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# Thermodynamic properties of polymorphic forms of theophylline. Part II: The enthalpies of solution in water at 298.15 K

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**Abstract** The enthalpies of solution $\Delta_{sol}H_m$ of polymorphic forms I and II of theophylline in water at 298.15 K using the isoperibol solution calorimeter have been determined in the range of concentration $(0.311–1.547) \cdot 10^{-3}$/mol $\cdot$ kg$^{-1}$. The enthalpies of hydration $\Delta_{hyd}H_m^o$ were determined from the experimentally obtained the enthalpies of solution for aqueous solutions and previously determined enthalpies of sublimation $\Delta_s^g H_m^o$.

**Keywords** Enthalpy of hydration · Enthalpy of solution · Physico-chemistry properties · Polymorphism · Solution calorimetry

## Introduction

The enthalpy of solution is one of the most important thermodynamic quantity and may be used effectively for characterization of different properties of drug molecules [1–4]. For example, the enthalpies of solution have been applied to describe crystallinity of drug amorphous materials [5] and to analyze various energetic drug-solvents interactions terms [6, 7]. The knowledge of the enthalpy of solution is useful for evaluation of solute-solvent interactions and the enthalpies of transfer between two different solvents [8]. The solution calorimetry also is used to characterize polymorphic forms of drug [3].

Characterization of polymorphic forms constitutes an important aspect of drug development. Polymorphism is an important problem in the pharmaceutical industry. Different polymorphs of drug may exhibit physicochemical properties such as solubility, dissolution rate, bioavailability and chemical and physical stabilities [9, 10].

Theophylline (3,7-dihydro-1,3-dimethyl-1H-purine-2,6-dione, 1,3-dimethylxanthine) is a typical drug, which exhibits polymorphism and has two anhydrous forms I and II [11, 12]. Theophylline has been used for many years for the treatment of acute asthma and chronic obstructive pulmonary disease (COPD) [13, 14].

Theophylline, diprophylline and aminophylline have found their application in the treatment of diseases connected with cramps of smooth muscles in bronchis [15].

Theophylline has been shown to reduce haematocrit in normal subjects and in patients with erythrocytosis following renal transplantation [16].

In order to get a better understanding of the behaviour of solid theophylline and determination properties polymorphic forms I and II, a thermodynamic study has been carried out. The present paper is continuation of investigations of theophylline monohydrate, and its anhydrous forms I and II [17]. The thermodynamic properties and behaviour polymorphic forms and monohydrate were studied using: calorimetric measurements, differential scanning calorimetry (DSC), thermogravimetric analysis (TGA), powder X-ray diffraction [17].

Also it is interesting to determine the thermodynamic properties of aqueous solutions of polymorphic forms of theophylline.

The paper presents the results of the determinations of the enthalpy of solution in aqueous solutions. The standard molar enthalpies of solution at infinite dilution $\Delta_{sol}H_m^0$ were calculated. The obtained results, combined with the previously determined data of the standard molar enthalpies of sublimation $\Delta_s^g H_m^o$ of polymorphic forms I and II, were

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used to determine the standard molar enthalpies of hydration $\Delta_{hyd}H^{o}_{m}$.

Undertake determination of the enthalpy of solution arose due to the lack of literature data for polymorphic form I and verification accessible literature data for polymorphic form II. Also in the literature lack data of the heat of transition calculate on the basis the values of the enthalpies of solution obtained for polymorphic forms I and II. And also the values of the enthalpies of hydration are unavailable.

The obtained values together with other thermodynamic data obtained by DSC, TG and X-ray diffraction can be use for accurate identification polymorphic forms of theophylline in pharmaceutical industry.

## Experimental

### Materials

The all substances studied were kindly supported by Prof. B. Legendre from the laboratory "Chimie-Physique Minérale et Bioinorganique "Matériaux et Santé", Faculté de Pharmacie Université Paris XI" in Châtenay-Malabry, France.

