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Using fast scanning calorimetry to study solid-state cyclization of dipeptide L-leucyl-L-leucine

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ABSTRACT

The possibility of using fast scanning calorimetry (FSC) to study the kinetics of the solid-state cyclization of dipeptide was demonstrated in the present work for the first time. The activation energy and Arrhenius constant of the cyclization of $_{L}$-leucyl-$_{L}$-leucine (Leu-Leu) were estimated. FSC data obtained at heating rates from 18,000 to 54,000 K min^{-1} were evaluated by non-isothermal kinetics. The dependence of the specific heat capacity c_p on temperature was determined for linear and cyclic Leu-Leu dipeptides using differential scanning calorimetry (DSC) and FSC. The application of FSC allows studies of solid-state reactions for expensive substances and compounds synthesized in very small amounts.

1. Introduction

2,5-Diketopiperazines (DKPs), also known as cyclic dipeptides (CDPs), are of great interest [1,2] due to their potential advantages for various applications [3,4]. These molecules, in comparison with their linear counterparts, have a unique structural rigidity and less conformational freedom [5], which reduces restrictions for their practical usage [6]. Small cyclic peptides are conveniently used as model compounds, since they can mimic the major secondary structural motifs (strands / sheets, turns, helices) found in proteins [7,8]. The formation of such structures increases the resistance of short cyclic peptides to cleavage by proteolytic enzymes [9]. Cyclic peptides have a better cell permeability compared to linear peptides, which polar nature prevents their penetration into the lipophilic cell membrane [10,11]. The orally bioavailable 2,5-DKPs exhibit exceptional biological activity [12–14] as anticancer [15,16], antiviral [17,18], antifungal [19,20], anticoagulant and antimicrobial agents [21,22].

Due to the ability to form various intermolecular bonds, including four hydrogen bonds per molecule, CDPs are capable to self-assembly with the formation of various highly ordered structures, which are used in a wide range of applications, such as design of nanodevices and sensors [23], hydro- and organogels [4,24] for ecology and biomedicine [4,25,26].

To expand the scope of CDPs, the development of methods for their synthesis is required, preferably using simple atom-economical procedures. The current methods of CDPs synthesis, including condensation of individual amino acids at high temperature in the solid state (solid phase synthesis) or under reflux in solutions [1], and microwave cyclization of dipeptides in water [27] have several disadvantages associated with the use of solvents and the formation of by-products [28]. The heat treatment of linear dipeptides in the solid state allows obtaining DKPs in one step without any by-products, except water [29–32]. Unfortunately, the solid-state reactions of dipeptide cyclization have not been studied sufficiently yet [33,34], because of the possibility of their thermal decomposition upon heating [35,36], as well as due to the relatively high cost of optically pure linear dipeptides.

The key to solving this problem may be the fast scanning calorimetry (FSC) [37]. The main idea of the FSC method is to use a tiny sample that allows to control the heating and cooling at scanning rates up to 10^6 K s^{-1}. The high heating and cooling rates help to avoid thermal decomposition of low volatile and thermally unstable compounds [38], to prepare the substances in the amorphous state [39] and in various polymorphic modifications [40]. FSC is a convenient experimental method for studying the melting of bio-polymers [41,42], amino acids [43], low molecular mass compounds [44–46] and nucleobases [47,48]. The undoubted advantage of FSC is the fast measurement (a few seconds) and low sample mass (less than 50 ng), which is especially beneficial from an economic point of view, when expensive substances of high purity should be studied.

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In the present work, FSC was used to study the cyclization of L-leucyl-L-leucine dipeptide in the solid state for the first time. Previously, the cyclization of this dipeptide was studied by conventional methods of thermal analysis [30]. In the present study, the kinetic parameters of the reaction were estimated within the approaches of non-isothermal kinetics using FSC data. The results obtained were compared with kinetic parameters of this reaction determined elsewhere [30]. The study of kinetics of solid-state reactions of minute amounts allows to develop effective and economical methods for preparation of biologically active substances based on oligopeptides.

2. Experimental

2.1. Materials

Dipeptide L-leucyl-L-leucine (Leu-Leu) was purchased from Bachem (Lot#: 1054344). Cyclic dipeptide *cyclo*(leucyl-leucyl) (*cyclo*(Leu-Leu)) was prepared by heating the Leu-Leu up to 473 K as described in Ref [30]. For the experiments, Leu-Leu was recrystallized from methanol and dried in vacuo (P = 7 kPa) to remove the solvent. Methanol (of grade "for GC" with purity ≥99.9 %) was used without additional purification.

