

Dehydration of theophylline monohydrate—a two step process

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Abstract

The physicochemical properties of theophylline monohydrate and anhydrous polymorphic form II were evaluated using crystallographic, calorimetric and computational methods. The heats of solution of theophylline monohydrate and its anhydrous form were 28.6 and 19.4 kJ/mol, respectively, and the heat of hydration of theophylline anhydrous was 12.2 kJ/mol, as determined by solution calorimetry. Dehydration of theophylline monohydrate was studied by DSC. Under closed, hermetic conditions, the heat of dehydration, 10.7 kJ/mol, was almost equal to the heat of hydration. Under open conditions, the measured heat of dehydration was 47.3 kJ/mol. The dehydration phenomenon was examined also by molecular modelling and the computed heat changes were equal to those determined experimentally. The obtained experimental and theoretical results indicated that the monohydrate–anhydrate transition of theophylline is energetically reversible. Under closed conditions and in the aqueous media, the reversible monohydrate–anhydrate transition comprised only the dehydration or hydration step and the heat of transitions were considerably lower than under open conditions. Under open conditions, the dehydration of theophylline monohydrate proceeds in two steps even though the steps are overlapping. The first step is dehydration and the second is evaporation of the loosened crystal water. © 1997 Elsevier Science B.V.

Keywords: Theophylline; Dehydration; Hydration; Crystal structure; Calorimetry; Molecular modelling

1. Introduction

Theophylline is widely used as a bronchodilator in asthma therapy and is usually administered in tablet form or in solutions. Theophylline has been reported to exist in both a monohydrate and

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an anhydrous form (Sutor, 1958; Naqvi and Bhat-tacharyya, 1981). In the crystal lattice of the monohydrate, one water molecule is associated via one hydrogen bond to a theophylline molecule and via two hydrogen bonds to two other water molecules creating a network of hydrogen bonds. Anhydrous theophylline has two polymorphic forms, i.e. I and II (Burger and Ramberger, 1979). The polymorphs have been found to be enantiotropic, where polymorph II is the stable form at room temperature and the form I is stable at high temperatures. Anhydrous theophylline has also a metastable polymorph which transforms to the stable anhydrous form on storage (Fokkens et al., 1983; Phadnis and Suryanarayanan, 1995). These crystal forms of theophylline have different physical properties, arising from the polymorphism and hydrate formation and, consequently, effect their process and biopharmaceutical properties (Shefter and Higuchi, 1963; Haleblan and McCrone, 1969; York, 1983; Giron, 1995). Several authors have studied the physicochemical properties (e.g. solid-state stability, dissolution behaviour and hygroscopicity) of the above mentioned theophylline forms (de Smidt et al., 1986; Suzuki et al., 1989; Otsuka et al., 1990). The effects of mechanical treatment (Puttipatkhachorn et al., 1990), particle size and sample weight (Agbada and York, 1994), temperature (Duddu et al., 1995), crystal packing and hydrogen bonding (Perrier and Byrn, 1982) on the mechanism and kinetics of the dehydration of the theophylline monohydrate have also been studied. Kinetic studies are sensitive to experimental conditions and this has led to some inconsistencies in the published results.

Recently, the effect of environmental factors on the dehydration of necrodomil salt hydrates was studied (Zhu et al., 1996). The ambient pressure was shown to influence the dehydration mechanism and the distribution of crystal water in the crystal lattice. The dehydration stages were different when differential scanning calorimeter (DSC) measurements were made in crimped and open pans. Giron (1995) has also stated that DSC sample pan type (i.e. the environment) has dramatic effects on DSC experiments, and therefore, on the desolvation reactions. In addition, one

cannot characterise the desolvation reaction with DSC experiments alone and other techniques are needed if one wishes to obtain an in-depth understanding of desolvation reactions.

The objective of this work was to characterise the thermophysical properties of theophylline. Thus, the energetics and mechanism of monohydrate–anhydrate transition were examined using calorimetric and computational methods. In addition, the crystal structure of theophylline monohydrate was resolved by single crystal X-ray diffractometry. The resolved crystal structure was used in the evaluation of the energetics of water–theophylline interactions in the crystal lattice of theophylline monohydrate by molecular modelling.

