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VAPOR PRESSURE AND HEAT OF SUBLIMATION OF CRYSTAL POLYMORPHS

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Abstract

In order to determine the applicability of vapor pressure studies on polymorphic modifications, pairs of enantiotropically related modifications of caffeine, theophylline and carbamazepine were investigated. The studies were performed over a wide temperature range (71 to 191°C) and accordingly over a wide vapor pressure range (0.02 to 400 Pa) using an automatic instrument constructed on the basis of the gas saturation principle. This instrument enables an analytical determination of the main component and the impurities present by the chromatographic separation of the substances transported in the gas flow. Therefore, the real partial pressure of the main component can be measured. Due to the high precision of the applied method it was possible to determine partial pressure curves and the thermodynamic transition temperature – the point at which the vapor pressure of two crystal polymorphs is equal. The thermodynamic transition temperatures of caffeine and theophylline were determined to be 136 and 232°C, respectively. These values are in agreement with experimental or calculated values derived from DSC investigations but are more reliable. Vapor pressure measurements of carbamazepine are only meaningful in the low temperature range due to its decomposition at high temperatures. The thermodynamics, advantages and limits of vapor pressure determinations of polymorphic modifications are discussed.

Keywords: caffeine, carbamazepine, crystal forms, heat of sublimation, polymorphism, theophylline, transition temperature, vapor pressure

Introduction

The physicochemical properties of active compounds, such as solubility, melting point and vapor pressure, are of great importance because they can affect the formulation characteristics, the shelf-life of the final drug product and even the therapeutic effect (bioavailability). All these properties depend strongly on the polymorphic form. It is therefore necessary to know the physicochemical data, the thermodynamic stability and the phase relationship of all crystal modifications.

In addition to classical methods, such as thermal analysis, X-ray powder diffractometry and spectroscopy, important thermodynamic features of polymorphic modi-

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fications can be obtained by solubility or vapor pressure measurements. The results of such investigations, amongst others, make it possible to determine the thermodynamic stability and transition temperature (T_{trs}) between two enantiotropically related polymorphs. Since the heat of sublimation is a key thermodynamic quantity for organic crystals and can be equated to the lattice energy of a crystalline state, there is considerable theoretical interest in reliable vapor pressure data of organic solids. Such data may help computational chemists to improve the algorithms for lattice energy calculations and the desired goal of predicting crystal structures [1]. Although schematic pressure–temperature phase diagrams are commonly used to show the relationship between different polymorphs [2, 3, 61], a rather small amount of experimental vapor pressure and heat of sublimation data are available for polymorphic pairs [4, 5]. This can be confirmed by reviewing Chickos comprehensive dataset of heats of sublimation [6]. The heats of sublimation of different polymorphs are given for only three of the 900 listed compounds (carbon tetrabromide, hexachloroethane and oxalic acid). According to Henck *et al.* [7] it is presumed that more than 50% of the active ingredients of pharmaceutical products show at least two polymorphic forms. However, it is not unlikely for certain compounds that some discrepancies of vapor pressure and heat of sublimation values obtained in different laboratories are based on the existence of polymorphic forms. One of many variations [8–10] can be observed for 2-naphtol which is known to exist in at least two crystal modifications [11]. Literature searches often reveal large discrepancies in reported heats of sublimation. Therefore, it is always a rather difficult task to select the most reliable data from all the published values [12, 13].

Although a great number of different methods are presently available to measure vapor pressures [14], only a few are applicable to crystalline organic substances which generally have very low vapor pressures – usually far below 10 Pa [15–17, 62]. The two methods most frequently used to measure the vapor pressure in this low range are the effusion technique [18, 53] and the gas saturation technique [19–21]. The main goal of this work is to show the applicability and the limits of vapor pressure measurements for polymorphic pairs applying the gas saturation method. Each of the selected compounds (caffeine, theophylline and carbamazepine) show enantiotropic pairs or, in other words, can exist in a low temperature and a high temperature stable modification. Other existing crystal forms and the hydrates of these compounds are not considered in this study.

