Dimorphism of the Prodrug L-Tyrosine Ethyl Ester: Pressure–Temperature State Diagram and Crystal Structure of Phase II

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ABSTRACT: Polymorphism is important in the field of solid-state behavior of drug molecules because of the continuous drive for complete control over drug properties. By comparing different structures of a series of L-tyrosine alkyl esters, it became apparent that the ethyl ester possesses dimorphism. Its structure was determined by powder diffraction and verified by density functional theory calculations; it is orthorhombic, $P2_12_12_1$ with $a = 12.8679(8)$ Å, $b = 14.7345(7)$ Å, $c = 5.8333$ (4) Å, $V = 1106.01(11)$ Å, and $Z = 4$. The density of phase II is in line with other tyrosine alkyl esters and its conformation is similar to that of L-tyrosine methyl ester. The hydrogen bonds exhibit similar geometries for phase I and phase II, but the H-bonds in phase I are stronger. The solid II–solid I transition temperature is heating-rate dependent; it levels off at heating rates below 0.5 K min^{-1}, leading to a transition temperature of 306 ± 4 K. Application of the Clapeyron equation in combination with calorimetric and X-ray data has led to a topological diagram providing the relative stabilities of the two solid phases as a function of pressure and temperature; phase II is stable under ambient conditions. © 2011 Wiley-Liss, Inc. and the American Pharmacists Association J Pharm Sci 100:4774–4782, 2011

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INTRODUCTION

Amino acids play an important role in the living organism as building blocks not only for proteins, but also for smaller molecules such as hormones, melanin, and neurotransmitters. Deficiencies in specific amino acids can lead to related pathologies that can be treated either by dietary supplementation or by medication.

Amino acid-based drugs generally have a low bioavailability due to low intestinal permeability, extensive metabolism in the intestines, and a rapid clearance by the liver.[1] Thus, the prodrug strategy, a transient modification of physicochemical properties through chemical derivatization, is the approach of choice for such drugs.[1,2]

Esterification is a tool in peptide synthesis[3] that has proved effective in the design of amino acid-based prodrugs. L-tyrosine carboxylic esters are more lipophilic[4] and are absorbed up to 10 times faster than L-tyrosine [(*S*)-2-amino-3-(4-hydroxyphenyl)propanoic acid].[5,6] They are hydrolyzed under physiological conditions so that L-tyrosine is available in higher concentrations at a targeted site.[6–8] Studies on the conversion rate of L-tyrosine esters indicate that short linear chains hydrolyze relatively slowly,[7–9] suggesting

Additional Supporting Information may be found in the online version of this article. Supporting Information

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that L-tyrosine methyl ester (L-TME) and L-tyrosine ethyl ester (L-TEE) [ethyl (*S*)-2-amino-3-(4-hydroxyphenyl)propionate] are useful lipophilic prodrug candidates for slow release of L-tyrosine at a targeted site.

Just as the prodrug is a strategy to deliver a drug molecule, solid-state studies serve as the basis for dosage form design and integrity of the drug during storage and release. Within the framework of a more general study concerning L-tyrosine alkyl esters, the thermal expansion of L-TEE was studied recently.[10] The crystal structure of the commercially available active pharmaceutical ingredient (form I) has been known since 1970.[11] Comparison of the structure of L-TEE with those of other tyrosine esters led to the suspicion that it could be polymorphic,[10] and a subsequent search resulted indeed in a previously unknown form, phase II. In this paper, its structural characterization and its thermodynamic properties are presented.

Once a substance is known to be polymorphic, the question arises under which conditions the different forms are stable. By making use of the thermal expansion data obtained from X-ray diffraction and the thermodynamic data obtained by differential scanning calorimetry (DSC), a topological diagram can be constructed,[12,13] providing the relative stabilities of the two phases toward each other, toward the liquid phase, and toward the vapor phase as a function of pressure and temperature. Experimental data as a function of temperature and pressure reinforce the results of the topological approach and, therefore, the melting of form I was studied under pressure.

In addition to the thorough analysis of the phase behavior of L-TEE, the present paper is an example of how the interplay between data and thermodynamic theory leads to a better understanding of a specific case of dimorphism, which may eventually lead to a better understanding of polymorphism in general.

MATERIALS AND METHODS

Materials

L-Tyrosine ethyl ester ($M = 209.24\,\mathrm{g\,mol^{-1}}$) was purchased from Sigma–Aldrich (Madrid, Spain) (98%) and used as provided. Phase II was obtained by melting the commercial sample and quenching the melt at 190 K. After heating the formed glass, phase II crystallizes around 300 K.

High Resolution X-Ray Powder Diffraction

X-ray powder diffraction was performed on a transmission mode diffractometer using Debye–Scherrer geometry equipped with a cylindrical position-sensitive detector (CPS120) from INEL (Artenay, France) containing 4096 channels (0.029° 2θ angular step)[14] with monochromatic Cu Kα_1 ($\lambda = 1.54061$ Å) radiation. For the measurements as a function of temperature, a liquid nitrogen 700 series Cryostream Cooler from Oxford Cryosystems (Oxford, UK) was used.

Lightly ground specimens were introduced in a Lindemann capillary (from Hilgenberg, Malsfeld, Germany) (0.5-mm diameter) rotating perpendicularly to the X-ray beam during the experiments to improve the average over the crystallite orientations. For the temperature dependent measurements in the range from 100 K up to the melting point of phase I, the sample temperature was equilibrated for about 10 min followed by an acquisition time of ca. 1 h. The heating rate in between data collection was 1.33 K $\mathrm{min^{-1}}$. For phase II, a specimen of phase I was molten in the sample holder, then quenched at 190 K and reheated stepwise to 365 K.

The anisotropy of the intermolecular interactions can be investigated with the isobaric thermal expansion tensor, which is a measure of how the interactions change with temperature. A small value for a tensor eigenvalue is commonly referred to as a "hard" direction and a large value as a "soft" direction.[15–18] Details of how this is applied to L-TEE have been published previously.[10]

Structure Solution from Powder Diffraction

For structure solution, the program DASH[19] was employed and the powder pattern was truncated to 52.2° in 2θ (Cu Kα_1), corresponding to a real-space resolution of 1.75 Å. The background was subtracted with a Bayesian high-pass filter.[20] Peak positions for indexing were obtained by fitting with an asymmetry-corrected pseudo-Voigt function.[21,22] Twenty peaks were indexed with the program DICVOL91.[23] An orthorhombic unit cell was obtained. The figures of merit given by *DICVOL* were $M(20) = 15.7$ and $F(20) = 32.5$ (0.0176, 35). Pawley refinement was used to extract integrated intensities and their correlations, from which the space group was determined using Bayesian statistical analysis.[24] $P2_12_12_1$ was returned as the most probable space group. It was the space group with the highest symmetry, and all other tyrosine alkyl esters also have this space group.[10] The space group $P2_12_12_1$ contains no improper symmetry elements, consistent with the crystal structure of an enantiomerically pure compound. It resulted in a Pawley χ^2 of 5.43. The high value of the Pawley χ^2 was caused by the presence of a significant quantity of phase I, visible in the background of the diffraction pattern. Simulated annealing was used to solve the crystal structure from the powder pattern in direct space. The starting molecular geometry was taken from the published phase I from the Cambridge Structural Database (reference code TYREST).[11] In 30