2. Materials and methods

2.1. Materials

Anhydrous theophylline (Orion Pharma, Finland) was dissolved in distilled water at 60°C to yield a supersaturated solution. When the solution was slowly cooled, needle-like monohydrate crystals were formed. The most perfectly-formed monohydrate crystals were chosen for the single crystal X-ray analysis. Anhydrous theophylline form II was prepared by heating the monohydrate at 110°C for 24 h (Suzuki et al., 1989). Crystalline theophylline samples were gently dispersed with a pestle and mortar and sieved through a 297 μm sieve. For the solution calorimetric measurements, samples were further milled with a vibration ball mill (Retsch K9MM, Retsch Mühle, Germany) for 5 min at a vibration speed of 65 rpm and sieved through an 88 μm sieve. The theophylline monohydrate form was stored at room temperature under 58% (saturated NaBr solution) and the anhydrous form stored at < 10% (silica gel) relative humidity, respectively.

2.2. Determination of material properties

The water content was determined by a Mettler DL35 Karl Fischer titrimeter (Mettler-Toledo, Greifensee, Switzerland) and the results are expressed as a mean of six measurements.

A Jeol JSM-35 scanning electron microscope (Jeol, Japan) was used to visualise the particle size distributions and surface structures of the milled powder samples used in the solution calorimetric experiments. The samples were covered with gold (Sputter Coater II E 5100, Polaron Equipment, England) and scanned using an acceleration voltage of 15 kV.

2.3. X-ray diffractometry

Theophylline samples were identified with a Philips PW1820 X-ray powder diffractometer (Philips, The Netherlands) with step scan (step size 0.010° , sample time 1.50 s). The diffractograms were recorded using two wavelengths of Ni filtered CuK_α radiation ($\lambda = 0.154060$ and 0.154439 nm), a voltage of 50 kV, a current of 40 mA and an automatic divergence slit (irradiated sample length 12.5 mm). Data were collected and analysed with the Philips ADP1700 program.

The crystal structure of theophylline monohydrate was determined by a single crystal X-ray analysis. Intensity measurements were made on a Nicolet R3m diffractometer (Nicolet Instruments, Madison, WI) using graphite monochromated CuK_α radiation ($\lambda = 1.54178$ Å), ω -scan mode with a scan width of 1.2° and a variable scan speed of 2.44 – $29.3^\circ/\text{min}$. The data set was corrected for Lorentz and polarisation factors. The crystal structure was determined both in the space group P2_1 and $\text{P2}_1/n$ by direct methods and subsequent Fourier synthesis using SHELXTL program package (Sheldrick, 1990). In P2_1 the asymmetric unit contains two theophylline and two water molecules and in $\text{P2}_1/n$ only half of those numbers. Nonhydrogen atoms were refined anisotropically. Hydrogen atoms were located from difference Fourier maps but not refined ($U = 0.08$ Å). Both the structure determinations gave the same R values. However, in P2_1 the estimated standard deviations for geometrical parameters are twice as high as in $\text{P2}_1/n$ due to the low ratio of reflections/parameters (1272/254). The space group $\text{P2}_1/n$ was chosen as being correct although all of the systematic extinctions caused by the n -glide plane were not fully valid.

Crystal and refinement data. $\text{C}_7\text{H}_8\text{N}_4\text{O}_2 \cdot \text{H}_2\text{O}$, $M = 198.19$, monoclinic, $a = 4.4844(3)$, $b = 15.404(2)$, $c = 13.286(1)$ Å, $\beta = 98.54(1)^\circ$, $V = 907.5(2)$ Å³ (by least-squares refinement on 2θ angles for 38 reflection), $T = 293$ K, space group $\text{P2}_1/n$, $Z = 4$, $D_x = 1.542$ g/cm³. Colourless crystal, $0.20 \times 0.25 \times 0.50$ mm, $\mu(\text{CuK}\alpha) = 0.99$ mm⁻¹, $F(000) = 416$. Independent reflections (1272) measured in the range $4^\circ < 2\theta < 114^\circ$ of which 53 of the type $h0l$ (systematically absent in space group $\text{P2}_1/n$ when $h + 1 = 2n + 1$) with mean intensity 13.1 while for all reflections 358.3 , $R = (\Sigma|F_o| - |F_c|)/\Sigma|F_o| = 0.077$ for 999 reflections having $F_o > 4\sigma(F_o)$ and $R = 0.0908$ for all data. All features in the final difference synthesis were within ± 0.35 eÅ⁻³.