Theory

Thermodynamics of vapor pressure and heat of sublimation

The pressure of a gaseous phase in equilibrium with its condensed phase at a specified temperature is called vapor pressure of the condensed phase (solid, liquid, or both at the triplepoint) and its temperature-dependence is represented by a p–T phase diagram, described elsewhere. Let p and T change infinitesimally, but in such a way that the two phases, which we label s (solid) and g (gas), remain in equilibrium. The free energies of the phases are then equal (G_s=G_g) and therefore the changes in them must be equal, thus we can write dG_s=dG_g. Since we know that

$$dG = -S_m dT + V_m dp \quad (1)$$

for each phase, it follows that

$$-S_{s,m} dT + V_{s,m} dp = -S_{g,m} dT + V_{g,m} dp, \quad (2)$$

where $S_{s,m}$ and $S_{g,m}$ are the molar entropies of the phases and $V_{s,m}$ and $V_{g,m}$ their molar volumes. Hence,

$$(V_{g,m} - V_{s,m})dp = (S_{g,m} - S_{s,m})dT, \quad (3)$$

which rearranges into the Clapeyron equation

$$\frac{dp}{dT} = \frac{\Delta S_m}{\Delta V_m}, \quad (4)$$

where $\Delta S_m = S_{g,m} - S_{s,m}$ and $\Delta V_m = V_{g,m} - V_{s,m}$ are the changes of molar entropy and molar volume when the transition occurs. This important result for the slope of the phase boundary at any point is exact and applies to any phase transition of a pure substance.

The sublimation entropy is linked to the sublimation enthalpy by the relation:

$$\Delta_{sub} S = \frac{\Delta_{sub} H}{T} \quad (5)$$

Moreover, we have to consider that changes of the molar volume can be described by the volume of the gas in a very good approximation. Since the vapor pressure of solids is very low we can assume that the gas obeys the perfect gas law: $V_{g,m} = RT/p$. These approximations turn the exact Clapeyron equation into the Clausius-Clapeyron equation:

$$\frac{d\ln p}{dT} = \frac{\Delta_{sub} H}{RT^2} \quad (6)$$

If we assume that the heat of sublimation is independent of temperature, integration of Eq. (6) leads to:

$$\ln p = -\frac{\Delta_{sub} H}{RT} + C, \quad (7)$$

which can be simplified to the analytical relationship of vapor pressure *vs.* temperature

$$\log p = -\frac{A}{T} + B \quad (8)$$

Thus, a plot of the logarithm of the vapor pressure *vs*. the reciprocal of the absolute temperature provides us with a slope equal to $-\Delta_{sub} H/\ln 10 R$ which is expressed as the coefficient $-A$.

Generally, the temperature range under study is not large enough to permit a precise determination of the temperature dependence for $\Delta_{sub} H$. The mean enthalpy of

sublimation determined by vapor pressure measurements $\Delta_{sub}H_{T1}$ can be extrapolated for other temperatures by the relation:

$$\Delta_{sub}H_{T_2} = \Delta_{sub}H_{T_1} + \int_{T_1}^{T_2} \Delta C_p \mathrm{d}T \tag{9}$$

where ΔC_p is the difference in heat capacities at constant pressure between the gas and solid phases ($C_{p,g}$–$C_{p,s}$). Assuming ΔC_p to be independent of temperature, yields:

$$\Delta_{sub}H_{T_2} = \Delta_{sub}H_{T_1} + \Delta C_p(T_2 - T_1) \tag{10}$$

If the required heat capacities of both solid- and gas-phase are not available, these data can be approximated by several estimation procedures [6, 16, 22, 23].

The vapor pressure Eq. (8) can be extended with terms, which take account of ΔC_p using the so-called Rankine-Kirchhoff equation [19, 24]:

$$\ln p = A + \frac{B}{T} + C\ln T \tag{11a}$$

$$\log p = A' + \frac{B'}{T} + C\log T \tag{11b}$$

where $C=\Delta C_p/R$, A' and B' corresponding respectively to A and B divided by ln10. Equation (11) can be turned into a more thermodynamic expression using relation (12) [6, 24, 25]:

$$\begin{cases} \Delta_{sub}H_{T_1} = R(T_1C - B) \\ \Delta_{sub}G_{T_1} = -R[B + T_1(A + C\ln T_1)] \\ \Delta_{sub}S_{T_1} = R[A + C(1 + \ln T_1)] \end{cases} \tag{12a}$$

$$\begin{cases} \Delta_{sub}H_{T_1} = R(T_1C - \ln 10B') \\ \Delta_{sub}G_{T_1} = -\ln 10R[B' + T_1(A' + C\log T_1)] \\ \Delta_{sub}S_{T_1} = R[\ln 10A' + C(1 + \ln 10\log T_1)] \end{cases} \tag{12b}$$

