Thermochimica Acta, 72 (1984) 31—40
Elsevier Science Publishers B.V., Amsterdam — Printed in The Netherlands

THERMOCHEMICAL INVESTIGATION OF THEOPHYLLINE, THEOPHYLLINE HYDRATE AND THEIR AQUEOUS SOLUTIONS

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ABSTRACT

Theophylline, although structurally very similar to caffeine, does not exhibit a solid state phase transition. In contrast to caffeine, it forms a monohydrate, of which the quadruple point and enthalpy of hydration have been determined. Furthermore, solubility and enthalpy of solution measurements are discussed.

INTRODUCTION

Purines are widespread in nature and play an important role in animal and human metabolism. Of the methylated dioxo-purines caffeine, theophylline and theobromine are the most important, Fig. 1. Theophylline, the subject of this paper, occurs inter alia in green tea, maté and other plants and may be a by-product in the decaffeination of coffee. It is an important drug in the treatment of asthma and cardial diseases and is used as a diuretic. It shows as well similarities with as distinct differences from its 7-methyl derivative caffeine.

MATERIALS

At 60°C, a saturated solution of theophylline (ICN Pharmaceuticals, Inc.) in dist. water was prepared, which on slow cooling yielded fine, long needles of theophylline hydrate. After centrifuging the rest of adhering solution was removed by storing the hydrate for several weeks at 92 % rel. humidity over a saturated solution of $Na_2CO_3 \cdot 10\ H_2O$ ("conditioning"). Desiccation at 90°C gave anhydrous theophylline. The purity was determined by DSC as 99,98 mol-%.

THEOPHYLLINE HYDRATE

Composition

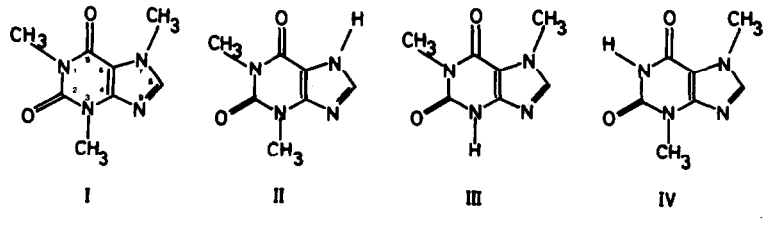
In the literature and pharmacopoe, theophylline and caffeine are both reported to form monohydrates. Since we had previously observed that caffeine in fact forms a 4/5-hydrate (ref. 1), we decided to check also the composition of theophylline hydrate. Both isothermal and dynamic TG measurements, however, showed that theophylline hydrate (if conditioned as described above) is indeed a monohydrate. The compositions theophylline·H_2O and caffeine·0.8 H_2O found are in accord with the X-ray structural analyses, see Fig. 2 (ref. 2, 3, 4).

Stability point

The stability point, often also referred to as the quadruple point, is the temperature ϑ_D up to which a hydrate is thermodynamically stable in the presence of its own saturated solution and vapour pressure. Literature data of ϑ_D show considerable discrepancies. From measurements of solubility resp. rate of solution of theophylline hydrate and theophylline SHEFTER and HIGUCHI deduce ϑ_D = 73°C (ref. 5) and WADKE and REIER ϑ_D = 73.6°C (ref. 6). ABOU-SHAABAN and SIMONELLI from TG and DTG curves obtain a range 52...80°C (ref. 7). FOKKENS et al. have undertaken powder X-ray diffraction, DSC and vapour pressure measurements and report ϑ_D = 63.8±1.3°C (ref. 8). We have determined the stability point in two ways. Theophylline hydrate was encapsulated in hermetic crucibles and the reaction

hydrate (s) ⟶ anhydrate (s) + sat. soln. (l) (1)

followed by DSC at various heating rates. Fig. 3 shows that the extrapolated temperature of peak onset decreases with decreasing heating rate. For vanishing heating rate, a value of ϑ_D = 67...68°C can be deduced. This value was checked by isothermal measurements: Samples of theophylline hydrate, enclosed in hermetically sealed crucibles, were held at constant temperatures for periods of 6...13 days and subsequently analysed by DSC whether the dehydration peak still showed up or not. Having approached ϑ_D first in greater steps, it was observed that after tempering 168 h at 66°C resp. 166 h at 66.9°C the hydrate was stable, where as a sample held 189 h at 67°C to about 99 % had converted.



