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Article

# Thermoanalytical studies of carbamazepine: hydration/ dehydration, thermal decomposition, and solid phase transitions

**Mônia Aparecida Lemos Pinto, Beatriz Ambrozini*, Ana Paula Garcia Ferreira, Éder Tadeu Gomes Cavalheiro**

*Department of Chemistry and Molecular Physics, Institute of Chemistry of São Carlos, University of São Paulo, São Carlos, SP, Brazil*

Carbamazepine (CBZ), a widely used anticonvulsant drug, can crystallize and exhibits four polymorphic forms and one dihydrate. Anhydrous CBZ can spontaneously absorb water and convert to the hydrate form whose different crystallinity leads to lower biological activity. The present study was concerned to the possibility of recovering the hydrated form by heating. The thermal behavior of spontaneously hydrated carbamazepine was investigated by TG/DTG-DTA and DSC in dynamic atmospheres of air and nitrogen, which revealed that the spontaneous hydration of this pharmaceutical resulted in a Form III hydrate with 1.5 water molecules. After dehydration, this anhydrous Form III converted to Form I, which melted and decomposed in a single event, releasing isocyanic acid, as shown by evolved gas analysis using TG-FTIR. Differential scanning calorimetry analyses revealed that Form III melted and crystallized as Form I, and that subsequent cooling cycles only generated Form I by crystallization. Solid state decomposition kinetic studies showed that there was no change in the substance after the elimination of water by heating to 120 °C. Activation energies of 98 ± 2 and 93 ± 2 kJ $mol^{-1}$ were found for the hydrated and dried samples, respectively, and similar profiles of activation energy as a function of conversion factor were observed for these samples.

**Uniterms:** Carbamazepine/thermal analysis. Polymorphism. Hydrate. Dehydration.

A carbamazepina (CBZ) é um anticonvulsivante frequentemente utilizado no Brasil e em vários países. Ela apresenta quatro formas polimórficas e um diidrato. Todas as formas são ativas farmacologicamente, porém a Forma III é a preferível do ponto de vista farmacêutico, em função de suas propriedades físico-químicas. Entretanto, essa forma é altamente higroscópica, podendo converter-se ao diidrato, menos ativo biologicamente. Nesse trabalho propõe-se avaliar o comportamento térmico da forma hidratada, visando à recuperação da forma ativa, por aquecimento. Para tanto, foi feito um estudo do comportamento térmico por TG/DTG-DTA e DSC em atmosfera dinâmica de ar e nitrogênio, que evidenciou hidratação espontânea da Forma III, gerando um hidrato contendo 1,5 moléculas de água. Essa forma sofre desidratação, seguida de fusão e conversão para a Forma I. Segue-se a decomposição em uma única etapa, na qual ocorre liberação do ácido isociânico, conforme análise de gases evolvidos, por termogravimetria acoplada ao infravermelho (TG-FTIR). Estudos por calorimetria exploratória diferencial mostraram que a Forma III se funde e se cristaliza imediatamente na Forma I, durante o aquecimento. A Forma I também se funde e ciclos de aquecimento/resfriamento posteriores evidenciaram que a substância se cristaliza apenas na Forma I por resfriamento. Estudos cinéticos da decomposição, em estado sólido, mostraram que não há alteração na substância pela eliminação da água por aquecimento, sendo determinados valores de energia de ativação da ordem de 98 ± 2 e 93 ± 2 kJ $mol^{-1}$, respectivamente, para a amostra hidratada e submetida à secagem, assim como perfis semelhantes nas curvas de energia de ativação em função do fator de conversão.

**Unitermos:** Carbamazepina/análise térmica. Polimorfismo. Hidratação. Desidratação.

***Correspondence:** B. Ambrozini. Departamento de Química e Física Molecular, Instituto de Química de São Carlos, Universidade de São Paulo. Av. Trabalhador São-Carlense, 400, Caixa Postal 780, 13560-970, São Carlos, SP, Brasil. E-mail: biaambro@gmail.com

## INTRODUCTION

Carbamazepine (CBZ) (Figure 1), 5*H*-dibenz-(*b*,*f*)azepine-5-carboxamide, is a white or almost white crystalline powder that is used as a first-generation anticonvulsant drug to treat epilepsy, trigeminal neuralgia, manic-depressive illness, and explosive aggression. The efficacy of CBZ was confirmed in the 1960s, when it was launched onto the commercial market (Liu *et al*., 2008; Ambrogi *et al.*, 2007; Krongauz *et al.*, 2007). When administered by the oral route, it presents a slow rate of absorption, which requires the use of a relatively large dose (Rose, Johnson, 1997; Dalkara, Karakurt, 2012).