The resulting equation is the Clarke and Glew [24, 25] equation:

$$R\ln\left(\frac{p}{p_o}\right) = -\frac{\Delta_{sub}G_{T_1}}{T_1} + \Delta_{sub}H_{T_1}\left[\frac{1}{T_1} - \frac{1}{T}\right] + \Delta C_p\left[\frac{T_1}{T} - 1 + \ln\left(\frac{T}{T_1}\right)\right] \tag{13a}$$

$$R\log\left(\frac{p}{p_o}\right) = -\frac{\Delta_{sub}G_{T_1}}{T_1\ln 10} + \frac{\Delta_{sub}H_{T_1}}{\ln 10}\left[\frac{1}{T_1} - \frac{1}{T}\right] + \Delta C_p\left[\frac{T_1}{T\ln 10} - \frac{1}{\ln 10} + \log\left(\frac{T}{T_1}\right)\right] \tag{13b}$$

where p_o is the standard pressure (1 Pa) and T_1 the mean temperature of the vapor pressure measurements.

Replacing T by T_1 in Eq. (13b) leads to the following expression of $\Delta_{sub}G_{T_1}$:

$$\Delta_{sub}G_{T_1} = -RT_1 \ln 10 \log\left(\frac{p}{p_o}\right) \quad (14)$$

Thermodynamics of polymorphs

From Eq. (1) it can be seen that the free energy differences of two phases are proportional to the pressure changes and it is well known that, at a given temperature, the phase which has the lowest free energy, and thus the lowest vapor pressure is thermodynamically stable. For an enantiotropic system at a given pressure the free energy functions of two polymorphs intersect (G_I–G_{II}=0) at a temperature below their melting point, which is the thermodynamic transition point (T_{trs}). At this temperature the vapor pressures of the two phases are equal. Using the analytical form (Eq. (8)) of the Clausius-Clapeyron equation, we can calculate the transition temperature by Eq. (15):

$$T_{trs} = \frac{A_{II} - A_I}{B_{II} - B_I} \quad (15)$$

However, the Rankine-Kirchhoff equation (Eq. (11)) presents the temperature of transition T_{trs} implicitly:

$$(A_I - A_{II}) + \frac{(B_I - B_{II})}{T_{trs}} + (C_I - C_{II}) \ln T_{trs} = 0 \quad (16)$$

Nevertheless, assuming that the ΔC_p of both polymorphic forms is not different, then C_I=C_{II} and the last term of Eq. (16) disappears. So the intersection of the sublimation curves is the same as the one determined by the Clausius Clapeyron equation (Eq. (15)).

If the substance is thermally stable at temperatures above the melting point, the evaporation curve and the heat of vaporization ($\Delta_{vap}H$) can be determined. Its intersection with the sublimation curves of the different polymorphic forms then give the melting points. Furthermore, assuming the amorphous state of a substance is not transformed into a crystalline phase, its vapor pressure and the glass transition temperature (T_{gt}) can be determined directly. Finally, the heats of fusion ($\Delta_{fus}H$) of a modification can be calculated from their relationship to the sublimation and vaporization enthalpies: $\Delta_{fus}H$=$\Delta_{sub}H$–$\Delta_{vap}H$. Figure 1 shows schematically the vapor pressure diagram of a polymorphic system with two enantiotropically related modifications I and II and a stable amorphous solid.

Experimental

Materials

Caffeine was obtained from a commercial source (Fa. Apoka, Austria, Coffeinum anhydricum – Ph. Eur.; K1-896/88), crystallized from water and annealed at 90°C in an oven for 3 days to obtain pure mod. II. Caffeine mod. I was produced by anneal-

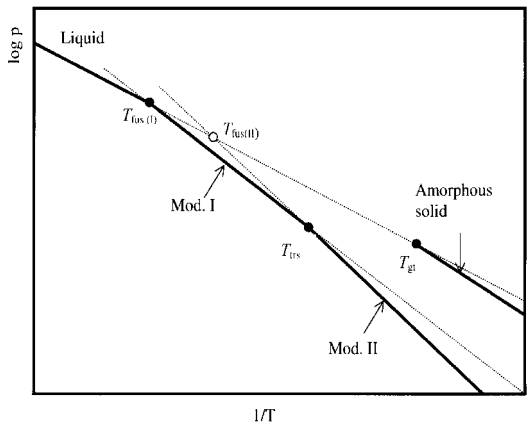

Fig. 1 Schematic vapor pressure diagram of an enantiotropic system; $T_{fus(I)}$ and $T_{fus(II)}$ are melting points of mod. I and mod. II; T_{trs}: transition temperature; T_{gt}: glass transition temperature. For simplification straight lines are drawn according to Eq. (8) (temperature dependence of $\Delta_{sub}H$ and $\Delta_{vap}H$ not shown)

ing mod. II at 160 to 200°C for 24 h in an oven. The purity (>99.9%) was determined by DSC.