I	II	III	IV
Caffeine (1,3,7-Trimethyl-xanthine)	**Theophylline** (1,3-Dimethyl-xanthine)	**Paraxanthine** (1,7-Dimethyl-xanthine)	**Theobromine** (3,7-Dimethyl-xanthine)

Fig. 1. Structural formulae of some methyl-substituted xanthines.

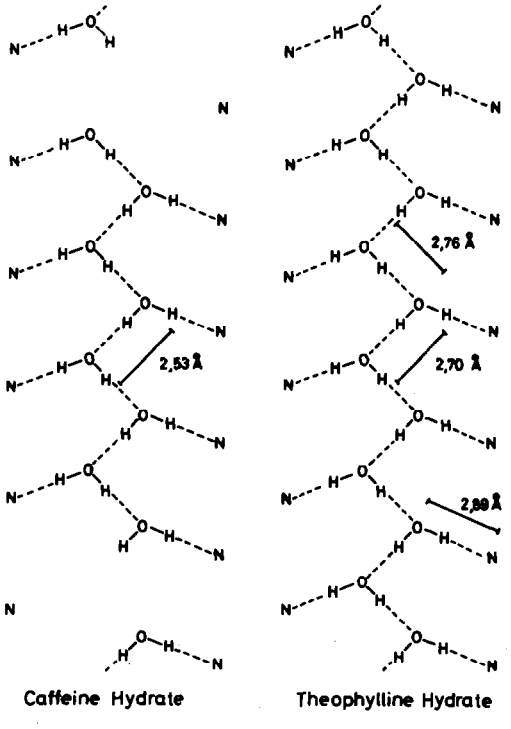


Fig. 2. The hydrogen bonding in the crystal structures of caffeine hydrate and theophylline hydrate. Projection on the (001) plane (ref. 2, 3, 4).

We thus conclude that ϑ_D = 67.0±0.2°C.

Fig. 3 shows the dependence of ϑ_D on the heating rate for the hydrates of theophylline and caffeine. It is seen that the ϑ_D-curve for caffeine hydrate for vanishing heating rate by far does not approach the stability point as determined by isothermal long-time measurements, which yield ϑ_D = 51.5°C. BOTHE and CAMMENGA (ref. 1, 9, 10, 11) have shown by DSC, X-ray diffraction and solution calorimetry that during the dehydration of caffeine hydrate besides the stable β-caffeine a considerable fraction of the metastable α-polymorph is formed, which subsequently reconverts to the β-form. This obviously results in a kinetic hindrance of the dehydration reaction. This example shows again that one should be careful in deducing solid state transition temperatures from DSC measurements even when having varied the heating rate. Thus CESÀRO and STAREC report ϑ_D = 86°C for the stability point of caffeine hydrate, which is 35°C too high (ref. 12)!

Enthalpy of dehydration

The enthalpy of dehydration was determined by DSC with samples of ≈ 10 mg at a heating rate of 2 K·min^{-1} in hermetically sealed capsules. The data observed were corrected for sat. solution and water vapour formation within the capsule as described previously (ref. 1). For the enthalpy of dehydration we obtain ΔH_D° = 10.5±0.3 kJ·mol^{-1}. As is seen from Table 1, this is 50 % higher than for caffeine hydrate. A higher value is expected from stronger hydrogen bonding of the water molecules in the crystal lattice of theophylline hydrate compared to that in caffeine hydrate, see Fig. 2. Theophylline hydrate shows continuous chains of bound water molecules whereas in caffeine hydrate the chains are interrupted.

Theobromine does not form a hydrate, whereas paraxanthine still has to be investigated in detail.

