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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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