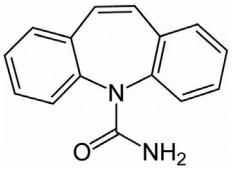


**FIGURE 1 -** Structure of carbamazepine.

At least four polymorphs and a dehydrate, as well as other solvates of CBZ, have been described in the literature (Qu, Louhi-Kultanen, Kallas, 2006; O'Mahony *et al.*, 2012). The melting points of the four polymorphs have been reported to be in the range 175-190 °C (Gosselin *et al.*, 2003). The most stable known anhydrous form under room conditions is Form III. It is also known that in a humid environment, the anhydrates take up water and convert to the hydrates (Liu, Dang, Wei, 2012). Forms I and III of the drug constitute an enantiotropic pair, whose relative thermodynamic stability changes at 70 °C. Below this temperature, Form III is most stable, while above this temperature, Form I becomes more stable (McGregor *et al*., 2004; Behme, Brook, 1991; Lowes *et al*., 1987).

Hydrates are molecular complexes containing water molecules incorporated (usually stoichiometrically) into their crystal lattices (Han, Suryanarayanan, 1997). The water molecules of a hydrate can be released from the crystal lattice under drying conditions, such as heating. Most hydrate–anhydrate transformations are reversible and are influenced by temperature, relative humidity, particle size, and surface area. It is possible for the transformation to occur at room temperature as well as during drug processing, transportation, and storage. Evaluation of the hydration and dehydration behavior of pharmaceutical substances is important for the development of stable formulations, because the anhydrous and hydrated forms of a drug can show differences in their physicochemical characteristics. Properties including heat capacity, density, crystal structure, chemical stability, hygroscopicity, powder flow, and dissolution rate ultimately affect the bioavailability of a drug (Solon *et al*., 2010; Ono *et al.*, 2002; McMahon *et al.*, 1996; Qu, Louhi-Kultanen, Kallas, 2006).

In work by Xu *et al.* (2011), the pharmacokinetics of the polymorphic Forms I and III and the dihydrate of carbamazepine were evaluated in mice and compared to the behavior of these substances in dogs and humans. The absorption of Form III in mice was very similar to that observed for humans, and the pharmacokinetic properties and stability of the polymorph proved to be satisfactory. The P-monoclinic form Form III is considered more suitable for commercial formulations of carbamazepine, due to it higher bioavailability, compared to the other polymorphs.

Knowledge of the interconversion of the various polymorphic forms of CBZ is needed because the performance of this drug depends on the form that is present (Krahn, Mielck, 1987; Rustichelli *et al.*, 2000; Kobayashi *et al.*, 2000; Cabeza *et al.*, 2007). However, information concerning the hydration/dehydration processes involved remains scarce.

The most active form of carbamazepine is its anhydrous Form III, which is highly hygroscopic. It is therefore important to investigate the stability and thermal behavior of the spontaneously hydrated form, the regeneration of the active anhydrous Form III, and the polymorphic conversions involved in this process. Thermal analyses employing DSC and TG-DTA have been used previously to gain insight into the thermal behaviors of hydrated CBZ and Form III (Liu, Dang, Wei, 2012; McGregor *et al*., 2004; Han, Suryanarayanan, 1997).Although Liu and co-workers (Liu, Dang, Wei, 2012) recently described the thermal behavior of hydrated carbamazepine, considering dehydration, degradation, and kinetic data, to the best of our knowledge there have been no detailed studies of the degradation of CBZ and the formation of volatile products using TG-FTIR and DSC with heat-cool-heat cycles in order to elucidate the crystallization processes.

This work therefore describes an investigation of the thermal behavior of the spontaneously hydrated CBZ Form III, in terms of the dehydration process, formation of volatile degradation products, polymorphic interconversion, and the kinetics of dehydration and decomposition, in order to evaluate the possibility of recovering carbamazepine that becomes hydrated due to its storage under unsuitable conditions.