ANHYDROUS THEOPHYLLINE

Polymorphism

Caffeine shows a first order polymorphic phase transition at 140...141°C (ref. 9). GRABOWSKA and KALISZAN from structural considerations have predicted polymorphism in a number of purines, inter alia in caffeine and theophylline (ref. 13). DOSER believed to have found some evidence for a polymorphic transition near 260°C, when theophylline was obtained by desiccation of its hydrate

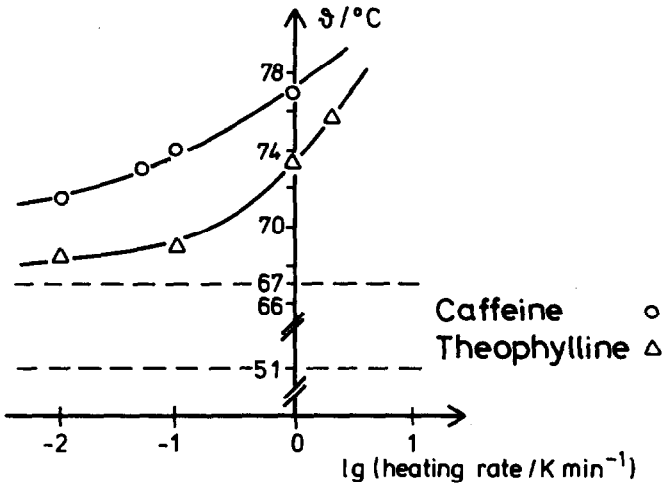


Fig. 3. Extrapolated temperatures of the onset of the dehydration peak (DSC curve) as a function of the heating rate, under which the measurements had been made.

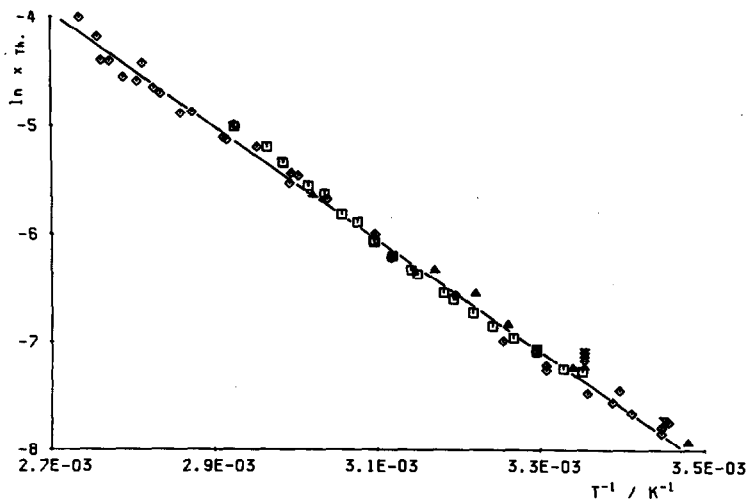


Fig. 4. Solubility of theophylline hydrate and theophylline in water. ◇ data of FOKKENS (ref. 8, 15); △ data of SHEFTER and HIGUCHI (ref. 5); ⧖ scattered literature data; □ data of this work.

TABLE 1

Comparison of some thermochemical data of important purines. The enthalpy of solution data are given in $kJ \cdot mol^{-1}$

Property	Theophylline	Caffeine	Theobromine
Phase transition	——	141°C (DSC)	——
		140°C (TMA)	
$\Delta H_t^\circ / kJ \cdot mol^{-1}$		4.1	
Melting point	271.2°C	236.1°C	348.5°C
$\Delta H_m^\circ / kJ\ mol^{-1}$	30.9	21.6	(13.1)
Thermal stability (DSC)	medium	very good	poor
Hydrate (TG)	$\cdot$ 1 H_2O	$\cdot$ 0.8 H_2O	——
Quadruple point	67°C	51.5°C	
$\Delta H_D^\circ / kJ\ mol^{-1}$	10.5	7.06	
Solubility in mol per 1000 g of water at 25°C	$3.72 \cdot 10^{-2}$	$1.092 \cdot 10^{-1}$	$(2.6 \cdot 10^{-3})$
Anhydrate			
$\Delta H^\circ_{sol,\ c \rightarrow o,\ 298}$	19.83	16.32	in prep.
$\Delta H^\circ_{sol,\ c_s,\ 298}$	in prep.	in prep.	in prep.
Hydrate			
$\Delta H^{\circ\prime}_{298}$	30.6	36.7	in prep.
$\Delta H^\circ_{sol,\ c \rightarrow o,\ 298} + \Delta H_D^\circ$	30.3	23.38	in prep.

(ref. 14). FOKKENS et al. report another uncertain observation (ref. 8, 15). We, however, found no evidence for a polymorphic phase transition in theophylline: neither quick dehydration of the hydrate nor fast crystallisation from non-aqueous solvents or quenching of the melt resulted in a sample showing thermal events other than melting.

