Thermochimica Acta, 156 (1989) 147–155
Elsevier Science Publishers B.V., Amsterdam – Printed in The Netherlands

DETERMINATION OF SOME THERMODYNAMIC CHARACTERISTICS OF MELTING OF 8-ALKYLTHEOPHYLLINES BY THE DSC METHOD

T. GONDOVÁ and P. KRÁLIK

Department of Physical and Analytical Chemistry, Faculty of Sciences, P.J. Šafárik University, Moyzesova 11, Košice CS-041 67 (Czechoslovakia)

J. GONDA

Department of Organic Chemistry, Faculty of Sciences, P.J. Šafárik University, Moyzesova 11, Košice CS-041 67 (Czechoslovakia)

(Received 19 April 1989)

ABSTRACT

The temperatures, enthalpies and entropies of melting of 8-alkyltheophyllines were determined by differential scanning calorimetry (DSC). Endothermic transitions exhibiting thermal hysteresis were observed for some derivatives of theophylline. These transitions preceded melting and corresponded to transition in the solid phase. DSC was also used for determining the purity of some selected 8-alkyltheophyllines, which were also tested by high-performance thin layer chromatography.

INTRODUCTION

The thermal properties of some derivatives of theophyllines or their complexes with transition elements are, at present, a subject of topical interest owing to the different biological and pharmacological effects of these compounds [1–4].

In earlier work [5,6], we have investigated the cyclization reaction of 1,3-dimethyl-4-alkylamino-5-nitrosouracils yielding 8-alkyltheophyllines, using differential scanning calorimetry (DSC). We have found that the reaction is rather exothermic and the yields are high (over 96%). In this study, the aim has been to investigate the melting and to determine the corresponding thermodynamic parameters for some members of the homologous series of 8-alkyltheophyllines.

EXPERIMENTAL

The 8-substituted theophyllines were prepared by the modified method according to the literature [7,8]. After repeated crystallization in methanol,

0040-6031/89/$03.50

the structure of the synthesized compounds was confirmed by elemental analysis as well as by IR, UV, ^{1}H-NMR, ^{13}C-NMR and mass spectrometry.

The temperature and enthalpy of melting as well as the purity of the products were determined using a DSC-2C differential scanning calorimeter (Perkin–Elmer) in dynamic nitrogen atmosphere, with a typical flow rate of 20 cm^3 min^{-1}. The samples were placed in pressed aluminium sample pans as used for volatile substances. The reference aluminium sample pan was empty. Indium and lead were used as standards for calibrating the temperature and determining the melting enthalpies. The position at the top of the melting peak endotherm on the temperature axis was corrected for thermal lag with reference to the result for indium (99.999%) obtained under identical conditions corresponding to the melting temperature of the sample [9].

The melting enthalpy was calculated from the area under the melting endotherm. The purity of some 8-alkyltheophyllines was determined by analysing the melting curves on the basis of the Gray equation [10,11]. The heating rate was 2.5 or 1.25 K min^{-1}. Every measurement and evaluation was repeated at least three times and in the case of the determination of melting enthalpies, even six or eight times.

The purity of the compounds was also tested by high-performance thin layer chromatography (HPTLC). High-performance thin-layer plates with chemically bound reverse phase RP-18 F_{254}s (Merck) were used. After development in mobile phase (volume ratio $V_{\text{acetonitrile}} : V_{\text{water}} = 9:1$), they were spectrophotometrically evaluated at 280 nm using a densitometer (Shimadzu CS-930).

RESULTS AND DISCUSSION

The values of the thermodynamic parameters describing the melting of 8-alkyltheophyllines are given in Table 1. The melting entropy (ΔS_f) was calculated from the relation $\Delta S_f = \Delta H_f / T_f$, where ΔH_f is the melting enthalpy and T_f the melting temperature. 8-Alkyltheophyllines exhibit relatively high vapour tension in proximity to the melting point. For this reason, many of them sublime during heating. Therefore, it was difficult to determine the melting enthalpies of some of the investigated derivatives of theophylline using our experimental equipment.

