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A NEW PROGRAM FOR DSC PURITY ANALYSIS

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DSC purity determinations have become very popular today [3]. The latest edition of the Mettler software package for thermal analysis, TA72.5 GraphWare, now comprises a powerful purity evaluation program. It is based on the simultaneous calculation of the mole ratio of the sum of the eutectic impurities, the melting point of the pure component, the melting point of the substance present and the linearization term. The portion of the melting curve investigated is selected appropriately.

Experience has shown, that the applied heating rate is a very important parameter which influences the duration of the measurement and also the possible exposure to elevated temperature where decomposition can become a problem and last but not least the accuracy of the calculated impurity value.

Introduction

Besides density the color the melting point of solids is part of the most important physical properties of a substance. Impurities lower the melting point provided that solid solutions are not formed and the melt is an eutectic system. This fact often is used to specify the purity indirectly by the melting point.

Using a classical melting point apparatus the substance in question is compared with the respective pure compound (standard) to determine the melting point depression. This melting point depression is also visible on DSC curves. Parallel to the melting point depression the presence of impurities broadens the melting peak.

The shape of a DSC curve enables the determination of the purity without reference to the same compound containing known amounts of impurities or no impurities at all. In this respect the DSC purity calculated from the shape of a DSC melting curve is an absolute purity determination [1].

DSC purity analysis should only be applied for samples that show normal melting ranges and no additional phenomena which overlap with the melting. Phenomena can be mentioned such as evaporation of impurities, splitting off

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volatiles (hydrates, solvates) polymorphism, crystal size distribution and also chemical decomposition.

The accuracy of the purity results calculated from DSC curves decreases normally proportional to the sum of the impurities. Given by different facts based on the instrumentation and the evaluation as well as on the substance under investigation there is a lowest accuracy level of the order of magnitude of one tenth of the actual impurity concentration. The DSC purity analysis is based on a simplified version of the Van't Hoff's equation:

$$T_{\mathrm{fus}} = T_{\mathrm{o}} - x_2 \frac{RT_{\mathrm{o}}^2}{\Delta_{\mathrm{fus}} H} \tag{1}$$

T_{fus} = temperature during fusion (liquidus temperature)

T_{o} = melting point of the pure component 1 (main component)

x_2 = mole fraction of the component 2 (impurities) in the liquid phase

R = gas content

$\Delta_{\mathrm{fus}}H$ = molar heat of fusion of the main component

According to the eutectic phase diagram the entire impurity is contained in the liquid phase above the eutectic melting point and the solid phase only consists of pure substance. At further heating pure substance dissolves in the eutectic solution and therefore dilutes the impurity in a proportional manner:

$$x_2 = x_{2,0} \frac{1}{F} \tag{2}$$

$x_{2,0}$ = mole fraction of impurity in the original substance

F = melted fraction = $A_{\mathrm{part}}/A_{\mathrm{tot}}$ where A_{part} is the partial area at any curve point before the top of the peak and A_{tot} is the total area of the melting peak.

Due to two reasons a linearization is required:

1. Often the eutectic is not measured, therefore A_{part} and A_{tot} are too small.

2. During fusion the rate of fusion increases rapidly thus Van't Hoff's law, that holds for equilibrium conditions is no longer valid.

The required correction therm is called c:

$$\frac{1}{F} = \frac{A_{\mathrm{tot}} + C}{A_{\mathrm{part}} + C} \tag{3}$$

Substituting x_2 in Eq. (1) by Eq. (2) shows that T_{fus} should be a linear function of $1/F$:

$$T_{\text{fus}} = T_{\text{o}} - x_{2,0}\frac{RT_{\text{o}}^2}{\Delta_{\text{fus}}H}\frac{1}{F}$$

The molar heat of fusion is calculated as follows:

$$\Delta_{\text{fus}}H = \frac{A_{\text{tot}} + C}{m}M \tag{4}$$

m = mass of sample

M = molecular mass of the main component

Substituting x_2, $1/F$ and $\Delta_{\text{fus}}H$ in Eq. (1) by the Eqs (2), (3) and (4) – after rearrangement – leads to the following multiple linear equation:

$$A_{\text{part}} = -c + T_{\text{o}}\frac{A_{\text{part}}}{T_{\text{fus}}} + (T_{\text{o}}c - RT_{\text{o}}^2x_{2,0}\frac{m}{M})\frac{1}{T_{\text{fus}}}$$

The TA72 software computes the three unknowns c, T_{o} and $x_{2,0}$ simultaneously using the method of least squares. The range of the DSC curve investigated is limited to 10% up to 50% of the peak height of the DSC melting curve (default values) to exclude the portion of very high impurity concentration in the liquid phase at the beginning and the portion of too high rates of fusion towards the peak top.