Fusion

Melting of theophylline occurs at 271.5±0.5°C. The enthalpy of fusion is 30.9±1.0 $kJ \cdot mol^{-1}$; this is about 40 % higher than for caffeine.

Thermal stability

The thermal stability, which is of great importance inter alia in food technology, has also been determined. Pure samples were -in the absence of oxygen- encapsulated in hermetic aluminium crucibles or sealed into glass ampoules. These were held isothermally for 1 h at various fixed temperatures, then cooled quickly and analysed by computer-assisted DSC purity analysis. The thermal stability is astonishing for organic compounds and markedly decreases in the order caffeine > theophylline > theobromine.

THEOPHYLLINE SOLUTIONS

FOKKENS has measured the solubility of theophylline hydrate and theophylline in aqueous buffer solutions of pH=5 (ref. 8, 15). Since it occured to him that a plot of his data gave no evidence of a quadruple point, he fitted an equation

$$\ln x_C = - \frac{\Delta H^{\circ\prime}}{R \cdot T} + \text{const.} \qquad (2)$$

to all his data, from which he deduced an "enthalpy of solution" of 43.1 $kJ \cdot mol^{-1}$. We had found, however, that aqueous caffeine solutions are far from being ideal (ref. 11). This is due to solvent/solute and solute/solute interactions, the latter resulting in molecular sandwiching between two or more purine molecules ("base-stacking"). Since one knows from osmotic coefficient measurements that the activity coefficient is a strong function of concentration, the $\Delta H^{\circ\prime}$ from equation (2) is far from the last enthalpy of solution of caffeine hydrate $\Delta H^{\circ}_{sol,c_s,298}$ = 18.6 $kJ \cdot mol^{-1}$, see Table 1. Furthermore, equation (2) is only a

very rough fitting equation for solubility data of non-ideal solutions, e.g. when the measurement accuracy is not good, Fig. 4. As we have shown e.g. in the case of caffeine, a much better fit for ln x can often be obtained with a polynomial of second power in 1/T (ref. 11). The same proved true for theophylline (Fig. 5) and from this equation $\Delta H^{o'}_{298} = 30.6\ kJ \cdot mol^{-1}$ is calculated. If ln x for the solubility measurements of FOKKENS (ref. 8, 15) is fitted by polynomials of second power in 1/T for theophylline hydrate and anhydrate separately, the curves intersect at 66°C, close to the stability point of $\vartheta_D = 67°C$ as found by us, Fig. 6.

The enthalpy of solution at infinite dilution for the hydrates is

$$\Delta H^{\circ}_{sol,\ c \longrightarrow o,\ 298} + \Delta H^{\circ}_{D}.$$

One obtains 30.3 $kJ \cdot mol^{-1}$ for theophylline hydrate and 23.38 $kJ \cdot mol^{-1}$ for caffeine hydrate. This is close to $\Delta H^{o'}_{298}$ in the case of theophylline (30.6 $kJ \cdot mol^{-1}$) but far from the value for caffeine (36.7 $kJ \cdot mol^{-1}$), which means that the solute/solute interactions in theophylline solutions must be much smaller. The much higher solubility (and its high temperature increment) of caffeine must thus be attributed to better "base-stacking" of caffeine molecules in solution. This is in accord with conclusions drawn by GUTTMAN and HIGUCHI from their partition coefficient measurements (ref. 16), which they defend against controversial but doubtful results obtained by NMR (ref. 17).

Such structure/interaction relationships in purine and other solutions are the subject of further studies under way in our laboratory.

ACKNOWLEDGEMENTS

We thank Deutsche Forschungsgemeinschaft, Bonn-Bad Godesberg, and Fonds der Chemischen Industrie, Frankfurt am Main, for financial support.