In the homologous series of 8-alkyltheophyllines the melting point decreases with increasing linear chain length of the alkyl group or with increasing molar mass (Fig. 1). A similar dependence of melting point on increasing molecular mass has been observed for some alkyl monoesters of *o*-phthalic acid with longer alkyl chains [12]. It is known that the analogous dependence of melting point on the number of carbon atoms in the homologous series of alkanes exhibits the opposite trend [13].

TABLE 1

Temperatures (T_f), enthalpies (ΔH_f) and entropies (ΔS_f) of melting of 8-alkyltheophyllines determined by DSC

Compound No.	R	T_f (K)	ΔH_f (kJ mol^{-1})	ΔS_f (J K^{-1} mol^{-1})
1	H	543.2	–	–
2	CH_3	599.8	–	–
3	C_2H_5	545.2 ± 0.5	37.2 ± 3.0	68.2
4	C_3H_7	534.3 ± 0.6	33.3 ± 2.2	62.3
5	C_4H_9	509.1 ± 0.2	32.3 ± 2.5	63.4
6	C_5H_{11}	498.3 ± 0.3	35.1 ± 3.5	70.4
7	C_6H_{13}	475.6 ± 0.2	26.1 ± 2.2	54.9
8	C_7H_{15}	472.6 ± 0.2	33.0 ± 3.6	69.9
9	$C_{11}H_{23}$	433.4 ± 0.2	25.8 ± 1.4	59.5
10 [a]	$C_{13}H_{27}$	430.5 ± 0.1	33.2 ± 0.7	77.3
11	$C_{15}H_{31}$	413.6 ± 0.1	27.2 ± 0.6	65.2
12	$C_{17}H_{35}$	415.0 ± 0.5	13.8 ± 0.1	33.3
13	CH_2OH	502.7 ± 1.0	–	–
14	$(CH_2)_2OH$	557.6 ± 0.2	–	–
15	$CH_2C_6H_5$	563.4 ± 1.0	–	–
16	$(CH_2)_2C_6H_5$	529.7	–	–
17 [b]	$CH(OH)C_6H_5$	400.9 ± 0.3	60.3 ± 2.5	–
18 [c]	$C(CH_3)_3$	402.3 ± 0.1	48.2 ± 1.2	–
19	$CH(CH_3)_2$	546.4 ± 0.5	–	–

[a,b,c] Two overlapping endotherms, the temperature of the first peak: a, 428.6 ± 0.1 K; b, 395.2 ± 0.1 K; c, 395.5 ± 0.1 K.

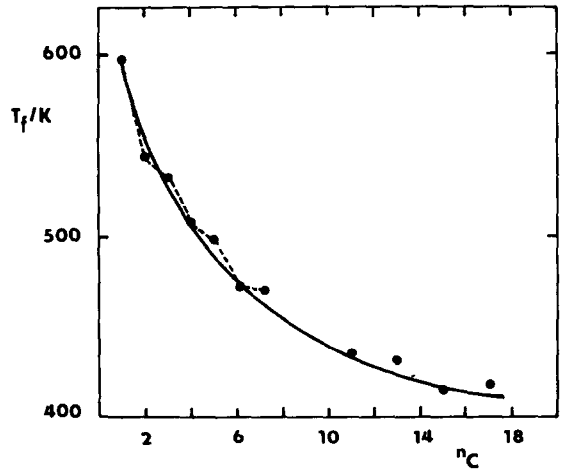

Fig. 1. Variation of melting point T_f with the number of carbon atoms n_C in the chain of the alkyl group of 8-alkyltheophyllines.

TABLE 2

Temperatures and enthalpies of melting according to literature values

Compound No.	R	T_f (K)	ΔH_f (kJ mol^{-1})
1	H	544 [1], 544.7 [2], 546–547 [7], 542–543 [14]	28.2 [1], 30.9 [15]
2	CH_3	602 [7], 598 [14], 602.6 [16]	–
3	C_2H_5	537 [2], 543 [14]	28.4 [2]
4	C_3H_7	554.7 [2], 536 [7], 529 [14]	31.1 [2]
13	CH_2OH	516–517 [7]	–
15	$CH_2C_6H_5$	571–573 [7]	–
19	$CH(CH_3)_2$	569.3 [2], 552 [7], 544 [14]	34.4 [2]

The values of T_f or 8-alkyltheophyllines obtained by DSC are in good agreement with data published in the literature (Table 2).

