

# Determination of the individual specific heat capacities of solids from multi-component powder mixtures and polymorphic mixtures

## A combined analysis of quantitative PXRD and calorimetry measurements

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**Abstract** This study describes a method to determine the specific heat capacities of individual solids from multi-component solid mixtures. To achieve this end, powder X-ray diffraction measurements are used to provide information on the number and identity of constituents as well as their compositions while calorimetry measurements give the specific heat capacities of the bulk solid mixtures. The method is applied to investigate three different solid mixture systems, namely (i) ternary organic mixtures containing  $\alpha$ -glycine,  $\alpha$ -lactose monohydrate, and paracetamol; (ii) ternary inorganic mixtures containing calcium fluoride, titanium nitride, and tungsten carbide; and (iii) polymorphic mixtures of  $\alpha$ - and  $\gamma$ -glycine. All systems are investigated at 298.15 K and at atmospheric pressure. The results show that the specific heat capacities of individual solids determined from multi-component solid mixtures are in good agreement with those directly determined from pure solid compounds.

**Keywords** Specific heat capacity · Quantitative phase analysis · Powder mixture analysis · Neumann–Kopp additive rule · Polymorphism

## Introduction

Inverse problems play a special role in many science and engineering disciplines [1, 2]. Such problems are often associated with complex physical systems which must be analyzed as a whole. In other words, the individual parts of the system cannot be isolated and measured separately. This can be illustrated by computed tomography (CT) where the 3-D interior or structure of complex objects and/or patients are imaged non-destructively [3]. The development of combined experimental and numerical solutions for specific classes of problems (e.g., combined X-ray absorption and the Radon transforms for CT) often opens considerable new opportunities, by enabling extensive qualitative and quantitative system identification of the individual parts of the complex system.

In the chemical sciences, multi-component liquid mixtures are frequently encountered. In some cases, i.e., during complex chemical reactions, the individual constituents of the sample cannot be isolated (i.e., transient intermediates), and hence the individual components' physico-chemical parameters cannot be readily determined. Nevertheless, it has been possible to successfully analyze many systems and determine the individual spectra [4], partial molar volumes [5, 6], dipole moments [7, 8], etc., of the species (some non-isolatable) present by combining the bulk measurements with appropriate numerical treatments [9].

Similarly, solids in material sciences often have complex compositions [10–15]. Here too, inverse problems can be identified, particularly in relation to the individual physico-chemical or thermo-physical of the phases/constituents present. The solution of such inverse problems is especially relevant to materials where new phases/constituents arise during processing, and hence cannot be easily measured. Examples may include the coexistence of more

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than one polymorph in pharmaceutical solids [11–13], or multiple phases in high-performance ceramics [14] and nanocomposites [15]. The bulk analysis of materials and the subsequent quantitative evaluation of the physico-chemical or thermo-physical parameters associated with the individual constituents present could afford unique insights into the role of the individual constituents.

In the case of pharmaceutical mixtures, polymorphism is undoubtedly important since different polymorphs can give rise to significant physico-chemical property differences. A recent review of various thermal-analytical techniques for analyzing polymorphs is available [16]. The use of combined thermal analysis and other techniques, such as XRD [17, 18], hot stage microscopy [19] on investigating polymorphs can also be found in various recent studies.

In the present study, an inverse thermo-physical material problem is addressed. Specifically, this contribution investigates multi-component solid mixtures as well as polymorphic mixtures with high crystallinity, where information on the heat capacity of each constituent is sought. Three different solid mixture systems are studied, namely (i) ternary organic solid mixtures consisting of  $\alpha$ -glycine,  $\alpha$ -lactose monohydrate, and paracetamol (I); (ii) ternary inorganic solid mixtures consisting of calcium fluoride ( $\text{CaF}_2$ ), titanium nitride (TiN), and tungsten carbide (WC); and (iii) polymorphic mixtures of  $\alpha$ - and  $\gamma$ -glycine. All systems are investigated at 298.15 K and at atmospheric pressure. Combined experimental measurements using quantitative powder X-ray diffraction (PXRD) and calorimetry are performed on each of these systems. The PXRD measurements provide information on the number of constituents, their identities and their quantitative compositions while the calorimetry measurements give the specific heat capacities of the bulk solid mixtures. Subsequently, the specific heat capacities of the individual solid components are determined from the multi-component mixtures via the Neumann–Kopp equation. The accuracies of the results are assessed by comparison to authentic references of the pure constituents.

## Experimental section

### Materials

The organic compounds,  $\alpha$ -glycine (Sigma, >99%),  $\alpha$ -lactose monohydrate (Sigma, >99%), paracetamol (I) (Aldrich, >98%) and inorganic compounds, calcium fluoride ( $\text{CaF}_2$ ) (Sigma-Aldrich, >99.0%), titanium nitride (TiN) (Alfa Aesar, >99.7%), and tungsten carbide (WC) (Aldrich, >99%) were used.

Pure  $\gamma$ -glycine (in gram scale) was obtained via aqueous solution-mediated transformation and crystallization of

$\alpha$ -glycine at room temperature (about 3 days). In order to accelerate the transformation, a small amount of  $\gamma$ -glycine seeds (the seeds were prepared according to the procedure described in literature [20]) was added to the supersaturated  $\alpha$ -glycine solution. The solid  $\gamma$ -glycine obtained was subsequently filtered from the solution and dried overnight. The purity of  $\gamma$ -glycine obtained was ca. 100%, as ascertained by PXRD measurement.