The main objects of investigation were:

(a) theophylline (powder, commercial product, France), from a storage bottle,

(b) anhydrous form I of theophylline prepared from hydrate by heating at (390 K + vacuum) and recrystallization in methanol. Hydrate was obtained by placing in an exsiccator a few grams of theophylline (original) together with a flat open vessel filled with distilled water. The substance was kept at room temperature during a few days in order to prepare a hydrate,

(c) anhydrous form II of theophylline, which was prepared from hydrate by heating in a glass tube for 14 h at 383 K under vacuum of near 0.02 Pa.

For investigated substances were determined the purities by DSC study (calorimeter Q 1000 T Instruments). The obtained purities for theophylline (powder, commercial product), forms I and II were 99.99, 99.98 and 99.84%, respectively [17].

The observed enthalpy of fusion $\left(\Delta H_{fus}\right)$ for theophylline (powder, commercial product), forms I and II were 30.43, 28.02 and 30.10 $\mathrm{kJ \cdot mol^{-1}}$, respectively [17].

The observed enthalpy of fusion for forms I and II were in good agreement with the reported values of 26.4 and 28.2 $\mathrm{kJ \cdot mol^{-1}}$ [11]. Temperatures of fusion $T_{\mathrm{fus}}$ for theophylline (powder, commercial product), forms I and II were 270.82, 274.66 and 270.73 °C, respectively [17].

For identification polymorphic forms was used X-ray diffractometry. The X-ray patterns on powder for investigated compounds are presented in paper [17].

When comparing the experimental DSC, diffractometric [17] results it is possible to conclude that the starting material (theophylline, commercial product) for prepared polymorphic form was form II of anhydrous theophylline.

Substances used are described in detail in the article about transitiometric analysis of solid II/solid I transition in anhydrous theophylline [18].

The chemical structure of anhydrous form of theophylline is presented in Figure 1. Molar mass of anhydrous theophylline ($C_7H_8N_4O_2$) is 180.166 g/mol.

### Methods

The enthalpies of solution $\Delta_{sol}H_m$ in water at 298.15 K were determined experimentally using an isoperibol solution calorimeter. The calorimeter and the working procedure have been described in detail elsewhere [19, 20].

The calorimeter consists of the following parts: the proper calorimeter, the measuring system and the thermostat. The proper calorimeter consists of: the measuring steel vessel of total volume 80 $\mathrm{cm^3}$ and a working volume 65 $\mathrm{cm^3}$; an external metallic shield; two thermistors each nominally 150 Ω at 25 °C; a glass ampoule of 1.5 $\mathrm{cm^3}$ in volume; a 98 Ω calibration heater and stirrer. The external shield is submerged in a water thermostat bath (30 L) in which the temperature is sensed by a 100 Ω resistance platinum thermometer and controlled by PID regulator UNIPAN (Poland) type 650 providing a temperature constants better than $1 \cdot 10^{-3}$ °C. The thermistors located in the calorimetric vessel form the arms of a Wheatstone bridge, which is coupled to a 181 Keithley nanovoltmeter and an IBM PC computer.

The studied heat effect was evaluated using the method of corrected temperature rise with the Regnault-Phaundler correction. The lowest heat effect detectable corresponds to 0.15 J.

The sample was weighed and introduced into a glass ampoule, which was then thermally equilibrated in the