2.2. Differential scanning calorimetry

The DSC experiments were performed using the DSC204 F1 Phoenix differential scanning calorimeter (Netzsch, Germany) in an argon atmosphere (flow rate 150 mL min^{-1}) with the heating/cooling rate of 10 K min^{-1}. DSC was calibrated according to the manufacturer's recommendations by measuring six standard compounds (Hg, In, Sn, Bi, Zn, and CsCl) as described previously [31]. The 40 μL aluminum crucibles sealed with a pierced lid having a hole of 0.5 mm hole were used. Before the experiment, aluminum crucibles were annealed at 473 K for 30 min.

The specific heat capacities of Leu-Leu and *cyclo*(Leu-Leu) were measured as described elsewhere [49]. The measurement procedure included three steps. Firstly, the baseline for the empty crucibles was determined. Then using the baseline obtained, a standard sample (sapphire disc) with a weight of 21.05 mg and a powder of dipeptide (8 − 9 mg) were sequentially measured in the same crucible. This procedure was repeated three times for each sample. The calculation of the heat capacity was performed using the Netzsch Proteus Thermal Analysis 6.1.0 according equation:

$$c_p = m_{sapphire}/m_{dipeptide} \times (DSC_{dipeptide} - DSC_{baseline})/(DSC_{sapphire} - DSC_{baseline}) \times c_{p,sapphire}$$

where c_p and $c_{p,sapphire}$ are specific heat capacities of dipeptide and sapphire [J g^{-1} K^{-1}], $m_{dipeptide}$ and $m_{sapphire}$ are masses of dipeptide and sapphire [mg], $DSC_{dipeptide}$, $DSC_{sapphire}$ and $DSC_{baseline}$ are DSC signals obtained for sample, standard sample and baseline [μW].

Leu-Leu was previously heated up to 428 K to remove adsorbed water [50]. The specific heat capacity (accuracy of 2%) was measured in the range between 313 K and 413 K in case of Leu-Leu and between 313 K and 483 K for *cyclo*(Leu-Leu). Calculation of heat capacities was made for a linear region on the DSC heating and cooling curves in the temperature range from 343 to 411 K (Leu-Leu) and 363–453 K (*cyclo*(Leu-Leu)).

2.3. Fast scanning calorimetry

The FSC experiments were performed using the Flash DSC1 calorimeter (Mettler-Toledo, Switzerland) with a UFS1 sensor and TC-100 cooler (Huber, Germany) [51] under an atmosphere of nitrogen with a flow rate of 50 mL min^{-1}. The sensor had been conditioned and calibrated before use as described previously [45]. The temperature calibration was carried out using standard samples of indium, tin, biphenyl and deionized water. The accuracy of the melting temperature determination was better than ± 1 K. Optical images of the samples were obtained using an Olympus BXFM microscope.

The Leu-Leu cyclization was studied at heating rates of 300, 700 and 900 K s^{-1}. The higher heating rates led to a substantial broadening of DSC peaks and an increase in errors.

Since the mass of the dipeptide FSC sample is not available due to the nanogram sample mass, several approaches have been developed for an indirect mass determination using the data on specific fusion enthalpy, the specific heat of the solid or liquid sample, and the heat capacity change at the glass transition [37]. In this study, we estimated the sample mass (m) using the specific heat capacities of Leu-Leu and *cyclo*(Leu-Leu) obtained from DSC and the heat capacities from FSC measurements, by the following equation:

$$m = C_p(T)/c_p(T) \quad (1)$$

where $C_p(T)$ is the heat capacity determined from the FSC experiment as described below.

The heat capacities of dipeptides were calculated from the heat flow rates on heating and cooling as described previously [46]. The heat flow rates of empty sensors were determined before each sample measurement. Then sample measurements were corrected by subtracting the empty sensor measurement. Further corrections were made for the heat loss from the sample and the reference to the surroundings. The measurements were carried out in a temperature range, in which there is no chemical reaction or phase transition: from 293 K to 423 K in the case of Leu-Leu and from 293 K to 483 K for *cyclo*(Leu-Leu). So, the corrected heat flow rates to the sample (Φ_h is the corrected heat flow rate on heating and Φ_c is that on cooling) may be represented as the sum of contributions from the heat capacity of the sample (C_p) and the differential heat loss (Φ_{loss}) [37].