Theophylline mod. II was supplied by Fluka (Analysis Number: 348041/1 496; HPLC purity >99%). Mod. I was obtained by annealing mod. II at 260°C for one hour.

Carbamazepine was available as the thermodynamic (20°C) stable mod. III (Pfannenschmidt, D-Hamburg, Batch-Nr: 8902 L 417, USP XXI/BP 88 certificated).

The different polymorphic forms were confirmed by X-ray analysis and DSC measurements.

Method

The vapor pressure measurements were performed using the automatic instruments Netzsch VPA 434 (Fig. 2) and the Ciba-Geigy prototype. The experimental arrangement is described in detail in [20, 21]. The instruments are based on the gas saturation method, which was developed and introduced to characterize agrochemicals and drug substances in the laboratory of Marti for Geigy AG in 1969. We carried out the experiments by passing a stream of inert gas (nitrogen) over the sample with a flow rate between 0.2 and 10 $cm^3\,min^{-1}$ to ensure an effectively complete saturation of the inert gas at the upper limit for any solid substance and to avoid a diffusion of the substance along the gas stream at the lower limit. About 50 mg of the substance was coated on glass beads without alteration of the crystal form. The saturated stream of gas was then passed over an adsorption segment (Tenax®). After a predetermined time the segment was heated to 200°C and the released substance was transferred (transferline temperature 220°C) into a packed column gas chromatograph (OV-17.3%) for quantification by FID. The response of the detector was

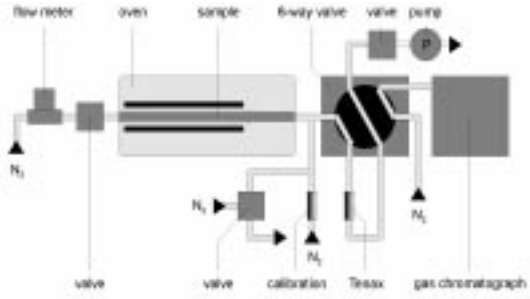

Fig. 2 Vapor pressure instrument Netzsch VPA 434

calibrated before starting the measurement by injecting different amounts of calibration samples. Based on the gas equation, the quantitative analysis allows the calculation of the vapor pressure at a given temperature:

$$p(T_1) = \frac{mRT_1}{VM} \tag{17}$$

where p is the vapor pressure [Pa], m the mass of the evaporated test substance [g], V the volume of the saturated gas [m^3], R the universal gas constant [J mol^{-1} K^{-1}], T_1 the temperature [K] and M the molar mass of the test substance [g mol^{-1}].

We assumed that the compounds obey the perfect gas law (i.e. no formation of dimers, trimers etc. in the gaseous phase) and used the molar masses of the monomers.

By varying the temperature, a full vapor pressure–temperature diagram can therefore be obtained. Typically 3 to 5 single measurements at each temperature were performed. Vapor pressure curves containing 21 to 55 data points, measured at various temperatures, were recorded.

Results and discussion

Caffeine

Caffeine is known to occur in two different polymorphic crystal forms and a hydrate [5, 26–30]. The anhydrous forms are related enantiotropically. The low-temperature modification II (or β-caffeine) is thermodynamically stable at 25°C and transforms at around 140°C [60] into the high-temperature modification I (or α-caffeine), which melts at 236°C. The physicochemical properties of caffeine have been extensively studied in various laboratories, but there are still uncertainties concerning the precision of some thermodynamic data reported in the literature. For the thermodynamic transition point (T_{trs}) between mod. II and I, at least four different temperatures (141°C [5], 150 to 153°C [31, 32], and 162°C [33]) have been reported (Table 5). All the studies are based on DSC investigations where an endothermic peak at about 145°C can be observed when mod. II is heated. However, the reverse transformation of the high temperature mod. I to mod. II is kinetically hindered and