As stated by Bondi [17], the structural arrangement of a molecule in the solid and liquid phase plays an important part in appreciating the change in the molar entropy of melting (ΔS_f). For instance, the homologous series of hydrocarbons, alcohols, aldehydes, etc. exhibit regular increases in molar entropy of melting with increasing chain length because the value of ΔS_f is a simple function of the length of the carbon chain or molar mass. Deviations from this relation have been attributed to a change in crystal structure or to an s–s transition in the solid phase [18].

On the basis of the values of ΔS_f, we may state that for the 8-*n*-alkyltheophyllines listed in Table 1, the length of the side alkyl chain does not have any significant influence on the overall value of ΔS_f which falls in the range 60–70 J K^{-1} mol^{-1}. It is worth noting that some endothermic s–s transitions were observed before melting for those 8-*n*-alkyltheophyllines containing 6, 11, 13 or 17 carbon atoms in the side chain, the ΔS_f values of which were outside the above-mentioned range. Thus, it may be supposed that the melting of these compounds is affected by a more complex interaction between the basic skeleton of theophylline and its side chain. The molar entropy of melting observed for 8-$C_{17}H_{35}$-theophylline is extremely low, presumably due to the existence of an s–s transition before melting [17]. However, we must emphasize that a rigorous analysis of the changes in melting entropy is problematic because there is insufficient information concerning the molecular and crystal structure of 8-alkyltheophyllines, which is important for the examination of a phase transition and which can also vary even within a homologous series.

There are interesting experimental observations in the literature concerning the different behaviour of even and odd members of a homologous series, e.g. the *n*-alkanes and their derivatives, which indicate the significant influence of the crystal structure on the melting entropy resulting from different conformational arrangement [17,19]. Slight indications of a similar

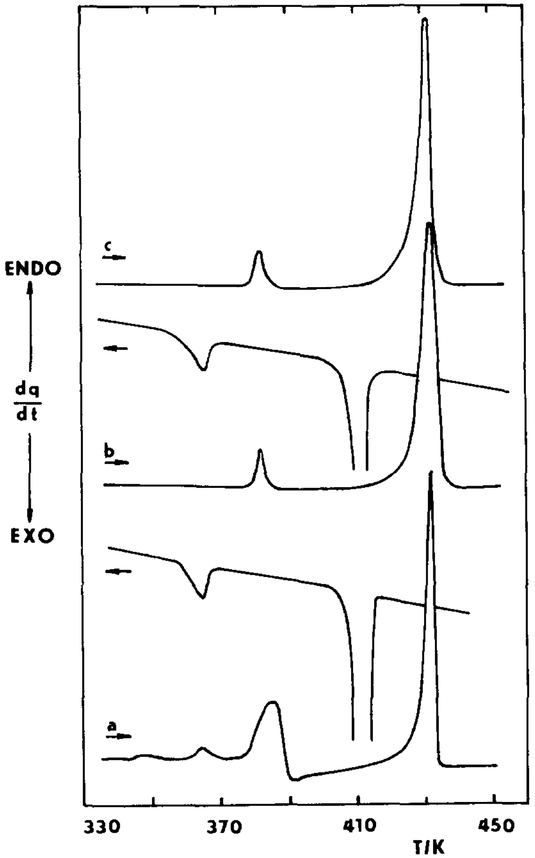

Fig. 2. DSC record for 8-$C_{11}H_{23}$-theophylline: (a) the first, (b) the second and (c) the third cycle of heating and cooling, heating rate 20 K min^{-1}.

alternation of melting point and melting enthalpy were also observed in the investigated homologous series of 8-alkyltheophyllines, see Fig. 1.