2.4. Calorimetry

Dehydration of theophylline monohydrate was studied with a Perkin-Elmer DSC7 differential scanning calorimeter (DSC) (Perkin-Elmer, Norwalk, CT). The results were expressed as a mean of three parallel measurements. All DSC runs were performed under an atmosphere of dry nitrogen using samples of 3–8 mg in weight. The heating rates were for open and closed pan runs 1 and $2^\circ\text{C}/\text{min}$, respectively. For the dehydration measurements at open conditions 50 μl aluminium pans with holes were used, while at closed conditions hermetically sealed 2 bar resistant 40 μl aluminium pans were used. Similar empty pans were always used as references. The temperature axis was calibrated with gallium (m.p. 29.78°C) and indium (m.p. 156.60°C).

The heats of solution and hydration were determined at room temperature ($23 \pm 1^\circ\text{C}$) using a Parr 1455 solution calorimeter (Parr Instruments, Moline, IL) equipped with a chart recorder. The heats of solution were determined in distilled water and the heat of hydration of anhydrous form II was determined in a supersaturated aqueous solution of theophylline, both weighing 90.00 ± 0.05 g. The sample weight was 95.0 – 105.0 ± 0.1 and 195.0 – 205.0 ± 0.1 mg in the heat of solution and hydration measurements, respectively. The solution calorimeter was calibrated and normalised using the exothermic reaction between

tris(hydroxymethyl)aminomethane (TRIS, Parr Instruments) and 0.1 N HCl. The thermograms were recorded at a sensitivity of 10 mV or 0.1°C full scale and a chart speed of 3 cm/min.

2.5. Molecular modelling

The crystal structure of theophylline monohydrate obtained from the single crystal X-ray diffractometric measurement was expanded by Sybyl 6.3 molecular modelling software (Tripos, St. Louis, MO). Semi-empirical quantum chemical calculations were made using AM1 parametrization (Dewar et al., 1985) as an implement in HyperChem™ molecular modelling software (HyperChem). Optimisation was considered complete after the root-mean-square gradient was lower than 0.04 kJ (0.01 kcal). Results from these calculations were used to calculate the theoretical energies for the theophylline–water interaction ($\Delta H_{\text{inter.}}$) by the following equation (Ketolainen et al., 1995):

$$\Delta H_{\text{inter.}} = \Delta H_{\text{hf(monoh.)}} - (\Delta H_{\text{hf(anhydr.)}} + \Delta H_{\text{hf(water)}}) \quad (1)$$

where ΔH_{hf} is the heat of formation. To study the hydrogen bonding between theophylline and water molecules a system containing one theophylline and one water molecule linked via one hydrogen bond, as present in the crystal lattice, was used. Theoretical heat of dehydration in open conditions was also calculated using a system containing two theophylline and two water molecules linked to each other via four hydrogen bonds (Fig. 1).