Diamond powder (Huifeng Diamond, size 0.8  $\mu\text{m}$ ) was used as an external standard in the PXRD measurements (used for organic mixture measurements). Synthetic sapphire,  $\alpha$ - $\text{Al}_2\text{O}_3$  (NIST, SRM720) was used as a reference material for heat capacity studies. The sapphire was heated to 1273 K in air for few hours prior to measurements to remove any organic surface impurities.

The pure solid samples and the solid mixtures were prepared by mass using a balance (GR-200, A&D, Japan) with a precision of  $\pm 10^{-4}$  g. A total of ten ternary organic mixtures (each of ca. 2.5 g), six ternary inorganic mixtures (each of ca. 6 g) and six polymorphic mixtures of glycine (each of ca. 1.5 g) were prepared with different compositions. Subsequently, the heat capacity and PXRD measurements were performed on these mixtures.

### Heat capacity measurements

Two different calorimeters were used in this study, namely TAM III microcalorimeter (TA Instruments) which was used to measure heat capacities of ternary organic and inorganic solid mixtures and Micro DSC III calorimeter (Setaram) which was used to measure heat capacities of polymorphic mixtures of  $\alpha$ - and  $\gamma$ -glycine. The polymorphic mixtures of glycine were found to be unstable. The presence of  $\gamma$ -glycine induces polymorph transformation from the metastable  $\alpha$ -glycine to the stable  $\gamma$ -glycine at room temperature [21]. The use of Micro DSC calorimeter is hence more suitable for investigating this system since it provides faster heat capacity measurements as compared with the TAM III microcalorimeter.

For the ternary organic and inorganic mixtures, the heat capacity measurements were performed in stainless steel gas tight ampoules (model 3320-1, with threaded caps and approximate sample volume of 4.5  $\text{cm}^3$ ) using a multi-channel heat flow TAM III microcalorimeter. A total of 12 microcalorimeters (model 3206) is available in the present instrument for simultaneous measurements of 12 different samples. The heat capacity measurements were carried out using a step-scan temperature increase from 297.65 to 298.65 K with a slow scanning rate of 0.083  $\text{K h}^{-1}$ . The slow scanning rate was used to minimize thermal gradients occurring in the samples. The baselines were taken 1800 s before and after the temperature scan. A typical minimum sample mass was 1 g. The differential heat flow between

the sample and the factory-installed reference was monitored and recorded by the TAM Assistant<sup>®</sup> software.

For the polymorphic mixtures of glycine, the heat capacity measurements were performed in a Hastelloy gas tight ampoule (volume of approximately 1 cm<sup>3</sup>) using a Micro DSC III calorimeter. The heat capacity measurements were performed using a step-scan temperature increase from 295.65 to 300.65 K with heating rate of 0.2 K min<sup>-1</sup>. The baselines were taken 2000 s before and after the temperature scan. A typical sample mass used was about 0.5 g. The heat capacity measurements of the polymorphic mixtures were completed within 2–3 h after the mixtures were prepared. Within this period of time, no substantial change of compositions due to polymorph transformation was found in these sample mixtures as verified by PXRD measurements. Detailed quantitative PXRD analysis on sample mixtures before and after heat capacity measurements are provided in the electronic supplementary material.

All heat capacity determinations required three separate heat flow measurements for (1) the blank ampoule, (2) the calibration standard (sapphire, SRM720), and (3) the sample [22, 23]. These three heat flow measurements were performed using identical instrument settings, i.e., the same step-scan temperature profiles.

#### PXRD measurements

Before the organic mixtures were prepared, each of the pure sample components was first ball milled for 15 min at 20 Hz in a Retsch MM200 mixer mill (Retsch GmbH, 42781 Haan, Germany) using a 25 cm<sup>3</sup> stainless steel beaker with a steel ball of 10 mm diameter to improve particle statistics and reduce preferred orientation. Prior to PXRD measurements, the mixtures were manually homogenized in an agate mortar. The diamond (used as an external standard) and the organic mixtures were measured with identical instrument setting.

For the inorganic mixtures, the samples were first intimately mixed by 5 min wet milling under acetone using a Retsch MM200 mixer mill (Retsch GmbH, 42781 Haan, Germany) in a 25 cm<sup>3</sup> stainless steel beaker and with a steel ball of 10 mm diameter. The inorganic samples were subsequently ground to micron size with a micronizing mill (McCrone Microscopes & Accessories, Westmont, IL 60559-5539, USA) using ethanol as a lubricant with a milling time of 10 min. The particle sizes were confirmed by a Mastersizer 2000 particle size analyzer (Malvern Instruments Ltd, Worcestershire WR14 1XZ, U.K.).