cannot be observed by DSC during cooling. Due to the kinetic control, experimental solid-solid transformation temperatures in real crystals are usually observed above (on heating) or below (on cooling) with respect to the thermodynamic temperature T_{trs}, even if the scanning rate is very low. Thus, the lowest reported T_{trs} of 141°C, observed by Bothe and Cammenga [5], is probably closer to the true thermodynamic T_{trs}. Recently, this phase transition was investigated by Lehto and Laine [34] using isothermal microcalorimetry. The transition temperature was reported to be between 130 and 135°C. Bothe and Cammenga also determined the vapor pressure of both crystal forms, applying a static technique (manometer) at high temperatures (173 to 236°C, mod. I) and the Knudsen-effusion method for the lower pressure region (77–100°C, mod. II). The extrapolated transition point, calculated from the vapor pressure data, is 145°C (Eq. (15), [5]).

Table 1 Experimental results for caffeine

Modification I				Modification II			
Temp./ °C	n[a)]	p_{mean}/ Pa	$\Delta p/p_{mean}$ %[b)]	Temp./ °C	n[a)]	p_{mean}/ Pa	$\Delta p/p_{mean}$ %[b)]
141.3	5	14.9	0.4	70.9	3	0.0182	2.9
146.3	5	21.6	0.6	81.2	3	0.0581	1.1
151.4	5	31.5	0.2	91.4	3	0.174	0.3
156.3	5	44.0	0.9	101.6	3	0.482	0.7
161.3	5	62.5	0.9	111.7	6	1.24	0.4
166.3	5	86.4	2.1	121.8	3	3.06	2.3
171.3	5	119	1.7				
176.2	5	160	0.3				
181.3	5	223	1.4				
186.3	5	291	1.1				
191.3	5	397	0.3				

a) Number of measurements
b) 95% c.i.

Vapor pressure measurements on caffeine crystal forms in this study were performed in the following ways: starting at 190°C mod. I was cooled towards the transition temperature. Data between 190 and 140°C (55 single measurements in total, Table 1) were used for the calculations. The DSC transition temperature gives the limit for the vapor pressure calculations. Crystal mod. II was heated starting at 70°C and the vapor pressures between 70 and 120°C (21 single measurements in total, Table 1) were used for the calculations. Further measurements with mod. I below the transition temperature show the vapor pressure curve approaching that of mod. II between 130 and 70°C. The examination of these samples after the vapor pressure measurements revealed the presence of mod. II. This was due to the backtransformation of mod. I to mod. II below the transition temperature, which starts at the crystal

surface (in accordance with [27]). The parameters for a linear fit to the data based on Eq. (8) are summarized in Table 3 and the experimental data are shown in Fig. 3.

Table 2 Experimental results for theophylline

Modification I				Modification II			
Temp./ °C	n[a)]	p_{mean}/ Pa	$\Delta p/p_{mean}$ %[b)]	Temp./ °C	n[a)]	p_{mean}/ Pa	$\Delta p/p_{mean}$ %[b)]
140.9	5	0.231	2.7	140.9	5	0.204	5.1
145.9	5	0.367	1.8	145.8	5	0.331	1.8
151.0	5	0.591	1.4	150.9	5	0.530	2.9
155.9	5	0.915	0.9	155.8	5	0.831	2.9
160.9	5	1.40	0.9	160.9	5	1.28	1.9
165.9	5	2.13	1.2	165.9	5	1.97	2.8
170.9	5	3.14	2.3	170.9	5	2.93	2.9
175.9	5	4.63	1.2	175.8	5	4.30	3.2
180.9	5	6.82	1.8	180.9	5	6.38	3.0

a) Number of measurements
b) 95% c.i.

Table 3 Results of the vapor pressure measurements according to Eq. (8): $\log p[\mathrm{Pa}] = -A/T[\mathrm{K}] + B$

Compound	Form	A	B	T_{range}/°C	Method	Reference
Caffeine	I	5477±9[a)]	14.395±0.020[a)]	140–190	gas saturation	this work
	I	5223±28[a)]	13.697±0.057[a)]	173–236	Hg-manometer	[5]
	II	5932±9[a)]	15.508±0.025[a)]	70–120	gas saturation	this work
	II	5781±35[a)]	15.031±0.113[a)]	77–100	mass loss effusion	[5]
	II	5879±64[a)]	15.289±0.189[a)]	42–92	Knudsen eff. cell	[56]
	b)	5491	14.102	76–83	mass loss effusion	[45]
Theo-	I	6896±17[a)]	16.027±0.040[a)]	140–180	gas saturation	this work
phylline	II	7009±17[a)]	16.251±0.040[a)]	140–180	gas saturation	this work
	b)	6503	15.039	131–161	torsion effusion	[18, 38]
	b)	6665	15.423	131–161	mass loss effusion	[18, 38]
	b)	6587	15.234	131–161	mean value of	[18, 38]

a) Standard error
b) Crystal form not given by the authors
Vapor pressure measurements using UV-spectroscopy by Ebling [54] and thermogravimetric measurements by Tesconi [55] are not included in Table 3 because these authors did not consider the polymorphism of caffeine