3. Results and discussion

3.1. Material properties

Scanning electron micrographs showed that theophylline anhydrous form II particles had very uneven surfaces (Fig. 2A). The particle surfaces consisted of numerous smaller primary particles which led to an increase in the effective surface area. The surface of the form II was irregular due

to desorption of the crystal water. The surfaces of theophylline monohydrate particles were smoother than the corresponding anhydrous form (Fig. 2B). The mean particle sizes could not be reliably measured, because of the cohesive multi-particulate structure, but it could be estimated to be considerably smaller for the anhydrous form than for the monohydrate. The water content

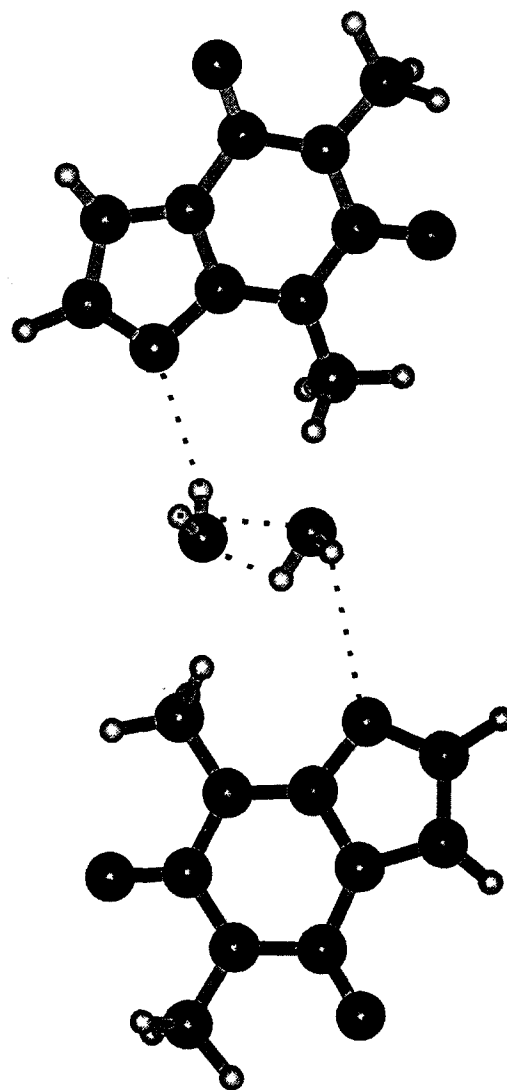


Fig. 1. The two theophylline and two water molecule systems with four hydrogen bonds used as a model for determination of the theoretical monohydrate–anhydrate transition enthalpy of theophylline.

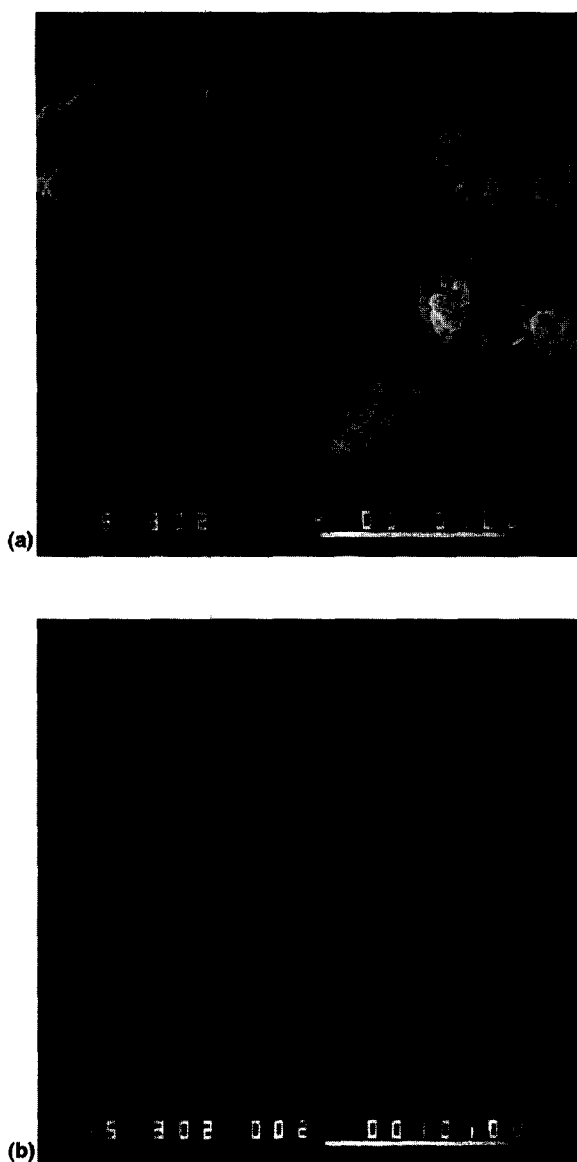


Fig. 2. The scanning electron micrographs taken from the powder particle surfaces of the anhydrous form II (A) and monohydrate (B) of theophylline. Bar is 10 μm .