For the polymorphic mixture, both pure  $\alpha$ - and  $\gamma$ -glycine were first ball milled for 5 min at 20 Hz in a Retsch MM400 mixer mill (Retsch GmbH, 42781 Haan, Germany) using a 25 cm<sup>3</sup> stainless steel beaker with a steel ball of 10 mm diameter in order to improve particle statistics and

reduce preferred orientation. Prior to PXRD measurements, the weighed in mixtures were homogenized in a Retsch MM400 mixer mill without a steel ball to avoid inducing polymorph transformation (from  $\alpha$ - to  $\gamma$ -form) due to grinding. The diamond (used as an external standard) and the organic mixtures were measured with the same instrument setting.

All samples were loaded into top loading sample holders with a mold depth of 1 mm and a width of 25 mm. The powder diffractograms were recorded in Bragg–Brentano geometry on a Bruker D8 Advance (Bruker AXS GmbH, Karlsruhe, Germany) equipped with a Cu K $\alpha$  source and a Bruker Vantec-1 position sensitive microgap detector. Sample spinning was used to improve measurement statistics. The data were collected over an angle range of 5°–135° with a step width of 0.0167° at a scanning speed of 5°/min. For further details concerning the PXRD experiments please see [24, 25].

#### Numerical section

##### Rietveld refinement and quantitative PXRD analysis

The first step of all quantitative phase analyses was quantitative Rietveld refinement using Topas V4.2 (Bruker AXS GmbH, 2009). Details of the quantitative Rietveld analyses have been reported elsewhere [24, 25].

For all mixtures, the Rietveld results showed systematic deviations from the weighed in compositions. This bias was primarily attributed to the presence of ‘amorphous’ (non-diffracting) phases in the organic case and to micro-absorption in the inorganic case. For each of these two cases, further corrections were necessarily employed to provide more reliable composition estimates.

In the organic mixture case, an external standard approach was employed to bring the crystalline intensities onto an absolute scale and thereby obtain the total non-diffracting content. The variations of the ‘amorphous’ (non-diffracting) contents among the components were evaluated to obtain a more accurate phase analysis. For further details see [24]. The quantitative results of the organic mixtures have been previously analyzed and the results (Method C in Ref. [24]) were used directly in this study.

In the inorganic mixture case, a multi-component calibration approach (MCCA) was employed to remove the systematic bias which was not accounted for in the conventional Rietveld analysis. In this regard, two of the six mixtures were arbitrarily chosen as calibration samples to determine the calibration parameters. These parameters were used to predict the compositions of the remaining mixtures. The details of MCCA have been published

elsewhere [25]. The quantitative results of the inorganic mixtures as previously reported [25] were used directly in this study.

In the study of polymorphic mixture of glycine, the same external standard approach used for analyzing the organic mixtures [24] was employed. The quantitative analysis was carried out in the present work using Method C. This method does not require the availability of pure constituents to perform quantitative PXRD analysis.

#### Determination of specific heat capacities

The specific heat capacity of the sample  $c_{p,x}$  was evaluated using Eq. 1, where  $m$  is the mass,  $c_p$  is the specific heat capacity, and  $A$  is the integrated value of the heat flow signal minus the integrated value of the heat flow signal of the blank ampoule. Subscripts  $x$  and  $std$  refer to the sample and the standard, respectively. In this work, synthetic sapphire (SRM720, with mass ca. 2 and 1 g used in TAM and Micro DSC calorimeter, respectively) is used as a calibration standard ( $c_{p,std} = 0.7749 \text{ J K}^{-1} \text{ g}^{-1}$ ) [26]. In the following results, only the evaluated specific heat capacities are reported.

$$c_{p,x} = \frac{m_{std}A_x c_{p,std}}{m_x A_{std}} \quad (1)$$

In order to assess the accuracy of the specific heat capacity measurements performed in this study, the synthetic sapphire was measured exactly the same way as the samples. The heat capacity measurements of sapphire at 298.15 K obtained using TAM and Micro DSC calorimeter are  $0.7743 \pm 0.006$  and  $0.7764 \pm 0.001 \text{ J K}^{-1} \text{ g}^{-1}$ , respectively. These values differ ca. 0.1 and 0.2% as compared with its corresponding literature value ( $c_p = 0.7749 \text{ J K}^{-1} \text{ g}^{-1}$ ).

#### Determination of individual specific heat capacities in mixtures

The individual specific heat capacity  $c_{p,i}$  can be estimated from the heat capacity of the mixture  $c_{p,m}$  and from the mass fraction  $w_i$  of each component- $i$  by employing the Neumann–Kopp additive rule as shown in Eq. 2.

$$c_{p,m} = \sum_i c_{p,i} w_i \quad (2)$$

A multivariate regression can be performed to determine the individual specific heat capacities using mass fraction information. Such mass fraction information can be obtained either from the sample mass preparation or from the quantitative PXRD analysis (see “Rietveld refinement and quantitative PXRD analysis” section). Both approaches are carried out and compared in this study.

## Results

### Specific heat capacities of pure solids

Although the heat capacities of the pure solids are not used in any way for the analysis of the mixtures, these heat capacities are useful to evaluate the accuracy of the results obtained using the present methodology. The heat capacity measurements of the pure constituents and solid mixtures were always carried out using the same calorimeter. Accordingly, the specific heat capacities at 298.15 K of the pure organic solid compounds, namely  $\alpha$ -glycine,  $\alpha$ -lactose monohydrate, paracetamol (I), and the pure inorganic solid compounds, namely  $\text{CaF}_2$ , TiN, and WC were measured using TAM microcalorimeter and the specific heat capacities of  $\alpha$ - and  $\gamma$ -glycine were measured using Micro DSC calorimeter. The corresponding specific heat capacities were evaluated using Eq. 1 and the results are summarized in Table 1.