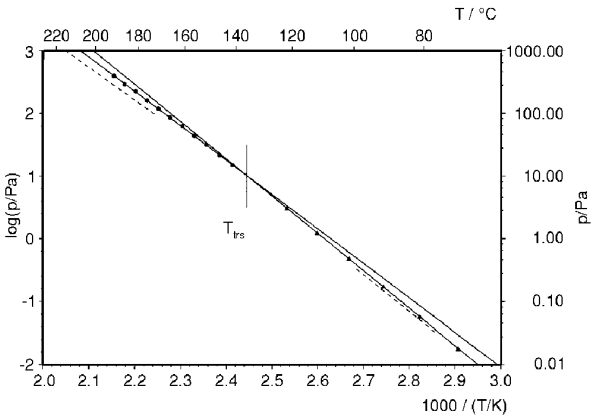

Fig. 3 Vapor pressure curves of mod. I (•) and mod. II (▲) of caffeine (Eq. (8)). The dashed lines are reproduced from the data of Bothe and Cammenga [5]

Our statistically based standard error is about three to seven times smaller than previously published data [5, 56], which reflects the precision of the method. Even though the temperature range for both of the polymorphs under study is 50 degrees, the relative error of the vapor pressure measurements should be less than 1% (ideally 0.1%), which would enable an estimation of ΔC_p. According to Table 1, the mean value of the relative error is about 1.0%. The temperature range of the measurements could not be extended. The upper temperature limit for mod. I is given by the vapor pressure limit for the gas saturation method which is about 1 kPa. The lower temperature limit is restricted by the thermodynamic transition temperature. The temperature region for which vapor pressure measurements are possible in the case of mod. II is restricted by the thermodynamic transition temperature and by the sensitivity limit of the instruments which is about 1 mPa. Moreover, since the calculation of $\Delta_{sub}H$ (T_{trs} or 25°C) needs to be corrected for ΔC_p (i.e. $C_{p,g}$–$C_{p,s}$), more reliable estimations of heat capacities are required. Benson's simulation method [23] could not be used for the estimation of ΔC_p of caffeine due to some caffeine specific increments being missing. Nevertheless, ΔC_p values have been cited to be generally between –50 and –100 J mol^{-1} K^{-1} for similar compounds [25, 38, 51, 52]. We chose the mean value of –75 J mol^{-1} K^{-1} for our calculations (Table 4). De Kruif [16] published ΔC_p -values for aromatic compounds as a function of the molecular mass. Caffeine (molecular mass 194.19) yields a value of –90 J mol^{-1} K^{-1}. Equation (15) gives the transition temperature T_{trs} assuming that ΔC_p of both polymorphic forms are not different. The intersection of the two vapor pressure curves gives 136°C (134 to 138°C; 95% c.i.) for the thermodynamic transition temperature T_{trs} between mod. II and I (Table 5), which agrees with Lehto and Laine [34]. The reliability of this value can be confirmed by the kinetic considerations discussed above. The heat of transition, calculated as the difference between the enthalpies of sublimation of the two forms at 136°C, was found to be 3.6 kJ mol^{-1}, which agrees with the DSC values (Table 5).

Table 4 Heats of sublimation ($\Delta_{sub}H$)

