituents in the benzene ring of the Ac derivatives.

On the basis of the experiments until now performed a further study will be necessary in the next future to understand the effect of excipients usually present in the formulations containing these active components.

5. Conclusions

Ac, *p*-Eto Ac and *p*-Br Ac were investigated with a simultaneous TG/DSC unit showing melting and vaporization processes when they were submitted to a linear rising temperature conditions. This work confirms that thermal analysis is an excellent tool to define and quantify the vaporization characteristics of a compound. Ac was used to determine the coefficient of vaporization of the Langmuir equation using the Antoine vapour pressure constants. Thus, the vapour pressures of the other two compounds were derived for a given temperature range.

Several methods to calculate $\Delta_{vap}H$ were presented in this work and the results were in close agreement with each other and with the values found in literature.

The vaporization process followed a zero-order kinetics for all the investigated compounds. Activation energies were determined using the Arrhenius equation and their values were in excellent agreement with the corresponding enthalpies of vaporization.

Acknowledgements

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