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# Direct Thermodynamic Characterization of Solid-state Reactions by Isothermal Calorimetry

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## 1. Characterization of reactants used for solid-state reactions

## 1.1 Aggregate size analysis

Microscopic image analysis was performed in transmission mode on Olympus SZX16 stereomicroscope equipped with CCD camera with 2K resolution (2048x1080 px). The sample was dispersed on a glass sampling plate and imaged at 7 different positions. The distance was calibrated using an internal standard. Particle information was extracted from images by utilizing the CV2 contour finding algorithm<sup>[1]</sup>. Particle size and weighted statistics were determined for all recognized particles.



(a)











**Figure S1.** Microscopic image of a sample of: a) 18-crown[6] ether, b) KHSO<sub>4</sub>, c) benzophenone, d) diphenylamine, e) *m*-chloroperoxybenzoic acid, f) 4-*tert*-butylcyclohexanone.

Sample	<i>d</i> <sub>10</sub> /μm	<i>d</i> ₅₀/µm	<i>d</i> ₀₀/μm
18-crown[6] ether	18	277	557
KHSO4	18	78	444
benzophenone	40	61	286
diphenylamine	31	174	615
<i>m</i> -chloroperoxybenzoic acid	33	158	360
4-tert-butylcyclohexanone	23	45	117

**Table S1.** Microscopic quantitative particle size analysis of reactants used for solid-state reactions.

## 2.2 Crystal domain size analysis

**Table S2.** Crystal domain size analysis by Rietveld refinement of powder diffraction data for reactants used for solid-state reactions.

Sample	Coherent crystal domain size / nm <sup>[2]</sup>
18-crown[6] ether	>1000
KHSO <sub>4</sub>	229(13)
benzophenone	303(54)
diphenylamine	75(3)
m-chloroperoxybenzoic acid	79(4)
4-tert-butylcyclohexanone	167(2)

Crystal domain size analysis by Rietveld refinement of powder diffraction data revealed that all of the samples used as reactants in calorimetric studies have well-defined crystal domains, *i.e.* there is no significant line profile broadening due to presence of nanoparticles or nanodomains. In other words, no influence of the particle size on the value of the reaction enthalpy is expected for the solid-state processes investigated in this work because the particle-dimesions of reactants were well beyond 10 nm.<sup>[3]</sup>







(b)







(d)



**Figure S2.** Rietveld refinement of powder diffraction data used for crystal domain size analysis of the following samples: a) 18-crown[6] ether, b) KHSO<sub>4</sub>, c) benzophenone, d) diphenylamine, e) *m*-chloroperoxybenzoic acid, f) 4-*tert*-butylcyclohexanone.

2. Evaluation of the heat effects related to membrane piercing/falling of a reactant and stirring



**Figure S3.** Thermogram for the piercing of membrane with a) KHSO<sub>4</sub> (40.59 mg), b) 4-*tert*butylcyclohexanone (24.99 mg), and c) diphenylamine (49.97 mg), performed in Setaram Calvet calorimeter. Total heat amounts to a) –8.7 mJ, b) 5.2 mJ, and c) –0.5 mJ, which corresponds to  $\leq 0.1 \%$ of a typical reaction or dissolution signal and has negligible effect on the measured results. Mixing has no heat effect but only slightly lifts up heatflow-baseline.



**Figure S4.** Thermogram for mixing of BZP (50 mg) with BZP (15 mg) fallen from the membrane in Setaram Calvet calorimeter. Heats obtained by tangential sigmoidal integration algorithm in the range of a) 30 min and b) 60 min, covering the duration of the investigated solid-state reactions, amounts to -27 mJ and -89 mJ, which corresponds to < 2% of a typically measured reaction heat effect.



**Figure S5.** Thermogram for mixing of BZP (50 mg) with NaCl (30 mg) fallen from the membrane in Setaram Calvet calorimeter. Heats obtained by tangential sigmoidal integration algorithm in the range of a) 30 min and b) 120 min, covering or exceeding the duration of the investigated solid-state reactions, amounts to -48 mJ and -83 mJ, which corresponds to < 2 % of a typically measured reaction heat effect.