$$\text{Heating:}\quad \Phi_h(T) = C_p(T) \times dT/dt_h + \Phi_{loss,h}(T) \quad (2)$$

$$\text{Cooling:}\quad \Phi_c(T) = C_p(T) \times dT/dt_c + \Phi_{loss,c}(T) \quad (3)$$

The difference between the heat flow rates measured during heating and cooling, taking into account, that $dT/dt_h = -dT/dt_c$, can be written

$$\Phi_h(T) - \Phi_c(T) = 2 \times C_p(T) \times dT/dt \quad (4)$$

So, heat capacity may be calculated as

$$C_p(T) = [\Phi_h(T) - \Phi_c(T)]2 \times dT/dt \quad (5)$$

Before the experiments, the dipeptides were heated three times from 293 K to 423 K with the rate of 100 K s^{-1} to remove residual water and methanol.

2.4. Kinetic analysis of cyclization of Leu-Leu in solid state

Kinetic analysis was performed following the ICTAC recommendations [52,53] using the NETZSCH Kinetics Neo 2.1.2.2 software package. The "model-free" Ozawa-Flynn-Wall (OFW) [54–56] and Kissinger-Akahira-Sunose (KAS) Eq. (6) methods [57,58] were used.

The same set of experimental data was used further for finding the topochemical equation as described in Ref. [29–31,59]. A suitable kinetic model was estimated using the following model-based approaches: reaction of *n*th order with autocatalysis by product (C*n*B) Eq. (7), reaction of *n*th order with *m*-Power autocatalysis by product (C*n*m) Eq. (8), expanded Prout-Tompkins equation (B*n*a) Eq. (9).

$$\ln(\beta/T^2) = \text{Const} - E_a/RT \quad (6)$$

$$d\alpha/dt = -A\exp(E_a/RT)(1-\alpha)^n(1 + k_{cat}\alpha) \quad (7)$$

$$d\alpha/dt = -A\exp(E_a/RT)(1-\alpha)^n(1 + k_{cat}\alpha^m) \quad (8)$$

$$d\alpha/dt = -A\exp(E_a/RT)(1-\alpha)^n\alpha^{k_{cat}} \quad (9)$$

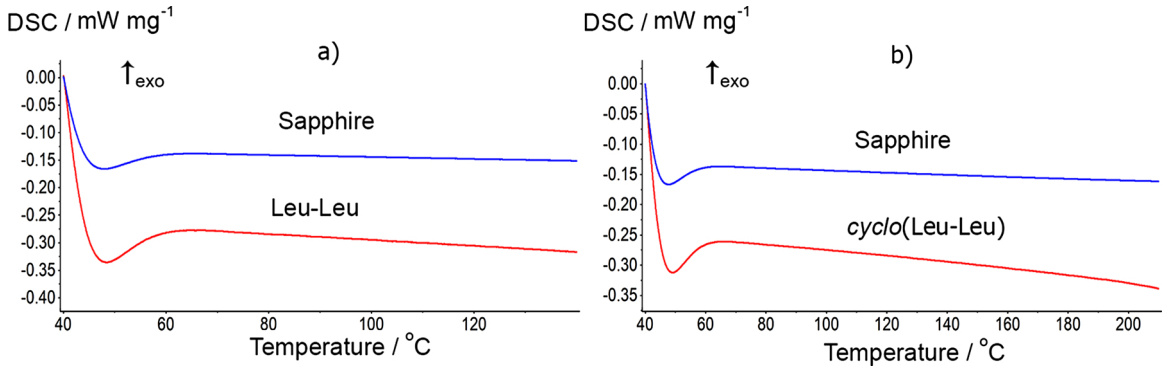

Fig. 1. DSC curves of (a) Leu-Leu, (b) *cyclo*(Leu-Leu) and sapphire.

where β is heating rate, $d\alpha / dt$ – reaction rate, A – Arrhenius constant (pre-exponential factor), E_a – activation energy, R – gas constant, T – temperature, n – reaction order, k_{cat} – catalytic rate constant, α – conversion degree (conversion rate), m – exponent.

3. Results and discussion

The cyclization of dipeptide leucyl-leucine in the solid state was studied using fast scanning calorimetry. Previously, for this dipeptide the temperatures of water desorption (397 K) and chemical reaction (450 K) were found using simultaneous thermogravimetry and differential scanning calorimetry with mass spectrometric analysis of the evolved gases [30].