## MATERIAL AND METHODS

Carbamazepine (pharmaceutical grade ≥ 99.0%, Sigma-Aldrich) was used without further purification and

was stored under room conditions (T = 18-25 °C; humidity = 40-80%) for one year.

Simultaneous TG/DTG and DTA measurements were carried out using a Model SDT-Q600 analyzer (TA Instruments) with alumina sample holders (90 μL). The sample 6 mg was heated to a final temperature of 800 ºC at a rate of 10 °C $min^{-1}$, under a flow of air (100 mL $min^{-1}$). Temperature calibration of the apparatus employed a zinc standard, as recommended by the manufacturer.

Thermogravimetry (TG) was used to study the kinetics of CBZ thermal dehydration and decomposition, employing the Flynn-Wall-Ozawa model (Flynn, Wall, 1996; Ozawa, 1970; Doyle, 1962). For the kinetic studies using spontaneously hydrated CBZ and samples of CBZ dried at 120 °C, TG analyses were performed at heating rates of were performed at heating rates of 2.5, 5.0, 10.0, and 15.0 $min^{-1}$, under the same conditions described above. Guinesi *et al*. (2006) provided a detailed description of the theory and equations involved in this method. Data analysis was performed using Thermal Specialty Library v.1.4 software (TA Instruments).

DSC curves were obtained using sample masses of ~2 mg, placed in covered aluminum pans with a central pinhole ($\phi$ = 0.7 mm) in the lid. The heating rate was 10 °C $min^{-1}$, in a temperature interval of -40 to 194 ºC, under a flow of $N_2$ at 25 mL $min^{-1}$. The curves were obtained in heat-cool-heat cycle mode. A DSC-Q10 unit controlled by Thermal Advantage for Q-Series software (both from TA instruments) was used in these analyses. Calibrations of the equipment for temperature and enthalpy measurements were performed using indium metal (99.99% purity) as a standard, according to the manufacturer's manual.

The TGA-FTIR experiments were performed using a TG-DSC 851 analyzer (Mettler-Toledo) coupled to a Nicolet iS10 FTIR spectrometer. The transfer line consisted of a stainless steel tube (120 cm length, 2 mm internal diameter), heated at a constant temperature of 200 °C. The FTIR measurements employed a DTGS detector with a gas cell heated at a constant temperature of 250 °C. The interferometer and the gas cell compartments were purged with highly purified $N_2$ at a flow rate of 50 mL $min^{-1}$, and the heating rate was 10 °C $min^{-1}$. The TG-DSC analyses were performed using a sample mass of 12 mg in alumina crucibles.

The carbon, hydrogen, and nitrogen contents of the samples were determined by elemental analysis, using a Model EA 1110 CHNS-O analyzer (CE Instruments).

X-ray powder diffraction patterns were obtained using a Rotaflex RU-200B X-ray diffractometer (Rigaku) employing $CuK_\alpha$ radiation ($\alpha$= 1.541 Å) and settings of 50 kV and 100 mA.

## RESULTS AND DISCUSSION

As commonly occurs with polymorphic systems, there has been much confusion about the naming of CBZ polymorphs. For the purposes of this article and for clarity, we have adopted the nomenclature described by Grzesiak *et al*. (2003).

### Thermal behavior of spontaneously hydrated CBZ and anhydrous form III

In an air atmosphere, the thermal decomposition of spontaneously hydrate CBZ proceeds in three steps of mass loss, between 19 °C and 332 °C, following the TG/DTG curves shown in Figure 2.