#### 3. Quantitative analysis of limit of detection in PXRD

Detection of a crystalline phase by powder diffraction is a well-established method.<sup>[4]</sup> Limit of detection for a particular mixture of phases is a complicated function of, among other, instrument source and optical setup, detector performance, crystal structures, macroscopic phase properties and counting time. Thus, it is infeasible to determine limit of detection for all the phase mixtures used in this study, particularly because the phase composition is not static (i.e. reactions occur in the solid mixture).

Powder diffraction setup used in this study has a limit-of-detection for crystalline phase of 2-5% based on peak observation in a set of solid mixtures of benzoic acid and sucrose. This mixture was used as both components have absorption coefficients and densities similar to ones used in this work. Moreover, benzoic acid and sucrose do not form any (known) multicomponent systems.



**Figure S6.** Rietveld powder diffraction patterns for a set of mixtures of sucrose and benzoic acid (0.1, 0.2, 0.5, 1.0, 2.0, 5.0 and 10.0% w/w). Peak of benzoic acid is marked with a black arrow. a) Complete recorded range of  $2\vartheta$ . b) Magnification of the  $2\vartheta$ -range of interest.

#### 4. Host-guest chemistry - Potassium complexation by 18-crown[6] ether

#### 4.1. Solid-state reaction of 18-crown[6]ether with KHSO<sub>4</sub>

**Table S3.** Conditions and calculated reaction enthalpies for the complexation of potassium ion (KHSO<sub>4</sub>) with 18-crown-6 ether (**18C6E**). Experiments were performed in Setaram Calvet calorimeter at 25 °C with the addition of small amount of water into **18C6E**.

Exp. No.	<i>n</i> (KHSO₄) / mmol	n( <b>18C6E</b> ) / n(KHSO <sub>4</sub> )	<i>V</i> (H <sub>2</sub> O) / μL	$\Delta_r H^\circ$ / kJ mol <sup>-1</sup>
1	0.282	2.0	10	-14.0
2	0.283	2.8	10	-14.5
3	0.169	3.5	7.5	-15.0
Average ± SEM				-14.5 ± 0.3



**Figure S7.** PXRD patterns of: KHSO<sub>4</sub>, 18-crown-6 ether (**18C6E**), complex of KHSO<sub>4</sub> with **18C6E** (anhydrous and dihydrate), product obtained by mill-grinding of **18C6E** with KHSO<sub>4</sub> in 1:1 stoichiometric ratio, and product mixture from the solid-state reaction of KHSO<sub>4</sub> (0.586 mmol) with **18C6E** (2.051 mmol) in calorimeter with the addition of small amount of water (7.5  $\mu$ L) at 25 °C. The product mixture contains (**18C6E**K)HSO<sub>4</sub>×2H<sub>2</sub>O and excess **18C6E**.



**Figure S8.** Thermogram for the dissolution of 18-crown-6 ether (17.411 mg) in water (17 mL) performed in TAM IV calorimeter at 25 °C.

**Table S4.** Conditions and calculated reaction enthalpies for the dissolution of 18-crown-6 ether in water (17 mL for TAM IV and 1.5 mL for Setaram Calvet calormeter). Experiments were performed in TAM IV (1 and 2) and in Setaram Calvet (3) calorimeter at 25 °C.

Exp. No.	<i>m</i> / mg	10 <sup>3</sup> <i>c</i> / mol dm <sup>-3</sup>	∆ <sub>r</sub> H° / kJ mol <sup>−1</sup>
1	17.411	3.88	-25.5
2	9.565	6.01	-24.2
3	11.020	27.82	-24.3
Average ± SEM			$-24.7 \pm 0.4$

## 4.3. Dissolution of KHSO<sub>4</sub> in water



**Figure S9.** Thermogram for the dissolution of KHSO<sub>4</sub> (21.510 mg) in water (1.5 mL) performed in Setaram Calvet calorimeter at 25  $^{\circ}$ C.