Compound	Form	$\Delta_{sub}H(T_1)$[a]/ kJ mol^{-1}	T_1/ °C	Reference	ΔC_p[b]/ kJ mol^{-1} K^{-1}	$\Delta_{sub}H(T_{trs})$[c]/ kJ mol^{-1}	T_{trs}/ °C	$\Delta_{sub}H$[c] (25°C)/ kJ mol^{-1}
Caffeine	I	104.8±0.2[d]	166	this work	–0.075	107.0	136	115
	I	99.99±0.54[d]	205	[5]	–0.056[f]	103.4	145	110
		100.3	205	[5] + Eq. 11b	–0.056[f]	103.7	145	110
	II	113.6±0.2[d]	96	this work	–0.075	110.6	136	119
	II	110.68±0.67[d]	89	[5]	–0.056[f]	107.5	145	114
	II	112.55±1.22[d]	66	[56]	–0.075	–	–	116
	e)	105.1±0.7[d]	80	[45, 13]	–0.075	–	–	109
Theophylline	I	132.0±0.3[d]	161	this work	–0.075	126.7	232	142
	II	134.2±0.3[d]	161	this work	–0.075	128.9	232	144
	e)	124.5±2[d]	148	[18, 38]	–0.072	–	–	133
	e)	127.6±2[d]	148	[18, 38]	–0.072	–	–	137
	e)	126.1±2[d]	148	[18, 38, 13]	–0.072	–	–	135
	e)	148	?	[46]	–	–	–	–

a) At mean temperature of vapor pressure measurement
b) $\Delta C_p = C_{p,g} - C_{p,s}$, estimated mean value given by [38]
c) Extrapolated (Eq. (10))
d) Standard error
e) Crystal form not given by the authors
f) Assuming ΔC_p(caffeine mod. I)=ΔC_p(caffeine mod. II)

Table 5 Transition temperature (T_{trs}) and heats of transition ($\Delta_{trs}H$) of the enantiotropically related crystal forms, for the transition of mod. II to I

Compound	Method	Reference	T_{trs}/ °C	$\Delta_{trs}H$[a)]/ kJ mol^{-1}
Caffeine	Vapor pressure	this work	136[b)c)]	3.6
	Vapor pressure	[5]	145[b)]	4.2
	Isothermal microcalorimetry	[34]	130–135	3.2
	DSC	[5]	141±2	4.03±0.1
	DSC	[32]	150–153	3.9
	DSC	[33]	162	3.57
Theophylline	Vapor pressure	this work	232[b)d)]	2.2
	DSC	[48]	197–215	1.2
	DSC	[36]	213[e)]	1.8±1.4
	DSC	[8]	195–231[e)]	1.2
	DSC	[49]	163[e)]	1.1±0.6

a) At transition temperature (T_{trs}) of the enantiotropically related crystal forms
b) Value calculated according to Eq. (15)
c) 134 to 138°C; 95% c.i.
d) 208 to T_{fus}= 276°C; 95% c.i.
e) Values calculated according to the mathematical procedure described in [2] using the heat of fusion and melting point data given in the cited literature

Theophylline

The polymorphism of theophylline is still a matter of discussion. The compound can exist in two enantiotropically related crystal forms and as a monohydrate. As in the case of caffeine, mod. II (T_{fus} 273°C) is thermodynamically stable at 20°C but no solid–solid transformation can be observed during heating. The existence of the high temperature mod. I (T_{fus} 276°C), first reported by Doser 1943 [35], was called into doubt by some researchers [63]. However, its existence and physicochemical data have been reported by different independent groups [8, 28, 36, 37] and is also verified in this study. The thermodynamic transition temperature can be calculated from the heats of fusion and melting points [2 ,8]. These calculations depend on a number of factors including: the precision of the data used, the level of approximation implied with the chosen equation, the temperature differences between the measured data and the temperature of transition.

The vapor pressure of mod. II has been previously determined for a small temperature region between 131 and 161°C [38]. In our study the vapor pressures of both crystal forms of theophylline were determined between 140 and 180°C. Because the solubility of theophylline is very low in commonly used solvents, we had some difficulties with the calibration of the vapor pressure instrument. Therefore,

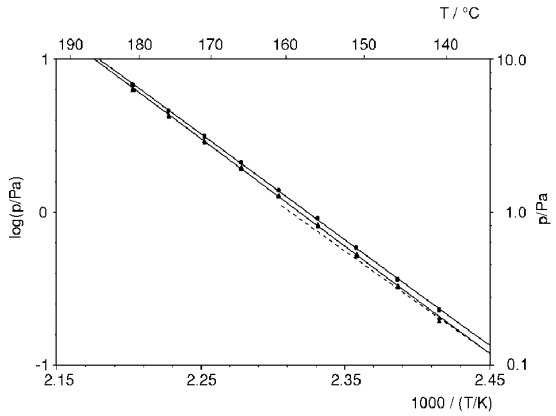

Fig. 4 Vapor pressure curves of mod.I (•) and mod.II (▲) of theophylline (Eq. (8)). The dashed line shows the data reproduced from Fokkens *et al*. [18, 38]

the same response factors as for caffeine were used for theophylline. The vapor pressure measurements were started at 140°C for both mod. I and II respectively (45 single measurements for each of the forms, Table 2). In contrast to caffeine, the transformation of the high temperature mod. I of theophylline to the mod. II below the transition point is very slow. Due to this, we were able to determine the vapor pressure of mod. I in the temperature region where this form is metastable. The parameters for a linear fit to the data are shown in Table 3 and the data are plotted in Fig. 4.