with the standard deviation for the theophylline monohydrate was $9.2 \pm 0.2\%$ whereas for the anhydrous form II it was $0.2 \pm 0.1\%$. The measured water content of theophylline monohydrate was consistent with the theoretical water content (9.1%).

3.2. Identification of theophylline forms

X-ray powder diffraction patterns were significantly different for the monohydrate and anhydrous form II (Fig. 3) and equivalent to those presented in the literature (Suzuki et al., 1989). The reflections used for identification of anhydrous form II and monohydrate forms were at 12.7 and 26.6° , at 14.7 and 25.7° 2θ , respectively.

3.3. Calorimetric measurements

According to the solution calorimetric measurements, the heats of solution with standard deviations for the theophylline monohydrate and anhydrous form II were 28.6 ± 1.4 ($n = 7$) and 19.4 ± 0.9 ($n = 6$) kJ/mol, respectively. The monohydrate was found to be the more thermodynamically stable form (i.e. more endothermic) at room temperature. The measured values for the monohydrate and anhydrous form II (differed from) those of Shefter and Higuchi (1963) who used van't Hoff plots (44.8 and 31.0 kJ/mol, respectively). Bruns et al. (1984) used also van't Hoff plots to determine the heat of solution for theophylline, but instead of linear fitting they used a polynomial fitting. The heat of solution for the monohydrate and anhydrous form II were 30.3

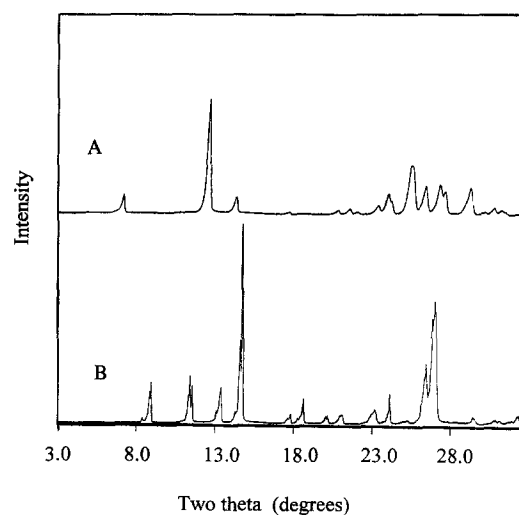


Fig. 3. X-ray powder diffractograms of the anhydrous theophylline form II (A) and monohydrate (B).

and 19.8 kJ/mol, respectively, which were virtually identical to our results. Milling has been reported to activate the particle surface of powders, especially for theophylline monohydrate (Puttipatkhachorn et al., 1990). Thus, it may have decreased the measured heats of solution.

Theophylline monohydrate is converted to anhydrous polymorphic form II during crystal water desorption (Suzuki et al., 1989). Due to this, the heat of hydration measurements were made in a super saturated aqueous solution of theophylline using the anhydrous form II. The heat of hydration calculated by subtracting the heat of wetting for the monohydrate (0.7 ± 0.6 kJ/mol, $n = 5$, measured also in super saturated solution) from the measured heat of hydration for the anhydrous form II (12.9 ± 2.4 kJ/mol, $n = 7$) was 12.2 kJ/mol. According to Hess' law, the heat of hydration of a compound is the heat of solution of the anhydrous form minus the heat of solution of the hydrated form. Using this law the calculated heat of hydration was 9.2 kJ/mol. Milling had probably activated the theophylline monohydrate particle surfaces, and thus the measured heat of solution might have slightly underestimated the heat of hydration. The measured and calculated heat of hydration values were almost the same, showing that the direct measurement of heat of hydration was possible. However, hydration is a part of the dissolution process and it cannot be differentiated completely from the dissolution. In addition, it should be noted that a supersaturated solution is not a stable system.