Table S5. Conditions and calculated reaction enthalpies for the dissolution of KHSO <sub>4</sub> in water (1	L.5 mL).
Experiments were performed in Setaram Calvet calorimeter at 25 °C.	

Exp. No.	<i>m</i> / mg	$10^2 c / mol dm^{-3}$	$\Delta_r H^\circ$ / kJ mol <sup>-1</sup>
1	31.760	4.853	15.5
2	10.980	1.678	14.3
3	21.510	3.287	15.7
Average ± SEM			$15.2 \pm 0.4$



**Figure S10.** Thermogram of dissolution of (18C6EK)HSO<sub>4</sub>×2H<sub>2</sub>O (7.398 mg) in water (17 mL) performed in TAM IV calorimeter at 25 °C.

**Table S6.** Conditions and calculated reaction enthalpies for the dissolution of (**18C6E**K)HSO<sub>4</sub>×2H<sub>2</sub>O in water (17 mL for TAM IV and 1.5 mL for Setaram Calvet calormeter). Values of the reaction enthalpies are shown for real dissolution of the complex ( $\Delta_r H^{\circ}_1$ ), where part of the complex remains undissociated, and for theoretical dissolution of the complex ( $\Delta_r H^{\circ}_2$ ), where complete dissociation into ions is assumed.<sup>a</sup> Experiments were performed in TAM IV (1 and 2) and in Setaram Calvet (3) calorimeter at 25 °C.

Exp. No.	<i>m /</i> mg	$10^2 c / mol dm^{-3}$	$\Delta_r H^{\circ}_1 / kJ mol^{-1}$	$\Delta_r H^{\circ}_2 / kJ mol^{-1}$
1	7.398	0.100	4.35	6.9
2	16.792	2.263	3.59 <sup>b</sup>	8.1
3	37.710	5.762	-3.00	8.0
Average ± SEM				7.7 ± 0.4

<sup>a</sup> The value of the reaction enthalpy for dissolution of the complex with the complete dissociation of ions ( $\Delta_r H_2$ ) is required to obtain in order to use thermodynamic cycle presented in scheme S1 for the check of the value of the reaction enthalpy for the solid-state complexation of K<sup>+</sup> with crown-ether. The value of  $\Delta_r H^{\circ}_2$  was calculated using the following equation:

$$\Delta_{\mathrm{r}}H^{\circ}_{1} \cdot n_{1} = \Delta_{\mathrm{r}}H^{\circ}_{2} \cdot n_{1} + \Delta_{\mathrm{r}}H^{\circ}_{3} \cdot n_{3},$$

where  $\Delta_r H^{\circ}_1$  is the reaction enthalpy for the real dissolution of the complex,  $\Delta_r H^{\circ}_3$  is the reaction enthalpy for the formation of the complex (**18C6E**K)<sup>+</sup> in water,  $n_1$  is the quantity of the complex dissolved, and  $n_3$  is the quantity of the complex that stays in the form of complex after its dissolution (calculated via constant of complexation of K<sup>+</sup> with **18C6E** in water). The values for the latter complexation constant (log*K* = 2.14(2)) and for the  $\Delta_r H^{\circ}_3$  (-23.4(8) kJ mol<sup>-1</sup>) were found in the literature (see main article).

<sup>b</sup> Cumulative heat effect from the dissolution of two sequential portions of complex in water ( $m_1 = 7.398 \text{ mg}$ ,  $m_2 = 9.394 \text{ mg}$ ).

#### 4.5. Thermodynamic cycle related to a reaction of 18C6E and KHSO<sub>4</sub>



**Scheme S1.** Thermodynamic cycle used for determination of the reaction enthalpy of  $(18C6EK)HSO_4 \times 2H_2O$  formation in solid-state from 18C6E (in excess) and  $KHSO_4$  at 25 °C (blue). Uncertainties of the last digit are given in parentheses as standard error of the mean (N = 3). The reaction enthalpy determined by direct isothermal solid-state calorimetry is **bolded (black)**.