The absolute vapor pressure values of mod. II, according to our measurements, agree well with the data reported by De Kruif and Fokkens *et al*. [18, 38]. Our measurement shows rather high precision. Over similar temperature ranges (40 degrees), the mean value of the relative error of the vapor pressure measurements is about 2.3%. The difference in vapor pressure between mod. I and II is small over the whole measured temperature range. As theophylline and caffeine differ only slightly in their molecular masses, the calculation of $\Delta_{sub}H$ (T_{trs} or 25°C) (Table 4) was corrected for ΔC_p using the same estimated value as for caffeine. From the intersection of the two vapor pressure curves a thermodynamic transition temperature of T_{trs} =232°C (208°C to T_{fus}=276°C; 95% c.i.) can be calculated (Table 5). The estimation from the enthalpies of fusion and the melting points, based on the data of Burger and Ramberger [8], leads to a range of T_{trs}=195–231°C, in agreement with our value.

Carbamazepine

Carbamazepine is reported to exist in different polymorphic modifications by a large number of authors [39–43]. The high-temperature mod. I (T_{fus}=190°C) and the thermodynamic stable form at 20°C (mod. III, T_{fus}=176°C), are related enantiotropically. The solid state properties of these two forms are very well characterized but no vapor pressure determination has been reported up to now.

From solubility studies Behme and Brooke [57] determined a T_{trs} of 73°C as the transition temperature between mod. I and mod. III, which agrees with the value of

71°C estimated from the heats of fusion and the melting points [57]. However, this result is not consistent with a study by Krahn and Mielck [47] who showed that mod. I transforms to mod. III at 72°C within several months. According to this study we have to assume that the T_{trs} is significantly higher and according to Krahn and Mielck higher than 100°C [39, 47]. The solid state characterization of mod. I and III has been studied in the laboratory of Marti since 1970. The transition temperature T_{trs} was calculated, applying linear Gibbs' free energy functions with careful measurements of the heat of fusion and the melting temperatures, as T_{trs}=120°C [58]. The determination of the molar heat capacities with DSC for the two modifications and the liquid phase of carbamazepine by Marti and Geoffroy in 1995 enabled them to calculate the transition temperature with nonlinear Gibbs' free energy functions as T_{trs}=115±5°C [59].

Vapor pressure experiments for the metastable mod. I need to be performed in the temperature range above the enantiotropic transition temperature. Mod. I was obtained by annealing mod. III at about 165°C for 1 h in the vapor pressure apparatus [50]. In our first experiment above 165°C, we noted a significant shift in the gas chromatographic retention times of the collected samples. The characterization of carbamazepine by TG-FTIR [44] confirms the lower thermal stability of the compound in this high temperature range and according to Krahn and Mielck [47] the degradation occurs even at much lower temperatures. Thus, we were not able to determine reliable vapor pressure data of the two modifications with the automatic instruments. Nevertheless, vapor pressure measurements on carbamazepine are still possible using the classical device [19] at lower temperatures and appropriate analytical testing procedures of the collected samples.

Conclusions

The gas saturation method using automatic instruments provides an economical way to determine reliable vapor pressure data over a wide temperature (35 to 200°C) and pressure (10^{-3} to 10^{3} Pa) range. Thus, particularly for substances with a low vapor pressure, this method has many advantages over other vapor pressure methods. The instrument enables an analytical determination of the main component and the impurities present by the chromatographic separation of the substances transported in the gas flow. The real partial pressure of the main component can therefore be selectively measured and thus this method is less sensitive to impurities than any other vapor pressure method. The results show that the method allows a precise determination of small energy differences of crystal forms and their transition temperatures in the case of an enantiotropic relationship. As demonstrated for theophylline, the determination of the vapor pressure is also possible in its thermodynamically metastable temperature region, provided that the crystal form exhibits high kinetic stability. However, the application of vapor pressure measurements is generally restricted to compounds, which are thermally stable in the temperature range under investigation.

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