The extrapolated onset temperature for the monohydrate–anhydrate transition of theophylline determined with DSC in open conditions was $55.6 \pm 0.2^\circ\text{C}$ and the total enthalpy was 47.3 ± 0.3 kJ/mol. The transition consisted of the dehydration and evaporation of the loosened crystal water from the monohydrate structure (Suzuki et al., 1989). The DSC measurements showed that the dehydration endotherm had two peaks suggesting that the water molecules are present in two environments corresponding to two different energy stages, the first corresponding to the dehydration and the second to the evaporation of crystal water (Fig. 4). The dehydration and evaporation overlapped and could not be

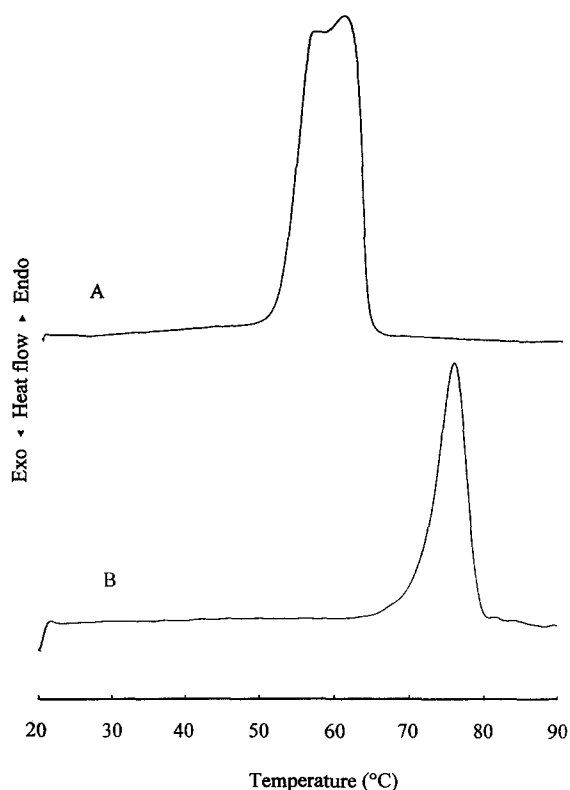


Fig. 4. DSC thermograms of dehydration of theophylline monohydrate under open conditions (A) and under closed conditions (B).

separated with DSC to determine the exact enthalpies for each transition step.

The stability point may be defined as the temperature up to which a hydrate is thermodynamically stable in the presence of its own saturated solution and vapour pressure. This point was determined for theophylline with DSC using closed 2 bar resistant sample pans. The stability point was $69.8 \pm 0.2^\circ\text{C}$. Further, the enthalpy of dehydration obtained from the same measurements, was 10.7 ± 0.1 kJ/mol. This result corresponded well to the heat of hydration (12.2 kJ/mol) of theophylline determined with the solution calorimeter and also to the measurements made by Bruns et al. (1984). It also permitted the calculation of the heat of evaporation, 36.6 kJ/mol, which is the heat of dehydration under open conditions minus the heat of dehydration under closed conditions.

3.4. Crystal structure and molecular modelling of theophylline monohydrate

The crystal structure of theophylline monohydrate was resolved by single crystal X-ray diffraction. On the basis of systematic absences, the space group has been determined to be $P2_1$, although the departure from $P2_1/a$ has been found to be very small and therefore the structure has been solved in the centrosymmetric alternative (Sutor, 1958). Our crystal structure determination in both space groups produced almost identical solutions. $P2_1/n$ was chosen as the correct one, because in $P2_1$ the estimated standard deviations for geometrical parameters are twice as high as in $P2_1/n$. In $P2_1/n$ centrosymmetrically and in $P2_1$ pseudocentrosymmetrically related theophylline molecules form hydrogen bonded dimers as shown in Fig. 5 and Table 1. These dimeric units are hydrogen bonded to water molecule chains running in the direction of the a -axis forming layers parallel to the ab -face. The shortest intermolecular interactions between these layers are $C(5)\cdots O(1)^i = 3.227(5)$ ($i = 1.5 + x, 0.5 - y, 0.5 + z$) and $C(5)\cdots O(1)^{ii} = 3.285(6)$ Å ($ii = 0.5 + x, 0.5 - y, 0.5 + z$).