Experimental

All measurements are performed in the DSC25 measuring cell of the Mettler TA4000 System using the new ceramic sensor with a time constant of approximately 3 seconds. The obtained data are stored and evaluated by the new Mettler TA72.5 GraphWare package installed on an IBM PS/2–60 personal computer equipped with 2 Mb Ram, coprocessor, 3 1/2 'floppy drive, a hard disk of 60 Mb and a color screen. The diagrams are drawn by the Fujitsu color plotter ImageGraph.

Normally 3 to 6 mg sample are weighed into an aluminum pan. For volatile samples the pan is sealed hermetically to avoid any endotherm of sublimation or vaporization. It is good laboratory practice to check the weight after an analysis. In a sealed pan volatile eutectic impurities are detected, whereas a pierced pan allows the desorption of moisture and other volatile impurities before fusion therefore only the non volatile impurities are considered (purity on dry base).

Verification of results

To show the accuracy of the method a pure compound (dimethylterephthalate of 99.99% purity, Merck 808177) is artificially contaminated with some impurities. We do not recommend producing mixtures on a large scale (e.g. in a mortar) because they are often too inhomogeneous. It is better to add a few micrograms impurity to the main component already weighed into the sample pan. With the typical sample size of a few milligrams, diffusion is fast enough to form the eutectic at the first heating which is proved by the appearance of the eutectic peak (Fig. 1).

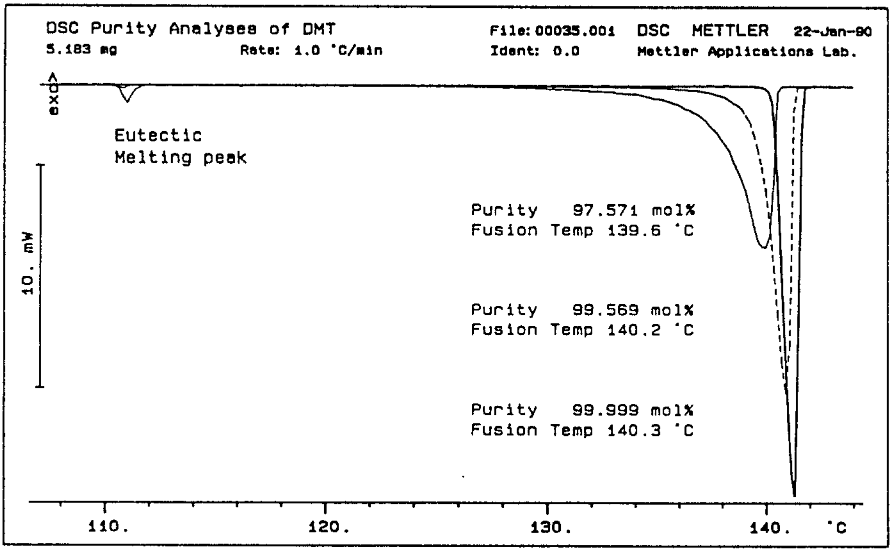


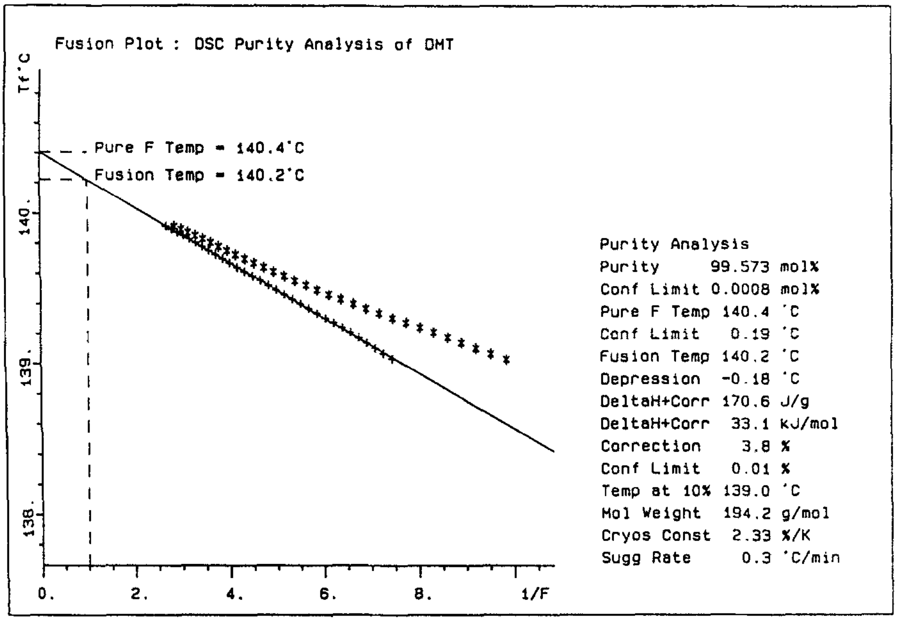
Fig. 1 DSC melting curves of pure and impure dimethylterephthalate, DMT