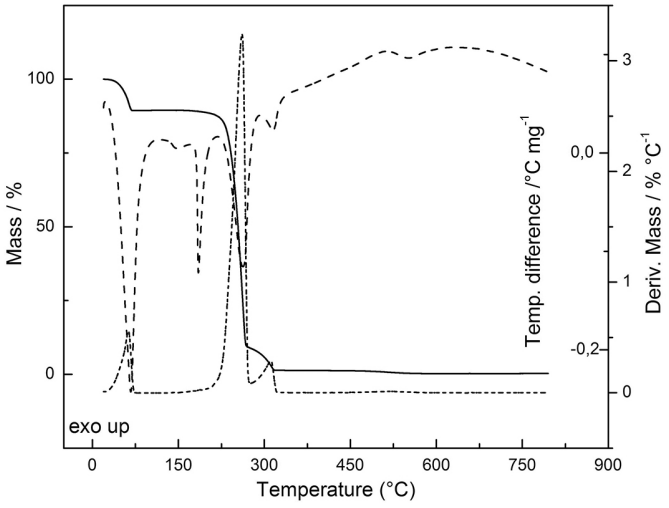


**FIGURE 2 -** TG (solid line), DTG (short dashed line), and DTA (dashed line) curves for carbamazepine heated in a dynamic air atmosphere (m = 6.186 mg).

The first mass loss, which occurred in a single thermal event in the range 19-74 °C, corresponded to dehydration, with the loss of 1.5 water molecules. The experimental and calculated mass losses were 10.61% and 10.26% respectively. In order to confirm the existence of 1.5 molecules of hydration water in the sample of carbamazepine analyzed, it was subjected to elemental analysis (considering the contents of C, H, and N), before and after heating to 120 °C. The TG results showed that the first step of mass loss was completed and that no further decomposition occurred. Table I presents the comparative data obtained for the anhydrous sample and samples containing 1.5 and 2.0 water molecules.

It could be concluded that after heating, the anhydrous form was regenerated, without decomposition and preserving the original stoichiometry. The results also

**TABLE I** - Experimental (exp) and calculated (calc) elemental composition of carbamazepine

| Carbamazepine | Element / %, *exp* (*calc*) | | |
|---|---|---|---|
| | C | H | N |
| $C_{15}H_{12}N_2O$ (anhydrous) | 76.6 (76.1) | 5.2 (5.1) | 12.1 (11.8) |
| $C_{15}H_{12}N_2O$. 1.5 $H_2O$ | 67.7 (68.4) | 7.1 (6.3) | 10.7 (10.6) |
| $C_{15}H_{12}N_2O$. 2 $H_2O$ | 67.7 (66.1) | 7.1 (5.9) | 10.7 (10.2) |

showed that the spontaneously hydrated sample contained only 1.5 molecules of hydration water per mol of CBZ, despite the fact that the literature suggests the existence of a dehydrate (Kobayashi *et al*., 2000). This can be explained by the occurrence of a spontaneous partial hydration, which then remained constant under ambient room conditions.

After dehydration, the second mass loss (79.8%), between 198 and 275 °C, was due to thermal decomposition of the anhydrous drug. The third mass loss (8.15%) in the range 275-332 °C, was attributed to the decomposition of residual carbonaceous material. A very small mass loss (1.2%) in the range 500-550 °C was related to the combustion of residual carbon.

The DTA curve obtained using an air atmosphere (Figure 2) exhibited six peaks and agreed with (and extended) the thermal data obtained from the TG/DTG curves. The first endothermic peak, at 67.1 °C, was attributed to dehydration, and the second endothermic peak, at 147.8 °C, was attributed to melting of the anhydrous polymorphic Form III (Liu, Dang, Wei, 2012; Kobayashi *et al*., 2000). The exothermic peak at 174.4 °C and the sharp endothermic peak at 184.9 °C corresponded to crystallization and to melting of the polymorphic Form I, respectively. The decomposition was accompanied by two endothermic peaks, at 262.4 and 314.8 °C, followed by an exothermic peak (at 530 ºC) attributed to combustion of the residual carbonaceous material.

The DSC curves obtained for the spontaneously hydrated carbamazepine using successive heating-cooling-heating cycles are presented in Figure 3. During the first heating cycle, a broad endothermic peak appeared at 70.1 °C ($T_{onset}$ = 58.5 ºC), corresponding to dehydration of the sample, in agreement with the TGA/DTG curve for the drug.

With further heating, a second endothermic signal was observed at ~ 173.5 °C ($T_{onset}$ = 158.9 °C), corresponding to the melting of Form III of carbamazepine, which immediately crystallized as Form I, represented by the exothermic signal at 174.7 °C ($T_{onset}$ = 173.8 °C). This was in agreement with the findings of Grzesiak *et al*. (2003).

Finally, a sharp endothermic peak at 191.3 °C ($T_{onset}$ = 190.6 °C) corresponded to the melting of Form I (Grzesiak *et al*., 2003).