3.1. The heat capacity of dipeptides

First, the heat capacities of the dipeptides were determined by DSC. For this, DSC curves were obtained for dipeptides and a standard sample (sapphire), Fig. 1. To calculate the heat capacities, linear regions of the curves were used.

The dependences of heat capacities of crystalline Leu-Leu and *cyclo* (Leu-Leu) on the temperature calculated using the methods of ratios and DIN 51007 are shown in Fig. 2. The linear dependences obtained were extrapolated to 298 K. The standard values of specific $c_p^{298.15}$ and molar heat capacities $c_{p,m}^{298.15}$ of crystalline Leu-Leu and *cyclo*(Leu-Leu) at $T = 298.15$ K are shown in Table 1. From the data obtained by the used methods of ratios and DIN 51007, the average values of $c_p^{298.15}$ were calculated.

Next, the heat capacity of the studies dipeptides was determined using FSC. The dipeptides were recrystallized from methanol to obtain individual crystals. Crystals were placed in the center of the measuring region of the sensor on a drop of methanol, Fig. 3a, b.

The heating and cooling curves were determined for the empty sensor and samples prepared by FSC, Fig. 4a–c. The calculation of heat capacities was made using the FSC heating and cooling curves in the temperature range from 323 to 413 K (Leu-Leu) and 323–443 K (*cyclo* (Leu-Leu). The examples of obtained dependencies are shown in Fig. 4d, e.

The values of absolute C_p and the values of specific c_p were used to estimate the mass of the dipeptide crystals. In the case of Leu-Leu, samples were heated and cooled with rates of 300, 700, and 900 K s^{-1}. Sample masses were determined from Eq.(1) as ca. 65, 53, and 13 ng. The heating and cooling curves shown in Fig. 4a correspond to the Leu-Leu sample with mass of 13 ng. The weight of *cyclo*(Leu-Leu) used to measure the heat capacity was approximately 79 ng.

3.2. Kinetic analysis of cyclization of Leu-Leu in solid state according to FSC

The state of the Leu-Leu sample before and after the reaction is shown in Fig. 5a, c, respectively. The FSC curves were measured at heating rates of 300, 700 and 900 K s^{-1}, Fig. 5b.

Calculations of activation energies and logarithms of the Arrhenius constant (pre-exponential factor) were made for temperature ranges corresponding to the chemical reaction: from 452 to 471 K for the heating rate of 300 K s^{-1}, from 445 to 478 K for the heating rate of 700 K s^{-1}, from 452 to 479 K for the heating rate of 900 K s^{-1}. Results of OFW and KAS analysis are given in Figs. 6 and 7.

According to the Ozawa-Flynn-Wall (OFW) and Kissinger–Akahira–Sunose (KAS) methods the value of E_a decreases from 584 ± 36 kJ mol^{-1} (OFW) and 584 ± 36 kJ mol^{-1} (KAS) to 371 ± 44 kJ mol^{-1} (OFW) and 371 ± 45 kJ mol^{-1} (KAS). The calculation was made for the interval of conversion 0.2 – 0.8.

The observed descending correlation indicates a complex nature of the reaction and is in agreement with the previously established autocatalytic nature of this reaction [30]. One can assume that the accumulation of the reaction product, which acts as a catalyst, leads to a decrease in the activation energy with increasing conversion.

The dependencies of the activation energy E_a and the logarithm of the Arrhenius constant (pre-exponential factor) log$A$ on the conversion α in Figs. 6 and 7 suggest the kinetic compensation effect. One can assume that this effect may be due to decrease the sample mass used simultaneously with increasing of the heating rate [60] as well as the autocatalytic nature of this reaction [30].

Using linear regression methods, a search for the optimal kinetic model was made. The best fit between theoretical and experimental curves was achieved using the equations CnB, Cnm and BnA (extended Prout–Tompkins equation), which are topochemical equations for the *n*th-order reactions with autocatalysis [61]. The kinetic parameters calculated using these models, as well as statistical quality parameters, are given in Table 2.

The correlation of experimental points from FSC curves with the calculated lines in accordance with equation CnB is shown in Fig. 8. We believe that an improvement in correlation can be achieved by using samples with equal masses. This will provide a close thermal contact area between crystals of different samples and the sensor surface, and a close topochemical reaction rate.