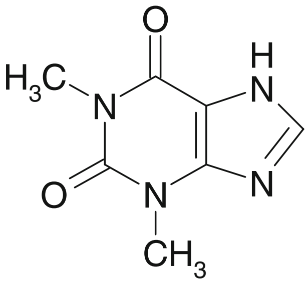

**Fig. 1** Chemical structure of anhydrous form of theophylline

**Table 1** The enthalpies of solution of theophylline (commercial product) and polymorphic forms I and II

| Theophylline (commercial product) | | Theophylline I form | | Theophylline II form | |
|---|---|---|---|---|---|
| $m \cdot 10^{-3}$ ($\mathrm{mol \cdot kg^{-1}}$) | $\Delta_{sol}H_m$ ($\mathrm{kJ \cdot mol^{-1}}$) | $m \cdot 10^{-3}$ ($\mathrm{mol \cdot kg^{-1}}$) | $\Delta_{sol}H_m$ ($\mathrm{kJ \cdot mol^{-1}}$) | $m \cdot 10^{-3}$ ($\mathrm{mol{\cdot}kg^{-1}}$) | $\Delta_{sol}H_m$ ($\mathrm{kJ \cdot mol^{-1}}$) |
| 0.601 | 20.01 | 0.311 | 18.73 | 0.450 | 19.54 |
| 0.644 | 20.50 | 0.472 | 18.26 | 0.455 | 19.27 |
| 0.690 | 20.03 | 0.480 | 18.20 | 0.497 | 19.79 |
| 0.840 | 19.95 | 0.484 | 18.43 | 0.514 | 19.10 |
| 1.004 | 20.02 | 0.560 | 18.77 | 0.520 | 19.66 |
| 1.014 | 20.20 | 0.605 | 18.25 | 0.729 | 19.03 |
| 1.232 | 20.06 | 0.620 | 18.52 | 0.757 | 19.47 |
| 1.547 | 20.70 | 0.661 | 19.00 | 1.033 | 19.10 |

calorimetric solution. Initiation of the solution process takes place after lowering the stirrer and breaking of the ampoule containing the substance studied.

Before each experiment the calorimeter was calibrated by means of electric Joule effect. The calorimeter was additionally tested by determination of the enthalpy of solution of potassium chloride (mass fraction 0.9999) in water [19]. The value 17.59 ± 0.03 $\mathrm{kJ \cdot mol^{-1}}$ obtained at 25 °C was very close to that of 17.55(0.04 $\mathrm{kJ \cdot mol^{-1}}$ recommended as the standard by IUPAC [21].

The obtained value also was in good agreement with the literature values: 17.577 kJ $\cdot \mathrm{mol^{-1}}$ [22], 17.586 ± 0.020 $\mathrm{kJ \cdot mol^{-1}}$ [23], 17.57 ± 0.05 [24], 17.542 ± 31 $\mathrm{kJ \cdot mol^{-1}}$ [25] and 17.54 ± 0.08 $\mathrm{kJ \cdot mol^{-1}}$ [26].

For each investigated substance 8 measurements were made with final solution concentrations in the range of $(0.311\text{–}1.547) \cdot 10^{-3}/\mathrm{mol \cdot kg^{-1}}$.

The enthalpies obtained for the solution processes provide information about the structural differences between the polymorphic forms and about solute/solvent interaction. For interpreting and analysis hydration data it is useful to consider the process as taking place into two steps: transfer of the solute molecule from the solid to the gas phase (sublimation) followed by the transport from gas to the solution [27].

The values of the enthalpy of hydration $\Delta_{hyd}H_m^o$ for aqueous solutions were calculated as a difference between the standard molar enthalpy solution of infinite dilution $\Delta_{sol}H_m^0$ and the enthalpy of sublimation $\Delta_s^g H_m^o$ [20, 28]:

$$\Delta_{hyd}H_m^o = \Delta_{sol}H_m^0 - \Delta_s^g H_m^o \qquad (1)$$

The heat of transition was calculated as the difference between the enthalpies of solution of the forms II and I at 298.15 K [29]:

$$\Delta H_{trs} = \Delta H_{sol}^{II} - \Delta H_{sol}^{I} \qquad (2)$$

where: $\Delta H_{sol}^{II}$ and $\Delta H_{sol}^{I}$ are the enthalpies of solution for polymorphs II and I, in the same solvent at the same temperature.