In general, these specific heat capacity values are shown to be in good agreement with the literature values. A slight discrepancy is observed between the specific heat capacities of paracetamol (I). The specific heat value of paracetamol (I) obtained in this study is in better agreement with the value reported by Boldyreva et al. [31] than the value reported by Xu et al. [30].

The measurements of pure  $\alpha$ - and  $\gamma$ -glycine were carried out in both types of calorimeters. The specific heat

**Table 1** The specific heat capacities of pure organic and inorganic solids at 298.15 K

Compound	$c_p/\text{J g}^{-1} \text{K}^{-1}$		Literature values
	This study <sup>a</sup>		
	TAM III	$\mu$ -DSC III	
$\alpha$ -Glycine	$1.303 \pm 0.017$	$1.328 \pm 0.001$	1.3218 <sup>b</sup>
$\gamma$ -Glycine	$1.256 \pm 0.011$	$1.287 \pm 0.003$	1.2788 <sup>b</sup>
$\alpha$ -Lactose monohydrate	$1.222 \pm 0.019$		1.2095 <sup>c</sup> , 1.2242 <sup>d</sup>
Paracetamol (I)	$1.216 \pm 0.035$		1.1475 <sup>e</sup> , 1.2548 <sup>f</sup>
Calcium fluoride ( $\text{CaF}_2$ )	$0.882 \pm 0.003$		0.8790 <sup>g</sup>
Titanium nitride (TiN)	$0.607 \pm 0.009$		0.6015 <sup>g</sup>
Tungsten carbide (WC)	$0.180 \pm 0.004$		0.1808 <sup>h</sup>

<sup>a</sup> The specific heat capacity values are the average values from three or four measurements with sample masses about 1 g and above

<sup>b</sup> With adiabatic calorimetry Ref. [27], <sup>c</sup> Ref. [28], <sup>d</sup> Ref. [29], <sup>e</sup> Ref. [30], <sup>f</sup> Ref. [31], <sup>g</sup> Ref. [32], <sup>h</sup> Ref. [33]

**Table 2** The specific heat capacities of bulk ternary organic solid mixtures at 298.15 K together with their compositions determined from sample mass preparation and from quantitative PXRD analysis

Mixt	Mass/% <sup>a</sup>			Mass from PXRD/% <sup>b</sup>			$c_{p,m}/\text{J g}^{-1} \text{K}^{-1c}$
	Gly	Lac	Para	Gly	Lac	Para	
1	18.04	45.56	36.40	18.1 ± 0.1	45.8 ± 0.5	36.1 ± 0.3	1.2042
2	33.33	33.32	33.35	33.4 ± 0.2	33.6 ± 0.4	32.9 ± 0.2	1.2079
3	62.35	25.21	12.44	62.7 ± 0.4	25.2 ± 0.3	12.1 ± 0.1	1.2581
4	16.75	66.55	16.70	15.9 ± 0.1	67.8 ± 0.8	16.3 ± 0.1	1.1971
5	35.76	28.51	35.73	35.9 ± 0.2	28.7 ± 0.3	35.4 ± 0.3	1.2314
6	36.36	45.61	18.03	36.3 ± 0.2	45.8 ± 0.5	17.9 ± 0.2	1.2512
7	33.30	33.34	33.36	33.3 ± 0.2	33.6 ± 0.4	33.2 ± 0.2	1.2365
8	44.38	11.24	44.38	44.8 ± 0.3	11.1 ± 0.2	44.1 ± 0.3	1.2501
9	12.45	25.19	62.36	12.5 ± 0.1	25.3 ± 0.3	62.3 ± 0.5	1.2378
10	40.04	20.03	39.93	40.3 ± 0.3	20.1 ± 0.2	39.6 ± 0.3	1.2273

$\alpha$ -glycine, gly;  $\alpha$ -lactose monohydrate, lac; paracetamol (I), para

<sup>a</sup> Determined from sample mass preparation

<sup>b</sup> Determined from quantitative PXRD analysis (see Table 5 in Ref. [24])

<sup>c</sup> Uncertainty of the measured specific heat capacity of the mixtures is ca. 1.1% (calculated from propagation error analysis)

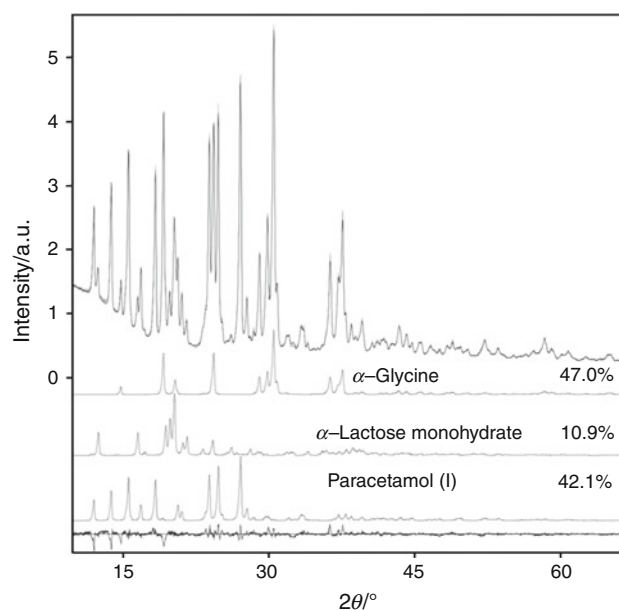
capacities of  $\alpha$ - and  $\gamma$ -glycine obtained using TAM III microcalorimeter are slightly lower (ca. 2%) than those obtained using Micro DSC calorimeter. The latter specific heat capacity values are in better agreement with the values previously reported by Drebushchak et al. [27].