Molecular modelling was used to evaluate the theoretical energy values for atomic level interactions between theophylline and water molecules (i.e. dehydration of the crystal water). To study

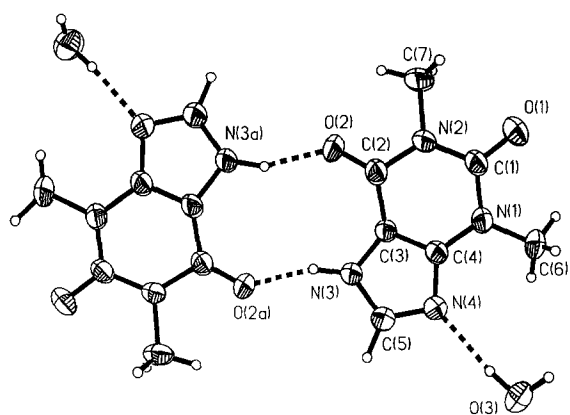


Fig. 5. Hydrogen bonded theophylline monohydrate dimer. Geometrical parameters for the numbered atoms are presented in Table 1.

the hydrogen bonding between theophylline and water molecules, a system containing one theophylline and one water molecule was used to compute the theoretical heat of formation of the monohydrate ‘molecule’ (i.e. one theophylline and one water molecule linked via one hydrogen bond), theophylline molecule and water molecule as mentioned earlier. The calculated (Eq. (1)) interaction energy including the hydrogen bonding and sterical interactions was 12.4 kJ/mol. This corresponds to the heats of hydration (12.2 kJ/mol) and dehydration under closed conditions (10.7 kJ/mol) obtained with solution calorimeter and DSC, respectively. Normally, the strength of a hydrogen bond is about 8–62 kJ/mol (Scheiner, 1991), thus the calculated result also corresponded well to the energy of a weak hydrogen bond. Therefore the energetics in the hydration or dehydration processes of theophylline are dominated by formation of hydrogen bonds between theophylline and water molecules whereas the sterical contribution is minor. Perrier and Byrn (1982) demonstrated the important effect of crystal packing on the dehydration of purine and pyrimidine hydrates, including theophylline monohydrate. Our results confirm this, the dehydration proceeds anisotropically along the parallel water molecule chains. The theoretical heat of dehydration under open conditions, where the crystal water can escape and evaporate from the crystal lattice was also calculated by Eq. (1), but in this case, a system containing two theophylline and two water molecules linked to each other via four hydrogen bonds was used (Fig. 1). The calculated enthalpy for the monohydrate–anhydrate transition was 48.4 kJ/mol, which corresponded to the heat of dehydration (47.3 kJ/mol) measured with DSC under open conditions. These results emphasise that the monohydrate–anhydrate transition proceeds in two steps, even though the steps overlapped and could not be totally separated and accurately detected.

In conclusion, the energetics of the reversible hydration-dehydration process of theophylline can be examined by studying the heat of hydration with a solution calorimeter. Since, hydration is a part of the dissolution process, it cannot be separated totally from the dissolution nor a super-