## Results and discussion

The values of the enthalpies of solution $\Delta_{sol}H_m$ of theophylline (commercial product) and polymorphic forms I and II are presented in Table 1. Within the experimental uncertainty, in the examined range of concentrations $(0.311\text{–}1.547) \cdot 10^{-3}/\mathrm{mol \cdot kg^{-1}}$, no concentration dependence of the enthalpy of solution was observed. The values of standard molar enthalpies of solution at infinite dilution $\Delta_{sol}H_m^0$ given in Table 2 have been calculated on the basis of the average value calculated from all the experimental data points for the enthalpies of solution.

The obtained values were compared with the literature data in Table 3.

In the literature lack the values of the enthalpy of solution for polymorphic form I of theophylline, what made it impossible estimation changes of energy between polymorphic forms I and II.

**Table 2** The standard enthalpy of solution at infinite dilution, the enthalpy of sublimation [33] and the enthalpy of hydration of theophylline (commercial product) and polymorphic forms I and II at 298.15 K

| Compound | $\Delta_{sol}H_m^\infty$ ($\mathrm{kJ \cdot mol^{-1}}$) | $\Delta_s^g H_m^o$ ($\mathrm{kJ \cdot mol^{-1}}$) | $-\Delta_{hyd}H_m^o$ ($\mathrm{kJ \cdot mol^{-1}}$) |
|---|---|---|---|
| Theophylline (commercial product) | 20.2 ± 0.3 | — | — |
| Theophylline I | 18.5 ± 0.3 | 132.0 ± 0.3 | 113.5 ± 0.4 |
| Theophylline II | 19.4 ± 0.3 | 134.2 ± 0.3 | 114.8 ± 0.4 |

**Table 3** The comparison between available literature data of the enthalpies of solution for anhydrous form II and monohydrate with experimental values obtained in this work for polymorphic forms I and II

| Compound | $\Delta_{sol}H_m^o$ (kJ · mol$^{-1}$) | Reference |
|---|---|---|
| Theophylline I | 18.5 ± 0.3 | This paper |
| Theophylline II | 19.4 ± 0.3 | This paper |
| | 19.4 ± 0.9 | Suihko et al. [30] |
| | 19.83 | Bruns et al. [31] |
| | 31.0 | Shefter et al. [32] |
| | 19.64 | Szterner et al. [17] |
| Theophyline monohydrate | 28.6 ± 1.4 | Suihko et al. [30] |
| | 30.3 | Bruns et al. [31] |
| | 44.8 | Shefter et al. [32] |
| | 25.23 | Szterner et al. [17] |

For polymorphic form I the value of $\Delta_{sol}H_m^0 =$ (18.5 ± 0.3) kJ · mol$^{-1}$ was determined in this work.

The obtained value $\Delta_{sol}H_m^0 =$ (19.4 ± 0.3) kJ · mol$^{-1}$ for form II of theophylline is consistent with those given by Suihko et al. [30] (19.4 ± 0.9) kJ·mol$^{-1}$ and Bruns et al. [31] (19.83) kJ · mol$^{-1}$.

Suihko et al. [30] determined the enthalpy of solutions by calorimetric measurements, whereas Bruns et al. [31] used van't Hoff plots, but instead of linear fitting they used a polynomial fitting.

Suihko et al. [30] and Bruns et al. [31] determined the enthalpy of solution for the theophylline monohydrate. Obtained values were (28.6 ± 1.4) kJ · mol$^{-1}$ and 30.3 kJ · mol$^{-1}$, respectively.

The obtained values for the anhydrous form II and monohydrate differ from those of Shefter and Higuchi [32] (31.0 and 44.8 kJ · mol$^{-1}$) who used van't Hoff plots.

Results obtained [17] from determinations the enthalpy of solution in water at 298.15 K by used a C80 Seteram calorimeter for form II and theophylline monohydrate are following: 19.64 kJ · mol$^{-1}$ and 25.23 kJ · mol$^{-1}$ . For analysis purposes the amount of the sample was used in a range 3–4 mg. For each measurement used 2.5 cm$^3$ water [17].