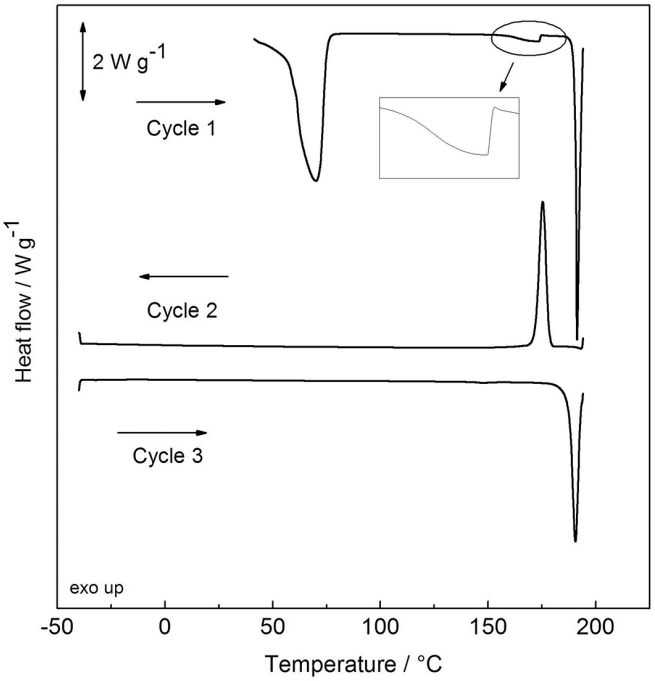


**FIGURE 3** - Heat-cool-heat DSC curves for carbamazepine, obtained under an $N_2$ atmosphere (m = 2.000 mg).

During the cooling step, a single thermal event was observed, represented by an exothermic peak at 175.3 °C ($T_{onset}$ = 178.2 °C), which was probably related to crystallization of the sample. Subsequent cooling to -40 °C did not reveal any other thermal events.

During the second heating step, no thermal event was observed in the -40 to 170 °C range. However, there was a sharp endothermic peak at 190.5 °C ($T_{onset}$ = 187.8 °C) that coincided with the peak observed in the first heating cycle and was therefore related to the melting of Form I.

The enthalpy changes measured for thermal events observed during the heating-cooling-heating cycles can be summarized as follows:

Cycle 1: Dehydration of Form III: $\Delta H$ = 74.35 kJ mol$^{-1}$
Melting of Form I: $\Delta H$ = 27.97 kJ mol$^{-1}$
Cycle 2: Crystallization of Form I: $\Delta H$ = -22.37 kJ mol$^{-1}$
Cycle 3: Melting of Form I: $\Delta H$ = 23.44 kJ mol$^{-1}$

Due to the fact that the carbamazepine Form III melting endotherm was followed by a subsequent Form I recrystallization exotherm, resolution of these two overlapping events was not possible using DSC. Consequently, it was not possible to measure the enthalpy changes involved in the Form III melting endotherm or the Form I crystallization in the first cycle (McGregor *et al*., 2004).

The melting of Form III followed by recrystallization of Form I was confirmed by heating the sample to 175 ºC in a glass tube and visually observing the changes.

In summary, it could be concluded that the sample used in this work was the spontaneously hydrated Form III of carbamazepine. When heated, this dehydrated to the anhydrous Form III in the solid phase, which then melted and converted to Form I by recrystallization. The Form I solid also showed melting, at a slightly higher temperature. Successive cooling and heating resulted in Form I in the solid and liquid phases, respectively. The present work therefore revealed that Form I was preferentially produced by cooling.

In order to confirm the phase transitions observed by DSC, a sample of the spontaneously hydrated CBZ was heated in an oven at 120 °C for 30 min. A second sample was heated at 196 °C for 30 min. X-ray diffraction analysis of the solids obtained after these thermal treatments revealed both were crystalline, as shown by the diffractograms (Figure 4). Specific peaks for spontaneously hydrated CBZ were observed at 2θ = 8.78, 12.15, 18.76, and 19.37 (Figure 4a). Form III showed diagnostic peaks at 2θ = 15.36, 19.36, 24.82, and 27.45 (Figure 4b). Specific peaks for Form I occurred at 2θ = 7.93, 9.40, 12.22, and 19.8 (Figure 4c).