The main component is dimethylterephthalate (194.2 g/mol) of 0.00 mol% impurity. *S* is the slope of the respective regression line. For comparison a line of the slope 1 is plotted too. The applied heating rate is 2 K/min.

The following chemicals have been used as impurities:

Salicylic acid	138.1 g/mol
Benzamide	121.1 g/mol
Benzoic acid	122.1 g/mol

The too small purity values for benzoic acid are mainly due to the limited validity of the Van't Hoff equation for high impurity concentrations. Salicylic acid and benzamide on the other hand clearly give too high values which can be explained by some dissociation of these impurities or by the presence of



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Purity Analysis
Purity        99.573 mol%
Conf Limit  0.0008 mol%
Pure F Temp  140.4 'C
Conf Limit    0.19 'C
Fusion Temp  140.2 'C
Depression   -0.18 'C
DeltaH+Corr  170.6 J/g
DeltaH+Corr   33.1 kJ/mol
Correction     3.8 %
Conf Limit    0.01 %
Temp at 10%  139.0 'C
Mol Weight   194.2 g/mol
Cryos Const   2.33 %/K
Sugg Rate      0.3 'C/min
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Fig. 2 The fusion plot of dimethylterephthalate shows T_{fus} as a function of $1/F$ before linearization (*) and afterwards (+). 'Pure F Temp' corresponds to T_0, the melting point of the pure component. 'Fusion Temp' is the melting point of the substance present. The confidence limits are a measure of the quality of the fit. 'ΔH+Corr' is the heat of fusion including the correction of linearization. 'Temp at 10%' is T_{fus} at a melted fraction of 10%. The suggested rate is calculated from the width of the fusion peak

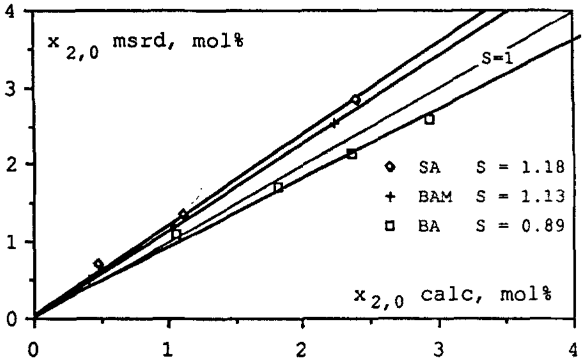

Fig. 3 Measured impurity concentration ($x_{2,0}$ msrd) as a function of the added impurities ($x_{2,0}$ calc). SA: salicylic acid, BAM: benzamide, BA: benzoic acid

moisture (water with its low molecular mass contributes very much to the impurity in mol%).

A good test of the applicability of DSC analysis is the comparison of results obtained by different ranges of investigation e.g. 10 to 50% and 10 to 80% of the peak height (or fraction melted respectively) [2]. When the purity results are close together (e.g. 2.74 and 2.78 mol%) Van't Hoff's equation holds otherwise (relative differences of 20% or more) the system most probably is not eutectic and thus the results questionable.

Many samples will recrystallize on cooling. The substance has been completely crystallized within the sample pan when the same heat of fusion is obtained for the second melt, otherwise there is some amorphous phase remaining. Samples which recrystallize ideally allow repeated purity analysis. Increasing purity indicates that some volatile impurities escape. On the other hand, decreasing values show the appearance of decomposition products that act as impurities in the next run. Other samples crystallize as well but in a different crystal modification with a different melting point and heat of fusion. Finally, some substances do not crystallize from melt; they form a glass on cooling.