In Table 2 are presented the enthalpies of hydration determined from the experimentally obtained enthalpies of solution and previously determined the enthalpies of sublimation by Griesser et al. [33].

It can be seen from the data collected in Table 2 that the smallest difference in the values of enthalpy of hydration are between form II and form I of theophylline (1.3 ± 0.6 kJ · mol$^{-1}$). Whereas the heat of transition, calculated as the difference between the enthalpies of solution of the forms II and I at 298.15 K (Eq. 2), was found to be 0.9(± 0.4) kJ·mol$^{-1}$.

Application of Student's $T$-test undoubtfully prove that at significance level $\alpha < 10^{-4}$ the average values of enthalpy in both series differ—thus the distinct polymorphic effect is observed. Consequently, its value can be roughly estimated as 0.9 ± 0.4 kJ · mol$^{-1}$, nevertheless the standard deviations are significant. Calculated deviations for the values the enthalpies of solution influence on the enthalpies of hydration. Finally the polymorphic effect was estimated as 1.3 ± 0.6 kJ · mol$^{-1}$.

The obtained value the enthalpy of transition can be compare with the values obtained on the basis the enthalpies of fusion by DSC study [11, 17] and transitiometric analysis of polymorphs of theophylline [18].

The fusion enthalpies $\Delta H_{fus}$ at 298.15 K were calculated by following equation [34]:

$$\Delta H_{fus}^{298} = \Delta H_{fus} - \Delta S_{fus}\left(T_{fus} - 298.15\right) \quad (3)$$

Whereas the fusion entropies $\Delta S_{fus}$ of investigated substances were calculated by equation [34]:

$$\Delta S_{fus} = \Delta H_{fus}/T_{fus} \quad (4)$$

where $T_m$ is fusion temperature.

The enthalpy of the polymorphic transition in theophylline $\Delta_{\mathrm{trs}}H_m$ (II/I) obtained on the base difference between recalculated the fusion enthalpies $\Delta H_{fus}^{298}$ of the two polymorphs was equal to: $\Delta_{trs}^{298}H_m(I/II) = 16.50 - 15.25 =$ 1.25 kJ · mol$^{-1}$ [17]. This value is similar to the value calculated on the basis the data obtained by Suzuki [11]: $\Delta_{trs}^{298}H_m(I/II) = 15.5\ \mathrm{kJ \cdot mol^{-1}} – 14.4\ \mathrm{kJ \cdot mol^{-1}} = 1.1\ \mathrm{kJ \cdot mol^{-1}}$.

The enthalpy of transition was determined by Legendre and Randzio during transitiometric analysis of solid II/solid I transition in anhydrous theophylline [18]. The recalculated values of the $\Delta_{trs}H_m$ (II/I) at 298.15 K was equal to $\Delta_{trs}^{298}H_m(I/II) = 17.08\ \mathrm{kJ \cdot mol^{-1}} - 16.03\ \mathrm{kJ \cdot mol^{-1}} = 1.05\ \mathrm{kJ \cdot mol^{-1}}$.

Based on previously obtained experimental data on the enthalpy of the sublimation of crystals polymorphs of theophylline [35] the crystal lattice energy $\Delta_{cr}E$ can be estimate according to equation:

$$-\Delta_{cr}E = \Delta_s^g H_m^I - \Delta_s^g H_m^{II} \quad (5)$$

where: $\Delta_s^g H_m^I$, $\Delta_s^g H_m^{II}$ are the sublimation enthalpies of polymorphic forms I and II.

The value the crystal lattice energy $\Delta_{cr}E$ is equal to: 2.2 ± 0.4 kJ · mol$^{-1}$

The essence this work was obtained and verification the enthalpies of solution of polymorphic forms of theophylline.

The values $\Delta_{sol}H_m^0$ obtained for the polymorphic forms I and II indicate that these quantities can be use for identification polymorphic forms of theophylline.

The comparison of the values of enthalpies of solution and solvation shows that intermolecular forces in form I and II are similar.

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