The majority of the investigated derivatives of theophylline passes from the solid crystalline state to the isotropic liquid state in the course of heating. We have found that some endothermic processes preceding the melting and exhibiting thermal hysteresis occur in some of the investigated compounds. These processes were observed (irrespective of the heating rate) for the derivatives with a longer alkyl chain, i.e. for $C_{11}H_{23}$-, $C_{13}H_{27}$-, $C_{15}H_{31}$- and $C_{17}H_{35}$-8-substituted theophyllines as well as for 8-tert-butyltheophylline and 8-(α-hydroxybenzyl)theophylline, (Figs. 2–6). These endothermic effects were also recorded by investigating 8-$C_{13}H_{27}$-theophylline prepared by direct thermal decomposition of the corresponding uracil, 1,3-dimethyl-4-tetradecylamino-5-nitrosouracil, in the calorimeter. The fact that the endothermic effects appear with the derivatives containing long alkyl chains leads to the assumption that these effects characterize the

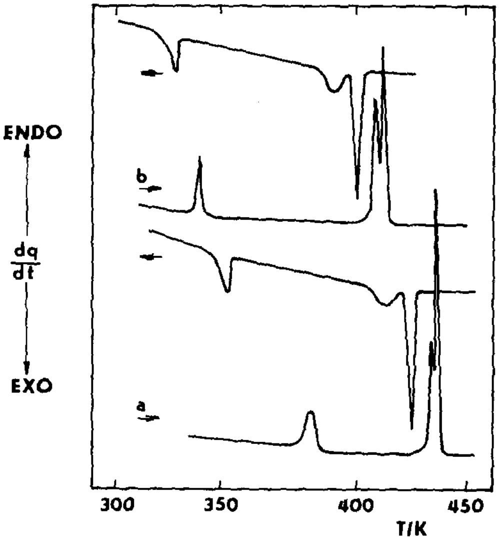

Fig. 3. DSC trace of 8-$C_{13}H_{27}$-theophylline: (a) the first and (b) the second cycle of heating and cooling, heating rate 20 K min^{-1}.

processes caused either by a change in conformational structures, i.e. reorganization of the flexible hydrocarbon chain, or by a reorientation of the molecular axes about which the rotational motion of the molecules takes

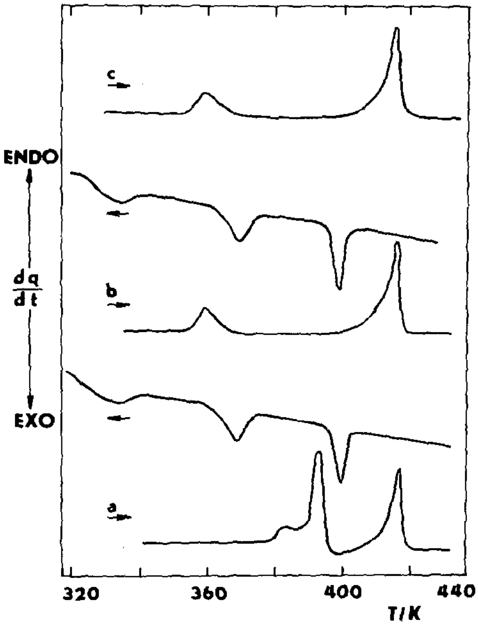

Fig. 4. DSC trace of 8-$C_{15}H_{31}$-theophylline: (a) the first, (b) the second and (c) the third cycle of heating and cooling, heating rate 20 K min^{-1}.

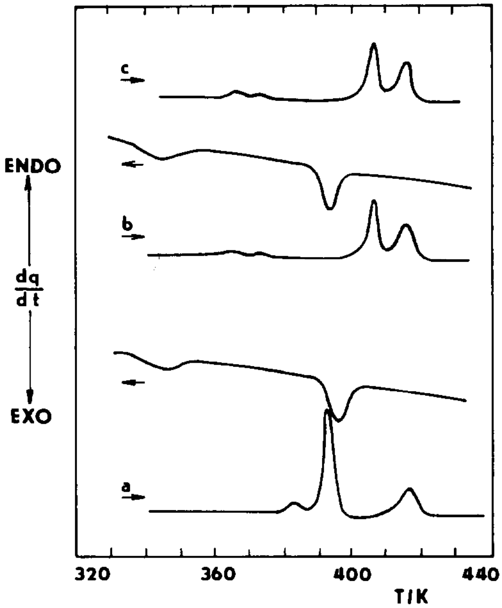

Fig. 5. DSC trace of 8-$C_{17}H_{35}$-theophylline: (a) the first, (b) the second and (c) the third cycle of heating and cooling, heating rate 20 K min^{-1}.