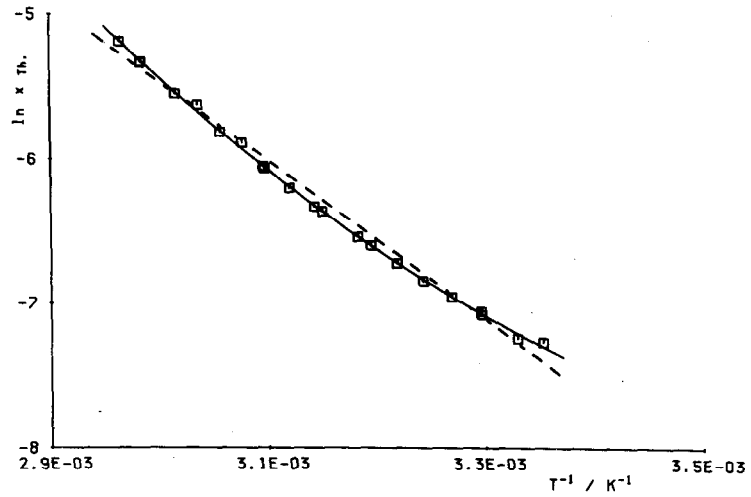


Fig. 5. Solubility of theophylline hydrate of this work alone. The data have been fitted as well by equation (2) (dotted line) as by a polynomial of second power in 1/T (full line).

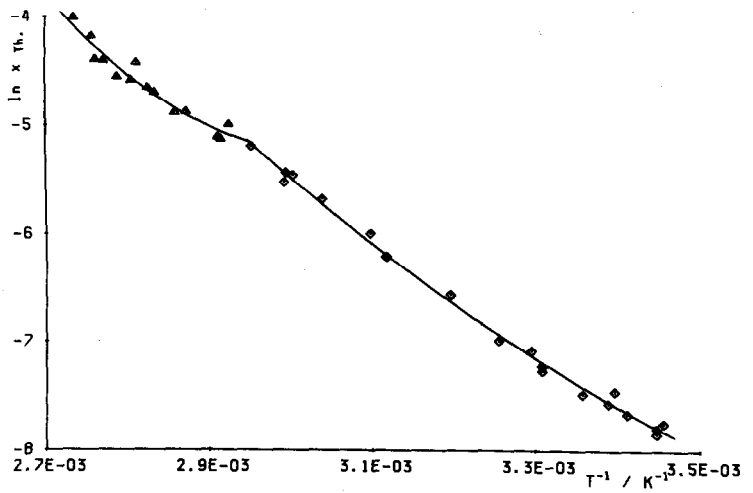


Fig. 6. In this figure the solubility data of FOKKENS (ref. 8, 15) have been fitted for theophylline hydrate and theophylline separately by polynomials of second power in 1/T. The intersection is at 66°C, see text.

REFERENCES

1 H. Bothe and H. K. Cammenga, Thermochim. Acta 40 (1980) 29-39
2 D. J. Sutor, Acta Crystallogr. 11 (1958) 83-87
3 D. J. Sutor, Acta Crystallogr. 11 (1958) 453-458
4 R. Gerdil and R. E.Marsh, Acta Crystallogr. 12 (1960) 166-167
5 E. Shefter and T. Higuchi, J. Pharm. Sci. 52 (1963) 781-791
6 D. A. Wadke and G. E. Reier, J. Pharm. Sci. 61 (1973) 868-871
7 R. R. A. Abou-Shaaban and A. P. Simonelli, Thermochim. Acta 26 (1978) 111-124
8 J. G. Fokkens, J. G. M. van Amelsfoort, C. J. de Blaey, C. G. de Kruif and J. Wilting, J. Pharm. - in press
9 H. Bothe and H. K. Cammenga, J. Thermal Anal. 16 (1979) 267-275
10 H. Bothe and H. K. Cammenga, Proc. IX Int. Coll. on Coffee ASIC, London, 1980, Vol. 1, p. 135-144
11 H. Bothe and H. K. Cammenga, Thermochim. Acta - in press
12 A. Cesâro and G. Starec, J. Phys. Chem. 84 (1980) 1345-1346
13 I. Grabowska and R. Kaliszan, Acta Polon. Pharm. 29 (1972) 537-538
14 H. Doser, Arch. Pharm. (1943) 251-256
15 J. G. Fokkens, PhD Thesis, Univ. of Utrecht, The Netherlands, 1983
16 D. Guttman and T. Higuchi, J. Pharm. Sci. 60 (1971) 1269-1270
17 A. L. Thakkar, L. G. Tensmeyer and W.L. Wilham, J. Pharm. Sci. 60 (1971) 1267-1269