#### Analysis of organic solid mixtures

A total of ten organic solid mixtures were prepared by mass according to the experimental design (see Table 2). A typical Rietveld refinement plot of a diffractogram of an organic mixture is shown in Fig. 1. This diffractogram confirms the identity of the three organic compounds, namely  $\alpha$ -glycine,  $\alpha$ -lactose monohydrate, and paracetamol (I) present in the mixture.

Subsequently, the quantitative PXRD analysis using the external standard approach as detailed in [24] was used to provide quantitative information for the mixtures. The corresponding mass fractions obtained from the PXRD measurements are provided with their uncertainties in Table 2.

The specific heat capacities of the mixtures were measured and evaluated using Eq. 1. The results are summarized in Table 2. The specific heat capacities of individual organic solid- $i$ ,  $c_{p,i}$  were subsequently evaluated from the specific heat capacity of mixtures  $c_{p,m}$  using Eq. 2. Multivariate regressions were performed using (i) the mass fractions from the sample preparation and (ii) the mass fractions from the quantitative PXRD analysis [24]. The calculated specific heat capacities of the individual solids are reported in Table 3 and subsequently compared with



**Fig. 1** Comparison of experimental and calculated diffractograms for organic case. *Top*: overlay of observed (gray) and calculated (Rietveld, black) pattern of one organic mixture, *middle*: calculated diffraction patterns of individual crystalline components, *bottom*: residual plot of observed and calculated mixture patterns. *Note*: the compositions found by the Rietveld methods were used as input for the external standard approach

those determined previously for the corresponding pure solids.

In Table 3, the specific heat capacities of the individual solids determined from the multi-component organic solid mixtures (using methods (i) and (ii)) are compared with those measured for the corresponding pure solids. The



**Table 3** The specific heat capacities of  $\alpha$ -glycine,  $\alpha$ -lactose monohydrate, and paracetamol (I) at 298.15 K derived from multi-component (MC) solid mixtures

Compounds	$c_p/J \text{ g}^{-1} \text{ K}^{-1a}$		
	Pure	MC (i) <sup>b</sup>	MC (ii) <sup>c</sup>
$\alpha$ -Glycine	1.303 $\pm$ 0.017	1.291 $\pm$ 0.025 (−0.9%)	1.290 $\pm$ 0.025 (−1.0%)
$\alpha$ -Lactose monohydrate	1.222 $\pm$ 0.019	1.175 $\pm$ 0.023 (−3.9%)	1.176 $\pm$ 0.023 (−3.8%)
Paracetamol (I)	1.216 $\pm$ 0.035	1.225 $\pm$ 0.025 (0.7%)	1.225 $\pm$ 0.025 (0.7%)

<sup>a</sup> Percentage relative error to the specific heat capacity of pure solid is given in the parenthesis

<sup>b</sup> Compositions determined from sample mass preparation

<sup>c</sup> Compositions determined from quantitative PXRD analysis

**Table 4** The specific heat capacities of ternary inorganic solid mixtures of  $\text{CaF}_2$ , TiN, and WC at 298.15 K together with their compositions determined from sample mass preparation and from quantitative PXRD analysis

Mixt	Mass/% <sup>a</sup>			Mass from PXRD/% <sup>b</sup>			$c_{p,m}/J \text{ g}^{-1} \text{ K}^{-1c}$
	$\text{CaF}_2$	TiN	WC	$\text{CaF}_2$	TiN	WC	
1	33.36	33.32	33.32	–	–	–	0.5449
2	62.45	25.01	12.54	–	–	–	0.7090
3	16.56	66.66	16.78	16.8 $\pm$ 0.3	66.8 $\pm$ 1.5	16.4 $\pm$ 0.4	0.5681
4	35.71	28.61	35.68	35.0 $\pm$ 0.4	29.5 $\pm$ 0.7	35.5 $\pm$ 0.7	0.5465
5	12.52	25.04	62.43	12.2 $\pm$ 0.2	25.6 $\pm$ 0.6	62.2 $\pm$ 1.3	0.3685
6	39.90	20.16	39.94	37.0 $\pm$ 0.4	21.4 $\pm$ 0.5	41.6 $\pm$ 0.8	0.5280

<sup>a</sup> Determined from sample mass preparation

<sup>b</sup> Determined from quantitative PXRD analysis (see Table 3 in Ref. [25])

<sup>c</sup> Uncertainty of the measured specific heat capacity of mixtures is ca. 1.1% (calculated from propagation error analysis)