The kinetic parameters obtained in the present work are in agreement with the results of kinetic studies obtained by thermogravimetry [30]. Thus, the FSC method allows to study the cyclization of dipeptide in the solid state. The mass of samples can be calculated by using their specific heat capacities. The information about samples mass allows to take into account possible effects of different sample masses on the

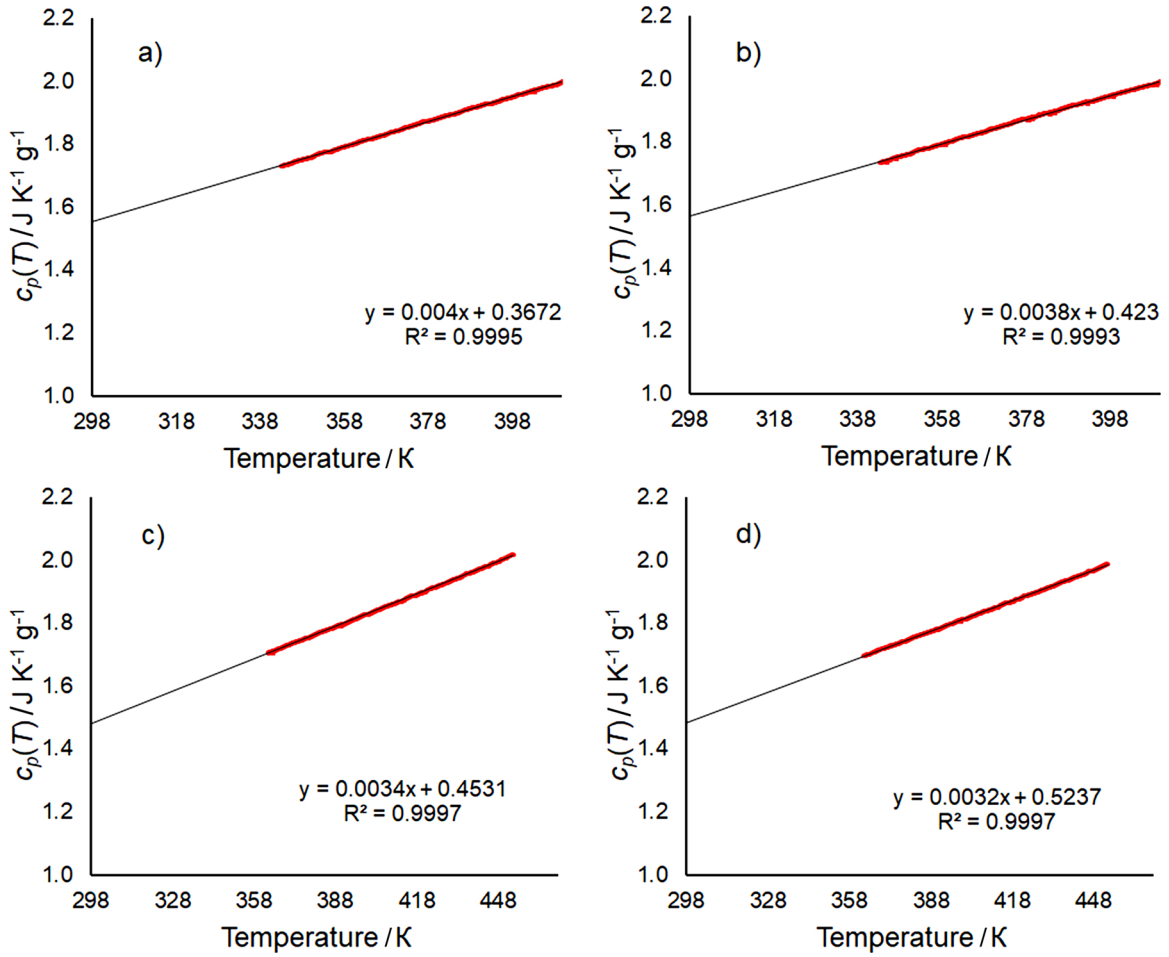

Fig. 2. The dependence of the heat capacity on the temperature of the Leu-Leu, calculated in accordance with the methods of (a) ratios and (b) DIN 51007, and *cyclo* (Leu-Leu), calculated in accordance with the methods of (c) ratios and (d) DIN 51007. Experimental data (red line) were extrapolated to temperature 298 K (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article).

Table 1
Standard specific heat capacity $c_p^{298.15}$ and average molar heat capacity $c_{p,m}^{298.15}$ of crystalline Leu-Leu (M_m = 244.33 g mol^{-1}) and *cyclo*(Leu-Leu) (M_m = 226.33 g mol^{-1}).