Although the results were consistent with those described in the literature (Rustichelli *et al*., 2000; Kobayashi *et al*., 2000; Grzesiak *et al*., 2003), they revealed that CBZ Form III was converted to CBZ Form I significantly faster than previously reported. In earlier work, the times required were 9 h at 140 °C (Javadzadeh *et al*., 2009), 4 h at 140 °C (McMahon *et al*., 1996), and 2 h at 170 °C (Behme, Brook, 1991). This time reduction included consideration of the melting of CBZ Form I, followed by its crystallization.

## Evolved gas analysis

The gaseous products released during thermal decomposition of the CBZ hydrate were monitored by FTIR. In these experiments, the sample was again submitted to thermogravimetry, but under a dynamic nitrogen atmosphere. The resulting TG curve (not shown) was similar to that obtained in air. The FTIR spectra of the gaseous products evolved during the decomposition of the drug are presented in Figure 5.

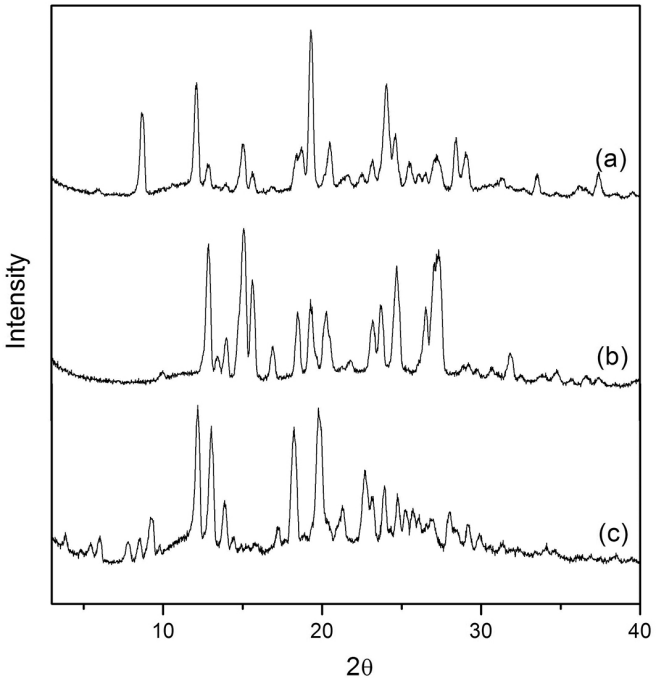


**FIGURE 4 -** X-ray powder diffraction patterns for carbamazepine: (a) hydrated, (b) Form III, and (c) Form I.

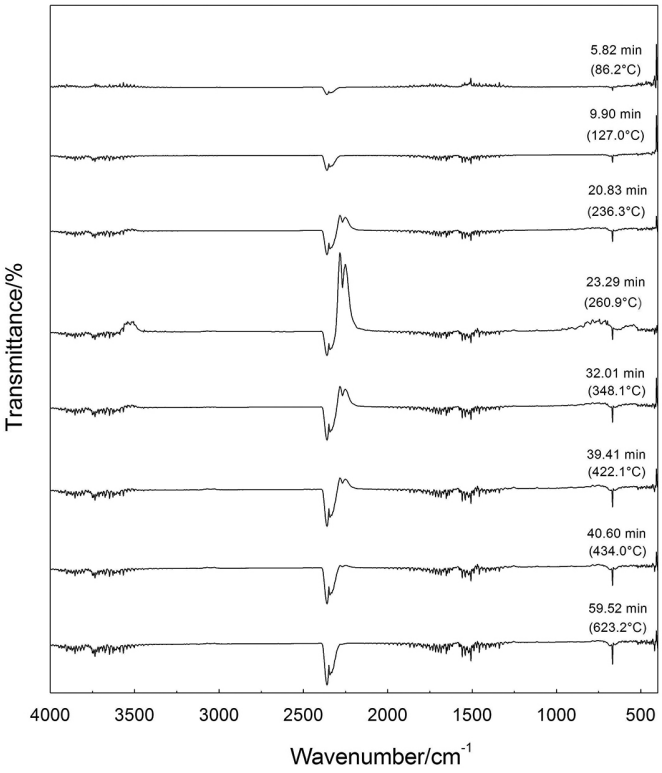


**FIGURE 5 -** Infrared spectra of the gases released during the decomposition of carbamazepine in an $N_2$ atmosphere.

The FTIR spectra of the gaseous products evolved during the thermal decomposition of carbamazepine were indicative of the release of water, with intense evolution at 5.82 min (86.2 °C) associated with positive absorbance signals in the 3500-4000 $cm^{-1}$ and 1250-1750 $cm^{-1}$ regions. Between 20.83 min (236.3 °C) and 40.60 min (434.0 °C), the evolution of isocyanic acid could be clearly observed, with signals at 3400, 2250, and 1000-500 $cm^{-1}$.