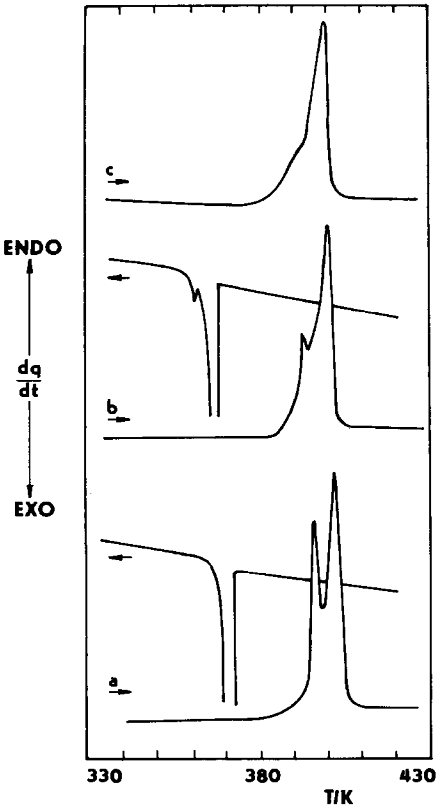

Fig. 6. DSC trace of 8-tert-butyltheophylline: (a) the first, (b) the second and (c) the third cycle of heating and cooling, heating rate 20 K min^{-1}.

TABLE 3

Data obtained by determining the purity of some synthetically prepared 8-alkyltheophyllines using DSC [a]

8-Alkyltheophylline R	Purity (mol%)	T_0 (K)	Correction (%)
Butyl [b]	99.83 ± 0.02	509.1 ± 0.3	–
Pentyl	99.87 ± 0.02	498.3 ± 0.1	–
Hexyl	99.55 ± 0.05	475.8 ± 0.1	7
Heptyl	99.71 ± 0.01	472.8 ± 0.1	5
Undecyl [c]	97.53 ± 0.23	434.6 ± 0.2	13
Pentadecyl	96.15 ± 0.02	419.1 ± 0.1	12

[a] The values of purity and T_0 were obtained from 3 measurements, rate of heating was 1.25 K min^{-1}, sensitivity was 1 mcal s^{-1}.

[b] The value of purity for the calorimetrically prepared 8-butyltheophylline was 99.33 ± 0.05 mol%, $T_0 = 509.4 \pm 0.1$ K, correction 5%.

[c] The value of purity for the calorimetrically prepared 8-undecyltheophylline was 98.70 ± 0.01 mol%, $T_0 = 436.6 \pm 0.1$ K, correction 6%.

place, as was described for *n*-pentadecane [19]. Also the presence of mixed crystals or of a meso-phase structure cannot be ruled out.

On the basis of analysis of the DSC melting curves, the purity of some theophylline derivatives was determined using the Gray equation (Table 3). In these experiments the purity of the compounds prepared by organic synthesis in solution was compared with the purity of the compounds obtained directly in the calorimeter by thermal cyclization of the corresponding uracils in the solid state. It follows from the results of these investigations that the purity of the 8-alkyltheophyllines prepared in solution decreases with increasing number of carbon atoms in the side chain, i.e. with the volume of the theophylline molecule. At the same time, the percentage correction necessary for achieving the linear relationship $T = f(1/F)$ increases, which may be because of the non-ideality of the investigated system. It was determined that the derivatives of theophylline prepared by thermal decomposition of uracils contained less impurities than the respective derivatives prepared in solution. These results were confirmed by spectrophotometric evaluation of the purity of these compounds in combination with HPTLC.

In spite of the fact that solid-state phase transitions were demonstrated for the investigated compounds, the classification of these phenomena remains uncertain at present because a more detailed study of the effects and their potential classification from the view-point of the phase transitions, require additional information obtainable by other methods, e.g. crystal structure analysis, polarization microscopy, etc.

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