## 5. Molecular complexation – Reaction between benzophenone and diphenylamine

## 5.1. Formation of metastable liquid mixture of BZP and DPA (n(BZP)/n(DPA) = 1)

**Table S7.** Conditions and calculated reaction enthalpies for the formation of metastable liquid containing equimolar amount of BZP and DPA (n(BZP) / n(DPA) = 1). Experiments were performed in Setaram Calvet calorimeter at 25 °C.

Exp. No.	<i>n</i> (BZP) / mmol	∆ <sub>r</sub> H° / kJ mol <sup>−1</sup>
1	0.274	30.8
2	0.412	30.5
3	0.494	31.0
Average ± SEM		30.8 ± 0.1

**Table S8.** Conditions and calculated reaction enthalpies for the formation of BZP–DPA cocrystals performed in one step with crystal seed present in the calorimeter cell. Experiments were performed in Setaram Calvet calorimeter at 25 °C.

Exp. No.	<i>n</i> / mmol	∆ <sub>r</sub> H° / kJ mol <sup>−1</sup>
1	0.165	-1.1
2	0.165	-1.7
Average ± SEM		$-1.4 \pm 0.3$



**Figure S11.** PXRD patterns of: benzophenone, diphenylamine, cocrystal of benzophenone with diphenylamine, and the product mixture from the solid-state reaction of BZP with DPA in 1:1 molar ratio in calorimeter with BZP–DPA seed placed in the calorimetric cell. The product mixture contains BZP, DPA, and BZP–DPA cocrystals.

5.3. Crystallization of metastable liquid mixture of BZP and DPA (n(BZP)/n(DPA) = 1) forming BZP–DPA cocrystal

**Table S9.** Conditions and calculated reaction enthalpies for the crystallization of metastable liquid BZP– DPA (n(BZP) / n(DPA) = 1) forming BZP–DPA cocrystal. Experiments were performed in Setaram Calvet calorimeter at 25 °C.

Exp. No.	<i>n</i> / mmol	Δ <sub>r</sub> H° / kJ mol <sup>-1</sup>
1	0.159	-33.8
2	0.231	-34.4
3	0.314	-34.5
Average ± SEM		-34.2 ± 0.2



**Figure S12.** PXRD pattern of product of crystallization of metastable BZP–DPA liquid in calorimeter compared with PXRD pattern of BZP–DPA cocrystal at 25 °C.



**Figure S13.** Thermogram for the dissolution of BZP (5.632 mg) in acetonitrile (17 mL) performed in TAM IV calorimeter at 25  $^{\circ}$ C.

Exp. No.	<i>m</i> / mg	$\Delta_{\rm r} H^{\circ} / \rm kJ \ mol^{-1}$
1	5.632	21.1
2	6.491	22.0
3	9.637	21.8
Average ± SEM		21.6 ± 0.3

**Table S10.** Conditions and calculated reaction enthalpies for the dissolution of BZP in acetonitrile (17 mL). Experiments were performed in TAM IV calorimeter at 25 °C.

## 5.5. Dissolution of DPA in acetonitrile



**Figure S14.** Thermogram for the dissolution of DPA (7.896 mg) in acetonitrile (17 mL) performed in TAM IV calorimeter at 25 °C.

**Table S11.** Conditions and calculated reaction enthalpies for the dissolution of DPA in acetonitrile. Experiments were performed in TAM IV (1 and 2) and in Setaram Calvet calorimeter (3) at 25 °C.

Exp. No.	<i>m</i> / mg	V / mL	Δ <sub>r</sub> H° / kJ mol <sup>-1</sup>
1	8.312	17	17.3
2	7.896	17	18.8
3	40.21	1.5	17.4
Average ± SEM			17.8 ± 0.5



**Figure S15.** Thermogram for the dissolution of BZP–DPA cocrystals (36.09 mg) in acetonitrile (1.5 mL) performed in Setaram Calvet calorimeter at 25 °C.