At the end of the experiment, at 59.52 min (623.2 °C), small signals corresponding to water and $CO_2$ were observed, which could be explained by the decomposition of carbonized material due to oxidation by traces of oxygen in the carrier gas. The gas phase spectra of water, $CO_2$, and isocyanic acid matched those from the spectral library (OMNIC v.8.0, 2008).

The TG/DTG, DTA, and DSC curves, together with the FTIR spectra of the volatile decomposition products, were used to propose a pathway for the thermal behavior of spontaneously hydrated carbamazepine, as shown in Figure 6.

Although the proposed thermal pathway suggests that the decomposition occurred with the elimination of isocyanic acid (HNCO) and iminostilbene ($C_{14}H_{11}N$), only isocyanic acid could be positively identified in the evolved gas analysis using TG-FTIR. This could be explained by the condensation of iminostilbene, whose boiling point (220 °C) (Chemical Book, 2012) is the same as the transfer line temperature utilized (220 °C). The release of iminostilbene must have occurred, because the mass loss was almost complete in the first degradation step.

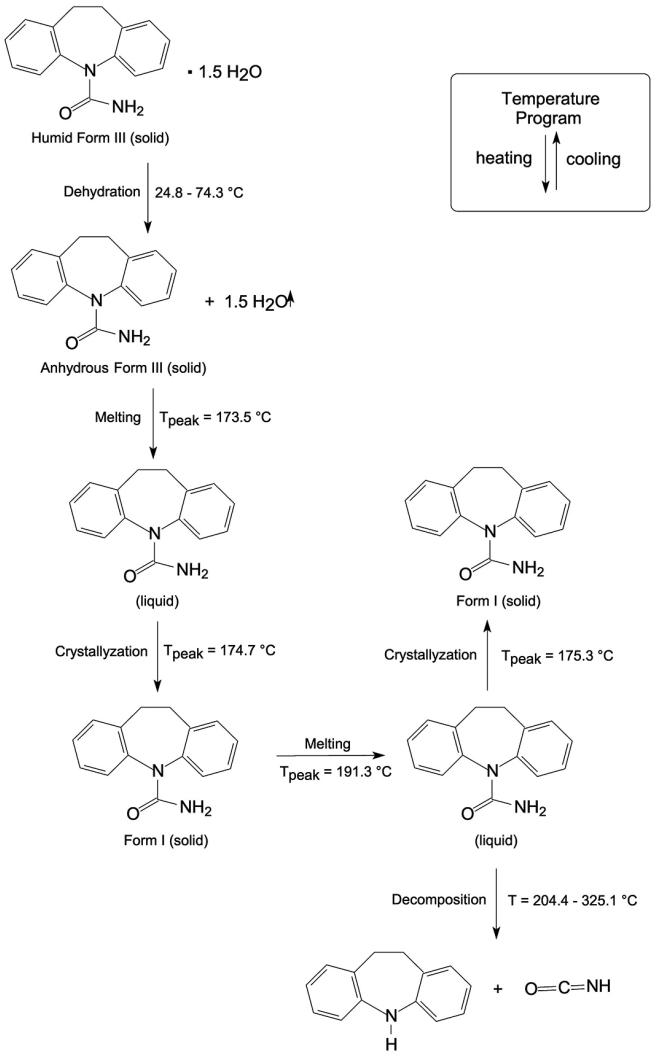


**FIGURE 6 -** Thermal pathway for the decomposition of carbamazepine.

## Thermal kinetics study

The aim of this study was to evaluate possible changes in the thermodynamic parameters of the carbamazepine decomposition processes due to either spontaneous hydration or dehydration by heating. Activation energies ($E_a$) and pre-exponential factors (log A) were measured for the dehydration and decomposition steps of the spontaneously hydrated sample, as well as for the decomposition of the sample heated to 120 °C (Table II). These values were obtained from the stable portions of the $E_a$ vs. α plots (Vyazovkin *et al*., 2011).