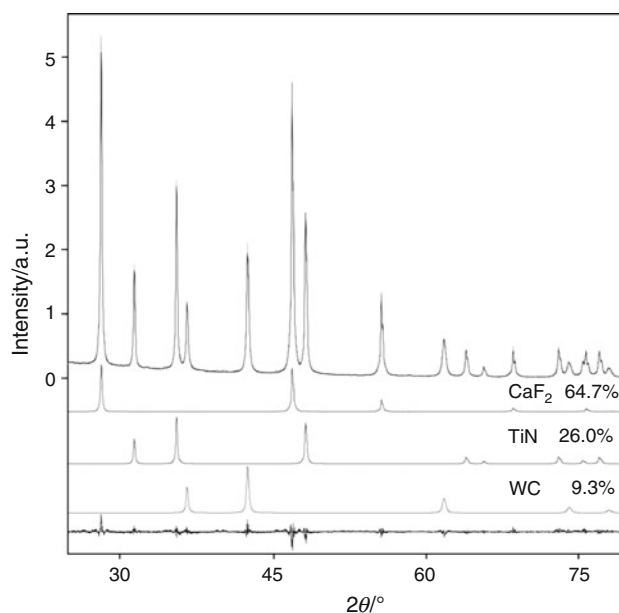
results indicate that specific heat capacity of each individual organic solid can be obtained from multi-component mixtures within an average error of ca. 2%.

#### Analysis of inorganic solid mixtures

A total of six ternary inorganic solid mixtures were prepared by mass according to the experimental design (Table 4). A typical Rietveld refinement plot of a diffractogram of an inorganic mixture is shown in Fig. 2. This diffractogram confirms the identity of the three inorganic compounds, namely calcium fluoride, titanium nitride, and tungsten carbide present in the mixture.

Subsequently, the quantitative PXRD analysis using the MCCA was used to provide quantitative information for the mixtures. The corresponding mass fraction values are provided with their uncertainties in Table 4.

It is important to note that the inorganic mixture analysis differed considerably from the organic mixture analysis. In the inorganic case, Mixtures 1 and 2 were analyzed to obtain the calibration parameters. The determined calibration parameters were subsequently used to provide quantitative predictions for the remaining mixtures (Mixtures 3–6). Detailed quantitative procedures can be found elsewhere [25].



**Fig. 2** Comparison of experimental and calculated diffractograms for inorganic case. *Top*: overlay of observed (gray) and calculated (Rietveld, black) pattern of one inorganic mixture, *middle*: calculated diffraction patterns of individual crystalline components, *bottom*: residual plot of observed and calculated mixture patterns. *Note*: the compositions found by the Rietveld methods were used as input for the MCCA

**Table 5** The specific heat capacities of CaF<sub>2</sub>, TiN, and WC at 298.15 K derived from multi-component (MC) solid mixtures

Compounds	$c_p/J\ g^{-1}\ K^{-1a}$		
	Pure solid <sup>b</sup>	MC (i) <sup>b</sup>	MC (ii) <sup>c</sup>
CaF <sub>2</sub>	0.882 ± 0.003	0.860 ± 0.008 (−2.5%)	0.889 ± 0.001 (0.8%)
TiN	0.607 ± 0.009	0.596 ± 0.009 (−1.8%)	0.583 ± 0.001 (−4.0%)
WC	0.180 ± 0.004	0.178 ± 0.008 (−1.5%)	0.178 ± 0.001 (−1.3%)

<sup>a</sup> Percentage relative error to the specific heat capacity of pure solid is given in the parenthesis

<sup>b</sup> Compositions determined from sample mass preparation

<sup>c</sup> Compositions determined from quantitative PXRD analysis

**Table 6** The specific heat capacities of bulk polymorphic mixtures ( $\alpha$ - and  $\gamma$ -glycine) at 298.15 K together with their compositions determined from sample mass preparation and from quantitative PXRD analysis

Mixt	Mass/% <sup>a</sup>		Mass from PXRD/% <sup>b</sup>		$c_{p,m}/J\ g^{-1}\ K^{-1c}$
	$\alpha$ -gly	$\gamma$ -gly	$\alpha$ -gly	$\gamma$ -gly	
1	10.07	89.93	9.3 ± 0.1	90.7 ± 0.3	1.2897
2	16.59	83.41	15.7 ± 0.1	84.3 ± 0.3	1.2931
3	34.49	65.51	33.8 ± 0.2	66.2 ± 0.2	1.2989
4	49.96	50.04	50.3 ± 0.2	49.7 ± 0.2	1.3078
5	66.65	33.35	65.7 ± 0.3	34.3 ± 0.2	1.3120
6	83.36	16.64	83.0 ± 0.4	17.0 ± 0.2	1.3191