Dipeptide	$c_p^{298.15}$, J K^{-1} g^{-1}			$c_{p,m}^{298.15}$, J K^{-1} mol^{-1}
	Method of ratios	DIN 51007	Average value	
Leu-Leu	1.56 ± 0.03	1.56 ± 0.03	1.56 ± 0.03	381 ± 8
Cyclo(Leu-Leu)	1.47 ± 0.03	1.48 ± 0.03	1.48 ± 0.03	335 ± 7

experimental results [52].

It is interesting to note that for dipeptides consisting of glycine and alanine residues, the cyclization was not observed under fast heating with rates of 2000 K sec^{-1} and more [62]. Moreover, the cyclization of Gly-Gly in the solid state is accompanied by its decomposition under heating with rates of 5 − 20 K min^{-1} [33,63]. So, one can assume that FSC can be used for study the cyclization of the dipeptides with relatively large substituents.

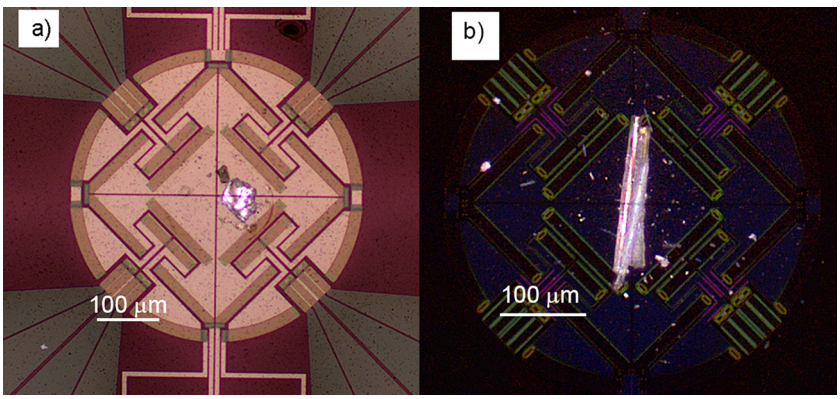

Fig. 3. Images of crystals of (a) Leu-Leu and (b) *cyclo*(Leu-Leu).