Exp. No.	<i>m</i> / mg	$\Delta_r H^\circ$ / kJ mol <sup>-1</sup>
1	40.16	40.1
2	36.09	40.2
3	20.47	39.0
Average ± SEM		39.8 ± 0.4

**Table S12.** Conditions and calculated reaction enthalpies for the dissolution of BZP–DPA in acetonitrile (1.5 mL). Experiments were performed in Setaram Calvet calorimeter at 25 °C.

5.7. Dissolution of metastable liquid mixture of BZP and DPA (n(BZP) / n(DPA) = 1) in acetonitrile



**Figure S16.** Thermogram for the dissolution of metastable liquid mixture of BZP and DPA (n(BZP) / n(DPA) = 1, m = 21.973 mg) in acetonitrile (17 mL) performed in TAM IV calorimeter at 25 °C.

**Table S13.** Conditions and calculated reaction enthalpies for the dissolution of metastable liquid mixture of BZP and DPA (n(BZP) / n(DPA) = 1) in acetonitrile. Experiments were performed in TAM IV (1 and 2) and in Setaram Calvet calorimeter (3) at 25 °C.

Exp. No.	<i>m</i> / mg	V / mL	∆ <sub>r</sub> H° / kJ mol <sup>−1</sup>
1	21.973	17	6.36
2	19.465	17	7.67
3	46.75	1.5	9.15
Average ± SEM			7.7 ± 0.8



**Figure S17.** a) Microcalorimetric titration of benzophenone ( $c = 5.40 \times 10^{-4}$  mol dm<sup>-3</sup>, V = 1.43 ml) with diphenylamine ( $c = 2.895 \times 10^{-2}$  mol dm<sup>-3</sup>) in acetonitrile at 25 °C; b) Dependence of successive enthalpy change on n(DPA) / n(BZP) ratio. The collected signals are within experimental noise and indicate that no interaction between the DPA and BZP are formed.

#### 5.9. Thermodynamic cycles related to a reaction of BZP and DPA



**Scheme S2.** Thermodynamic cycles used for calculation of the reaction enthalpy of BZP–DPA(I) and BZP–DPA(s) formation in solid-state from BZP and DPA at 25 °C (**blue**). Uncertainties of the last digit are given in parentheses as standard error of the mean (N = 3, except \*N = 2). The reaction enthalpies determined by direct isothermal solid-state calorimetry are **bolded (black)**.

#### 6. Organic synthesis – Baeyer-Villiger oxidation

Exp. No.	<i>n</i> (4- <i>t</i> BuCH)ª / mmol	n(mCPBA) / n(4-tBuCH) <sup>max b</sup>	$\Delta_r H^\circ$ / kJ mol <sup>-1</sup>
1	0.129	6.9	-224
2	0.100	9.0	-209
3	0.265	3.9	-208
4	0.262	3.9	-226
Average ± SEM			-217 ± 5

**Table S14.** Conditions and calculated reaction enthalpies for Bayer-Villiger lactonization. Experiments were performed in Setaram Calvet calorimeter at 25 °C.

<sup>a</sup> 4-*t*BuCH = 4-*tert*-butylcyclohexanone.

<sup>b</sup> As assay of *m*CPBA is < 77 %, molar ratio of reactants can not be exactly calculated. Therefore, its maximum value is written (for the case assay(mCPBA) = 77 %).



**Figure S18.** Comparison of <sup>1</sup>H NMR spectra of acid (*m*CPBA), ketone (4-*t*BuCH), PM (product mixture from calorimetric experiment), and lactone ( $\gamma$ -*tert*-butyl- $\epsilon$ -caprolactone isolated from PM) recorded in CDCl<sub>3</sub> at 25 °C. No traces of ketone are observed in PM (green lines & arrows). PM contains excess of acid.

## 7. Literature

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