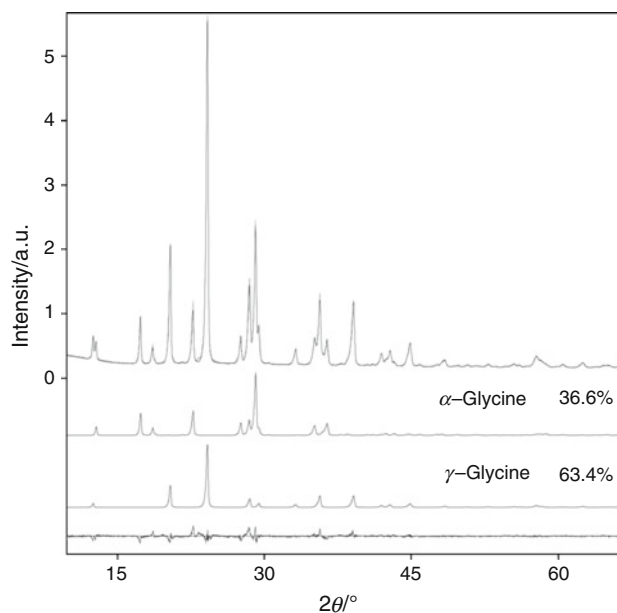
<sup>a</sup> Determined from sample mass preparation

<sup>b</sup> Determined from quantitative PXRD analysis (this study)

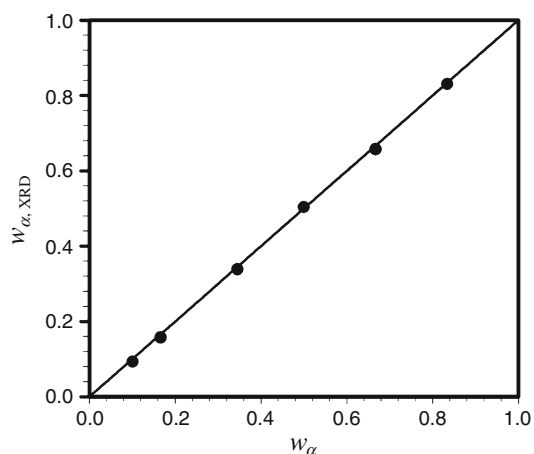
<sup>c</sup> Uncertainty of the measured specific heat capacity of the mixtures is ca. 0.4% (calculated from propagation error analysis)

The specific heat capacities of the mixtures were measured and evaluated using Eq. 1. The results are summarized in Table 4. The specific heat capacities of individual inorganic solid- $i$ ,  $c_{p,i}$  were derived from the specific heat capacity of mixtures  $c_{p,m}$  using Eq. 2. Multivariate regressions were performed using two different solid mass fraction compositions obtained (i) from the sample mass preparation (using all six mixtures) and (ii) from the quantitative PXRD analysis (using only four mixtures). The determined specific heat capacities of individual solids are reported in Table 5 and compared with those previously determined using pure solids.

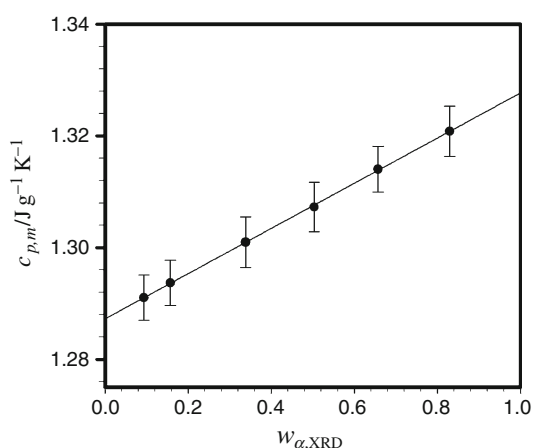
It can be seen from Table 5 that the specific heat capacities of individual solids determined from the multi-component inorganic solid mixtures are consistent with those measured from the corresponding pure solids. This is true for both methods of evaluating the specific heat capacities, namely (i) using the known mass fractions obtained from the sample preparations as well as (ii) using the mass fractions obtained from quantitative PXRD analysis. The results indicate that the specific heat capacity of each individual inorganic solid can be obtained from multi-component inorganic mixtures with an average error of ca. 2%.



**Fig. 3** Comparison of experimental and calculated diffractograms for polymorphic case. *Top*: overlay of observed (*gray*) and calculated (Rietveld, *black*) pattern of one polymorphic mixture, *middle*: calculated diffraction patterns of individual crystalline components, *bottom*: residual plot of observed and calculated mixture patterns. *Note*: the compositions found by the Rietveld methods were used as input for the external standard approach



**Fig. 4** Comparison of the weighed in and the calculated weight percentages from PXRD measurements for the polymorphic mixtures of glycine. The PXRD compositions were obtained using external standard approach (Method C, see Ref. [24])



**Fig. 5** Specific heat capacities of polymorphic mixtures  $\alpha$ - and  $\gamma$ -glycine at 298.15 K versus mass fraction of  $\alpha$ -glycine (determined from PXRD analysis)

#### Analysis of polymorphic mixtures of glycine

The combined PXRD and calorimetry method is further applied to analyze the individual heat capacity of  $\alpha$ - and  $\gamma$ -glycine from their polymorphic mixtures. A total of six

polymorphic mixtures were prepared by mass according to the experimental design (see Table 6). The freshly prepared mixtures were subsequently analyzed by PXRD. A typical Rietveld refinement plot of a diffractogram of a polymorphic mixture is shown in Fig. 3. This diffractogram confirms the identity of only two organic compounds, namely  $\alpha$ - and  $\gamma$ -glycine in the mixture.