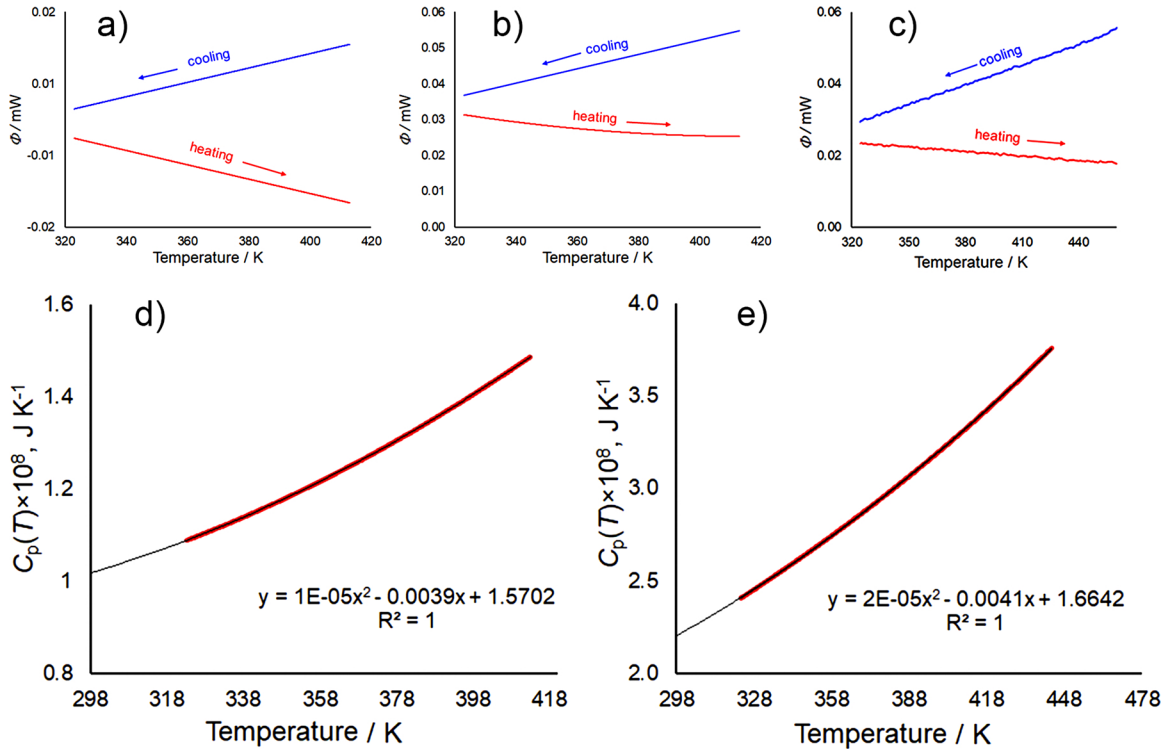

Fig. 4. Examples of heating and cooling curves obtained by FSC for (a) empty UFS1 sensor, (b) Leu-Leu sample without correction by subtracting the empty sensor measurement, (c) *cyclo*(Leu-Leu) sample with correction by subtracting the empty sensor measurement and the dependences of the heat capacity of (d) Leu-Leu and (e) *cyclo*(Leu-Leu) on temperature, calculated from the FSC data.

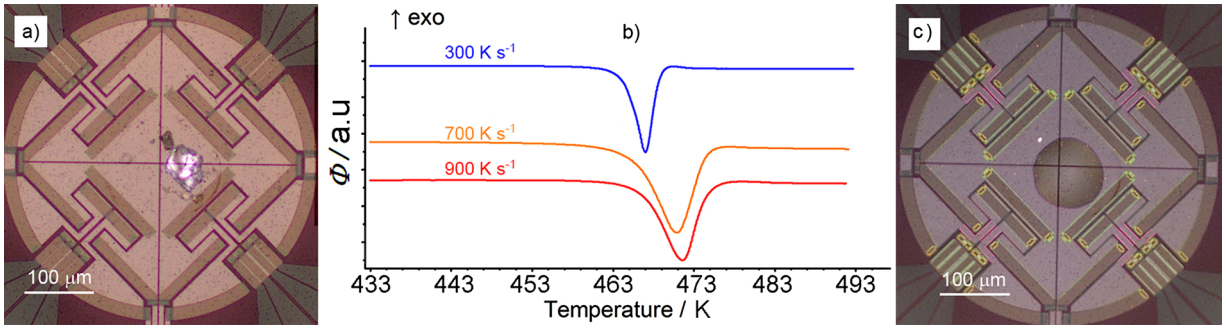

Fig. 5. Images of Leu-Leu sample before (a) and after (c) heating up to 220 °C with rate of 900 K s^{-1}, (b) data of FSC analysis for Leu-Leu at different heating rates. The curves were scaled for a better view.

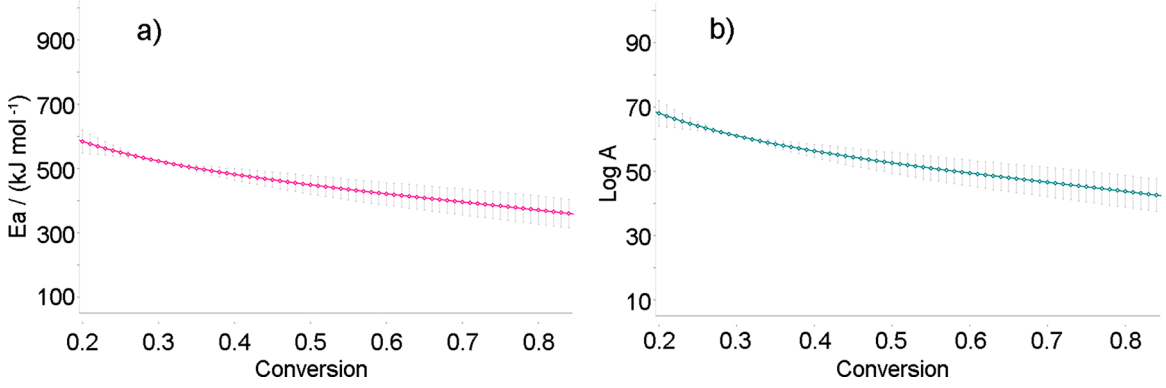

Fig. 6. OFW analysis of Leu-Leu cyclization in solid state: correlations of (a) the activation energy E_a and (b) the logarithm of the Arrhenius constant log$A$ (A = [s^{-1}]) versus degree of conversion α.