Table 1
Geometrical parameters (Å, °) for theophylline monohydrate in P2₁/n

O(1)–C(1)	1.230(5)	C(1)–N(1)–C(4)	118.6(4)	C(1)–N(1)–C(6)	120.0(4)
O(2)–C(2)	1.216(5)	C(4)–N(1)–C(6)	121.3(4)	N(1)–C(1)–N(2)	117.9(3)
N(1)–C(1)	1.369(5)	N(1)–C(1)–O(1)	120.9(4)	N(2)–C(1)–O(1)	121.2(4)
N(1)–C(4)	1.382(5)	C(1)–N(2)–C(2)	126.8(3)	C(1)–N(2)–C(7)	116.7(3)
N(1)–C(6)	1.447(6)	C(2)–N(2)–C(7)	116.5(3)	N(2)–C(2)–C(3)	111.4(4)
N(2)–C(1)	1.387(6)	N(2)–C(2)–O(2)	121.3(4)	C(3)–C(2)–O(2)	127.2(4)
N(2)–C(2)	1.404(5)	C(2)–C(3)–C(4)	122.9(4)	C(2)–C(3)–N(3)	131.2(4)
N(2)–C(7)	1.492(6)	N(3)–C(3)–C(4)	105.9(3)	C(3)–C(4)–N(1)	122.2(4)
N(3)–C(3)	1.379(5)	C(3)–C(4)–N(4)	111.8(3)	N(1)–C(4)–N(4)	126.0(4)
N(3)–C(5)	1.336(6)	C(3)–N(3)–C(5)	105.2(3)	N(3)–C(5)–N(4)	114.5(4)
N(4)–C(4)	1.362(5)	C(5)–N(4)–C(4)	102.6(4)	C(3)–N(3)–H(3)	121
N(4)–C(5)	1.331(6)	C(5)–N(3)–H(3)	133	N(3)–C(5)–H(5)	121
C(2)–C(3)	1.423(6)	N(4)–C(5)–H(5)	124	N(1)–C(6)–H(61)	110
C(3)–C(4)	1.360(6)	N(1)–C(6)–H(62)	111	N(1)–C(6)–H(63)	105
N(3)–H(3)	0.99	H(61)–C(6)–H(62)	110	H(61)–C(6)–H(63)	110
O(3)–H(31)	0.94	H(62)–C(6)–H(63)	111	N(2)–C(7)–H(71)	109
O(3)–H(32) ^a	0.98	N(2)–C(7)–H(72)	110	N(2)–C(7)–H(73)	110
O(3)–H(33) ^a	0.85	H(71)–C(7)–H(72)	110	H(71)–C(7)–H(73)	109
C(5)–H(5)	1.01	H(72)–C(7)–H(73)	109	H(31)–O(3)–H(32)	107
C(6)–H(61)	0.96	H(31)–O(3)–H(33)	98		
C(6)–H(62)	0.96				
C(6)–H(63)	1.05				
C(7)–H(71)	0.96				
C(7)–H(72)	0.96				
C(7)–H(73)	0.95				
H(3)···O(2) ^b	1.82	N(3)···O(2) ^b	2.762(4)	N(3)–H(3)···O(2) ^b	158
H(31)···N(4)	2.00	O(3)···N(4)	2.912(5)	O(3)–H(31)···N(4)	164
H(32)···O(3) ^c	1.74	O(3)···O(3) ^c	2.700(7)	O(3)–H(32)···O(3) ^c	164
H(33)···O(3) ^d	1.98	O(3)···O(3) ^d	2.760(8)	O(3)–H(33)···O(3) ^d	153

^a Population parameter 0.5; ^b equivalent position 1–x, –y, 1–z; ^c equivalent position 1–x, 1–y, 1–z; ^d equivalent position 2–x, 1–y, 1–z.

saturated solution is a stable system. Under closed, hermetic conditions, where the surrounding pressure is high and the evaporation of water to gaseous phase is prevented, the reversible monohydrate–anhydrate transition consisted of only the dehydration step and the change in enthalpy was considerably lower than that seen under open conditions. Hydration of theophylline anhydrous in saturated aqueous media is an energetically identical process as the dehydration under closed conditions since absorption of water to the crystal lattice of theophylline is facilitated by the aqueous environment. Under open conditions, the dehydration of theophylline monohydrate is a two step process, the first step being the dehydration (i.e. molecular loosening and breaking of hydrogen bonds between theophylline and

water molecules), and the second step is the evaporation of the loosened crystal water. These observations are clear evidence that the experimental conditions may change the mechanism of dehydration. This is supported by DSC, solution calorimetric and molecular modelling experiments.

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