Subsequently, the quantitative PXRD analysis using the external standard approach (Method C) as detailed in [24] was applied to provide quantitative information on these mixtures. The corresponding mass fractions obtained from the PXRD measurements are provided with their uncertainties in Table 6. The results from quantitative PXRD analyses are quite accurate and they are compared with the mass fractions (from sample preparation) in Fig. 4.

The specific heat capacities of the mixtures were subsequently measured using Micro DSC calorimeter and completed within 2–3 h after the fresh mixtures were prepared. A faster characterization was necessary since polymorph transformation could occur in these mixtures [21]. The measured heat capacities of these mixtures are summarized in Table 6 and are plotted versus the mass fraction of  $\alpha$ -glycine in Fig. 5. The specific heat capacity of polymorph glycine mixture increases with the increase of  $\alpha$ -glycine content.

The specific heat capacities of individual polymorph-*i*,  $c_{p,i}$  were subsequently evaluated from the specific heat capacity of mixtures  $c_{p,m}$  using Eq. 2. Multivariate regressions were performed using (i) the mass fractions from the sample preparation and (ii) the mass fractions from the quantitative PXRD analysis. The calculated specific heat capacities of the individual solids are reported in Table 7 and subsequently compared with those determined previously for the corresponding pure polymorphs.

It can be seen from Table 7 that the specific heat capacities of the individual solids determined from the polymorphic mixtures (using methods (i) and (ii)) are consistent with those measured for the corresponding pure constituents. The results show that specific heat capacity of each individual polymorph can be accurately determined from polymorphic mixtures within an average error of ca. 0.2%.

**Table 7** The specific heat capacities of  $\alpha$ - and  $\gamma$ -glycine at 298.15 K derived from multi-component (MC) polymorphic mixtures

Compounds	$c_p / \text{J g}^{-1} \text{K}^{-1a}$		
	Pure	MC (i) <sup>b</sup>	MC (ii) <sup>c</sup>
$\alpha$ -Glycine	$1.328 \pm 0.001$	$1.326 \pm 0.001$ (0.12%)	$1.326 \pm 0.001$ (0.12%)
$\gamma$ -Glycine	$1.287 \pm 0.003$	$1.286 \pm 0.001$ (0.06%)	$1.286 \pm 0.001$ (0.04%)

<sup>a</sup> Percentage relative error to the specific heat capacity of pure constituent is given in the parenthesis

<sup>b</sup> Compositions determined from sample mass preparation

<sup>c</sup> Compositions determined from quantitative PXRD analysis



## Discussion

In the present contribution, the individual heat capacities of the constituents were obtained from the bulk measurements of mixtures alone. The bulk PXRD measurements were combined with the bulk heat capacity measurements to analyze the mixtures. The PXRD measurements were used (1) to confirm the number and identity of the constituents and (2) to provide reliable quantitative estimates of the mass fraction of each constituent. The accuracy of these quantitative analyses was significantly improved by combining the Rietveld refinement with the external standard approach [24] or the MCCA [25]. Thereafter, the specific heat capacities of each constituent could be determined using multivariate regression of Eq. 2.

In the case of the organic mixtures, the samples with unknown compositions can be analyzed using the external standard approach and the individual specific heat capacities can be determined directly from the multi-component mixtures. Meanwhile, there are some limitations in the utility of the combined PXRD and calorimetry techniques to analyze the present inorganic mixtures. In the inorganic case, the mixtures exhibited absorption contrast and the MCCA method was employed using some forms of calibration mixtures to provide reliable quantitative information. Calibration mixtures (with known compositions) were required to obtain calibration parameters which were subsequently utilized to correct the systematic bias in the remaining samples. Alternatively, other analytical techniques (i.e., X-ray fluorescence (XRF)) can be employed to provide composition estimates on the calibration mixtures [25].

With respect to the specific heat capacity results obtained from the organic (Table 3), inorganic (Table 5) as well as polymorphic mixtures (Table 7), relatively accurate specific heat capacities can be obtained (with average error of ca. 2% for the ternary organic and inorganic mixtures and average error of ca. 0.2% for the binary polymorphic mixture). These accuracies are considered acceptable since the specific heat capacity uncertainties for the pure constituents are within the same order (i.e., on the order of 1–2% measured with TAM III calorimeter and of ca. 0.5–1% measured with Micro DSC calorimeter).

The present results also support the validity of the simple Neumann–Kopp additive rule. The rule appears to be reliable for obtaining the specific heat capacities of individual components from the bulk solid mixtures. Interactions between components in the present solid mixtures (both ternary organic and inorganic mixtures as well as binary polymorphic mixture), if any, are not significant as clearly indicated by the good fit ( $R^2 = 0.9999$  for all analysis) in the least squares analyses.

## Conclusions

The present study demonstrates a method to determine the individual heat capacities of each constituent in solid mixtures including polymorphic mixture from bulk X-ray diffraction and bulk calorimetry measurements. This method was successfully applied to investigate ternary organic and inorganic mixtures as well as a binary polymorphic mixture of  $\alpha$ - and  $\gamma$ -glycine. The results show that the specific heat capacity of each component can be determined from their corresponding solid mixtures with average errors of ca. 2% for both the organic system and the inorganic system and with average errors of ca. 0.2% for the binary polymorphic mixture of glycine.

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