From the data shown in Table II, it could be concluded that the of activation energies and log A factors for both the spontaneously hydrated sample and the sample heated to 120 °C were quite similar, confirming that these samples presented very similar characteristics. The TG curves obtained using different heating rates are presented in Figure 7.

**TABLE II -** Activation energies ($E_a$) and pre-exponential factors (log A) for hydrated and dried carbamazepine

| Sample | Event | $E_a$ / kJ $mol^{-1}$ | log A / $min^{-1}$ |
|---|---|---|---|
| CBZ 1.5 $H_2O$ | Dehydration | 73 ± 2 | 11.3 ± 0.4 |
| | Decomposition | 98 ± 2 | 9.3 ± 0.1 |
| CBZ | Decomposition | 93 ± 2 | 8.6 ± 0.1 |

## CONCLUSIONS

The present investigation showed that Form III of anhydrous CBZ can become spontaneously hydrated,

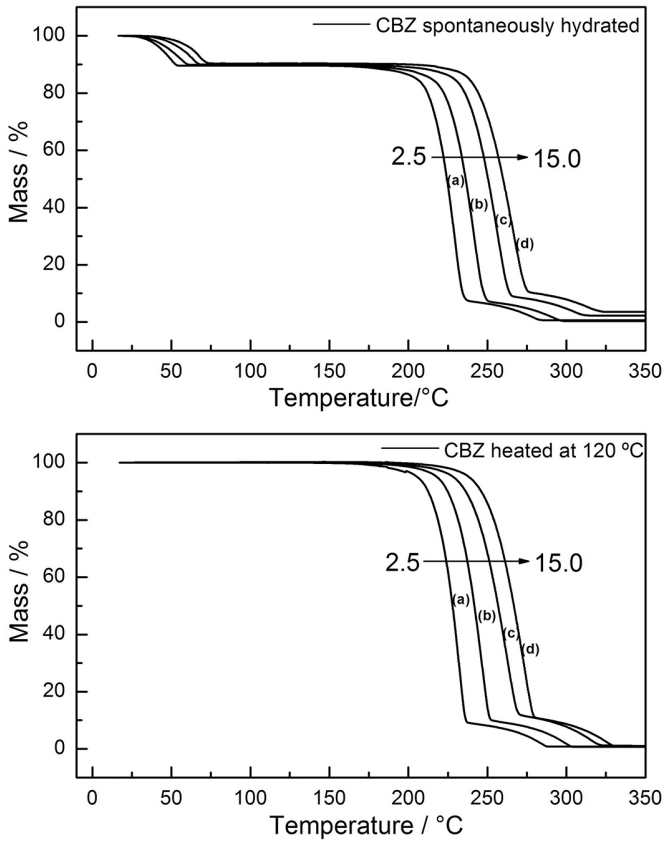


**FIGURE 7 -** TG curves for spontaneously hydrated CBZ and CBZ heated at 120 ºC in an $N_2$ atmosphere, using different heating rates: (a) 2.5; (b) 5.0; (c) 10.0; (d) 15.0 ºC $min^{-1}$ (m = 6.0 mg).

producing a 1.5 hydrate. The water molecules could be removed by heating the sample to 120 °C, without risk of decomposition of the active Form III. These findings were supported by the results of TG/DTG, DTA, X-ray diffraction, and thermal kinetics analyses.

A detailed pathway of the thermal behavior of the spontaneously hydrated sample is proposed, based on the TG-FTIR and DSC data and supported by X-ray diffraction analyses of the solids and the FTIR spectra obtained for the gases evolved during sample decomposition.

The melting of CBZ at temperatures near 200 °C seems to indicate that Form I is most stable. Form I was formed preferentially by cooling, under the conditions used here; any subsequent conversion observed during the cooling-heating cycles occurred after Form I was obtained.

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