The following figures show repeated fusion curves of dimethylterephthalate, DMT with benzoic acid as an impurity.

Heating rate

Despite the low heating rates of 0.3 to 0.7 K/min proposed by ASTM E928 [4], much higher rates often are applied to save time and to avoid decomposition. As a rule we can state, that 10 K/min leads to a higher purity value than 1 K/min.

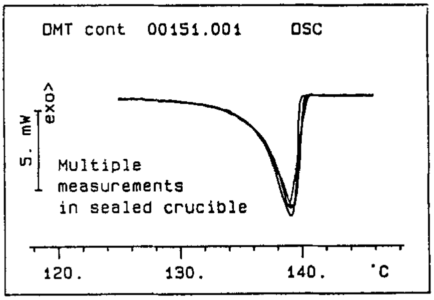

Fig. 4 Good repeatability of the fusion endotherm using a hermetically sealed pan

Samples of high purity require rather slow heating rates otherwise Van't Hoff's equation for equilibrium between solid and liquid phase does not hold true. There is an optional estimation of a suggested heating rate based on the shape of the melting curve [5].

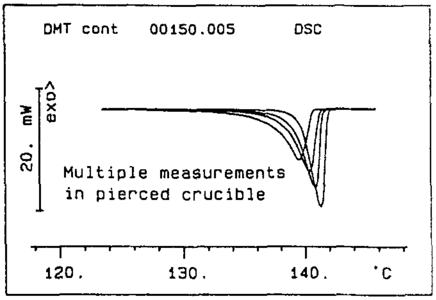

Fig. 5 Increasing purity in a pierced pan due to volatile impurities

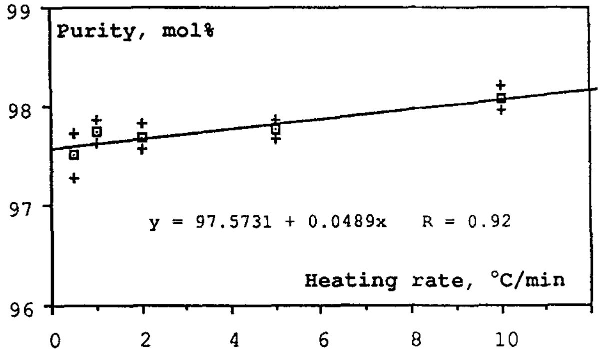

Fig. 6 Mean values of obtained purity (□) with indicated standard deviation (+) based on 8 determinations per heating rate (0.5, 1, 2, 5, 10°C/min). Sample: 5.940 mg dimethylterephthalate plus 0.090 mg benzamide; crucible: hermetically sealed. The calculated purity is 97.63 mol%. There is a clear tendency of obtaining higher purities with increasing heating rates.

Conclusion

DSC purity analysis is a fast and reliable technique for eutectic systems provided there are no other phenomena overlapping with the fusion process. The technique offers the following advantages over chromatographic and spectrometric analyses: the sum of all (eutectic) impurities is monitored; no standards are required; the melting point, another important property, is measured simultaneously (even the melting point of the absolutely pure compound is obtained). The heat of fusion allows the crystallinity of the sample to be checked, and thus amorphous fractions are recognized; even optical purity of an enantiomer with small amounts of the antipode can be assessed (sum of antipode and other impurities); occasional polymorphism is determined as well.

References

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2 O. Heiber, Poster Session ICTA Bayreuth (1980).
3 R. L. Blaine *et al.*, Purity Determinations by Thermal Methods, ASTM Special Technical Publication 838 (1984).
4 ASTM Test Method for Mol Percent Impurity by DSC, E928–83.
5 E. Marti, Ciba-Geigy AG, Basel, private communication.

Zusammenfassung — Die DSC-Reinheitsbestimmung ist heute eine weit verbreitete Methode, die mit einer einzigen Messung und unter Verwendung geeigneter Auswerteprogramme eine Bestimmung der absoluten eutektischen Reinheit einer Probe zulässt. Gleichzeitig können weitere thermodynamische Daten bestimmt werden, wie Schmelzpunkt der Probensubstanz und der reinen Hauptkomponente und die Schmelzenthalpie der Probe.

Durch experimentelle Befunde konnte gezeigt werden, dass die Wahl der Aufheizrate kritisch ist in bezug auf die Genauigkeit und die Signifikanz der ermittelten Daten.