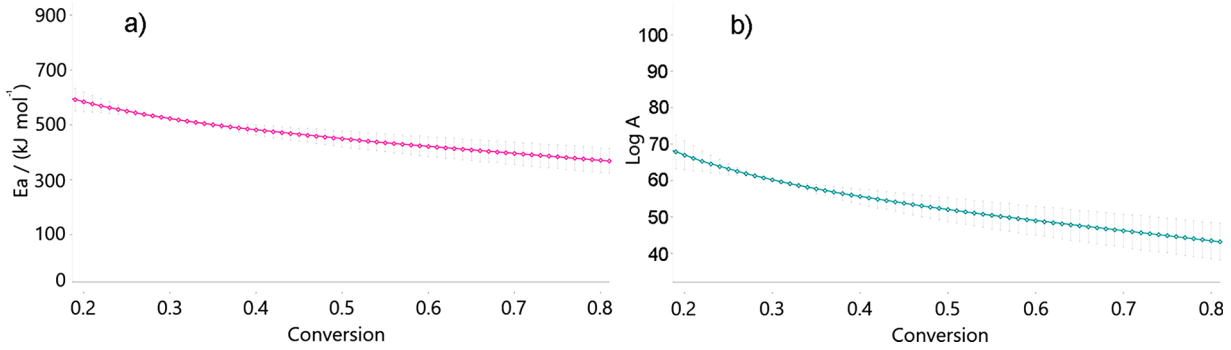

Fig. 7. KAS analysis of Leu-Leu cyclization in solid state: correlations of (a) the activation energy E_a and (b) the logarithm of the Arrhenius constant log$A$ (A = [s^{-1}]) versus degree of conversion α.

Table 2
Kinetic parameters of the reaction of Leu-Leu cyclization in solid state and statistical parameters of the calculation.

Equation A → B	E_a, kJ mol^{-1}	log A, log(s^{-1})	Reaction order	Corr. coeff.
CnB	475	54.4	1.2	0.99311
Cnm	477	54.4	1.1	0.99317
Bna	479	55.8	1.0	0.99229

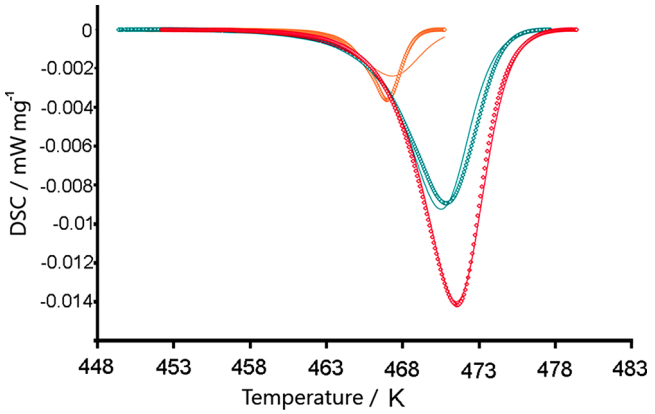

Fig. 8. Correlation of experimental points from FSC curves with the calculated curves in accordance with the equation CnB. The curves were normalized to sample mass.

4. Conclusions

The principal possibility of using the fast scanning calorimetry to study the cyclization of dipeptides in the solid state has been demonstrated for the first time. The kinetic parameters of the leucyl-leucine cyclization were determined, which are in good convergence with the results obtained by classical thermal analysis, regardless of the huge difference in the used scanning rates of $\sim 10^3$ times of these two methods. The heat capacities of leucyl-leucine and *cyclo*(leucyl-leucyl) determined by the methods of classical differential calorimetry and fast scanning calorimetry were used for calculation of the samples weight. The relatively small amount of dipeptide required for FSC experiments allows the studies of expensive and hardly available highly pure substances. One can assume that the high heating and cooling rates in FSC will allow to study cyclization of dipeptides even if it decomposes upon heating with relatively slow rates of several degrees per minute. This approach may be also applied for non-homogeneous samples, from which crystals with different habits may be selected and studied.

Author contributions

The manuscript was written through contributions of all authors. All authors have given approval to the final version of the manuscript. All authors contributed equally.

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CRediT authorship contribution statement

Aisylu S. Safiullina: Investigation, Formal analysis. **Aleksey V. Buzyurov:** Investigation. **Sufia A. Ziganshina:** Writing - original draft. **Alexander V. Gerasimov:** Formal analysis. **Christoph Schick:** Writing - review & editing. **Valery V. Gorbatchuk:** Writing - original draft. **Marat A. Ziganshin:** Conceptualization.

Declaration of Competing Interest

The authors report no declarations of interest.

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