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Crystal structure determination and thermal behavior upon melting of *p*-synephrine

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ABSTRACT

The crystal structure of *p*-synephrine was solved from a high-resolution X-ray powder diffraction pattern optimized by energy-minimization calculations using the Dreiding force field. The title compound crystallizes in a monoclinic system (space group $P2_1/c$, $Z=4$, with $a=8.8504(11)$ Å, $b=12.1166(15)$ Å, $c=9.7820(11)$ Å, $\beta=122.551(2)^\circ$, $V=884.21(19)$ Å^3 and $d=1.256\,g\,cm^{-3}$). Since *p*-synephrine degrades upon melting, its melting data were determined from DSC experiments carried out as a function of the heating rate. This method allowed determining a melting temperature and enthalpy equal to $199.8\pm1.3\,^\circ C$ and $57\pm3\,kJ\,mol^{-1}$, respectively.

1. Introduction

Synephrine, and more specifically *p*-synephrine, 4-[1-hydroxy-2-(methylamino) ethyl]phenol, is an alkaloid that is naturally contained in some plants [1]. It is one the most popular stimulants present in weight-loss products, becoming the main substitute of ephedrine after this latter was banned in the dietary products by the Food and Drug Administration. The market of these products is flourishing, this results that many counterfeit products containing synephrine arose. The effects of synephrine are close to those of caffeine or ephedrine: increase of blood pressure and heart rate. This cardiotoxicity may be enhanced when it is combined with other stimulants, as previously reported [2]. A low subchronic toxicity and possible side effects such as reduction in locomotor activity have also been reported [1,3].

P-Synephrine is the para isomer of synephrine. It is a crystalline racemate the chirality of which is due to the presence of a sp3-hybridized carbon with four different moieties, including the hydroxyl group (Scheme 1). Hence, two enantiomers, the dextrorotatory (D-) and the levorotatory (L-) synephrine, as well as the equimolar mixture between the two enantiomers are encountered. The D-isomer corresponds to the s-configuration, and the levorotatory L-isomer to the r-configuration.

However, very few data are available regarding the solid state of *p*-synephrine. For instance, its crystal structure has never been reported. It is therefore not possible to decide on the type of crystalline racemates: conglomerate, racemic compound or pseudoracemate. Then, the first aim of the present work is the refinement of the crystal structure obtained from X-ray powder diffraction experiments carried out at room temperature.

Similarly, from a thermodynamic point of view, very few thermal data are available regarding the melting characteristics [4–6]. Some authors give a melting temperature value approximately equal to 184–185 °C, [4,5] and another one reports a melting point of 186–187 °C with decomposition upon melting [6]. But no indication is given on the measurement technique of the melting point and no enthalpy value has been determined. More recently, a DSC study carried out at $10\,^\circ C\,min^{-1}$ reports that synephrine melts at 190.53 °C with a $99.7\,kJ\,mol^{-1}$ associated enthalpy [7]. However, the authors suspect that the product degrades upon melting in these experimental conditions. Consequently, the reported enthalpy value does include the heat of fusion as well as a part of the heat of degradation.

To overcome this lack of information, differential scanning calorimetry (DSC) and thermogravimetric analysis (TGA) were conducted on commercial *p*-synephrine in order to determine if degradation occurs during melting and then, to propose accurate

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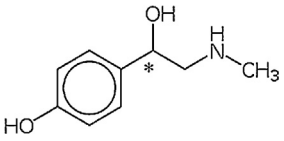

Scheme 1. Molecular structure of *p*-synephrine (*: asymmetric carbon).

melting values. Indeed, it has been previously demonstrated that the temperature and the enthalpy of melting of a compound that degrades upon melting depend on the DSC scan rate since the degradation process can be bypassed at high scan rates [8].

2. Experimental

2.1. Chemicals

p-Synephrine was purchased from Sigma Aldrich, with a mass percentage purity higher than 98%. The compound was used without further purification. The water content of *p*-synephrine was determined by the Karl–Fischer method using a DL 38 volumetric titrator from Mettler-Toledo (Switzerland). Methanol from Sigma Aldrich, with a mass purity higher than 99.9%, was used as solvent. The moisture content was found to be less than 0.07%.

2.2. X-ray diffraction

X-ray powder diffraction experiments were performed with a horizontally mounted cylindrical position-sensitive detector CPS-120 (Debye-Scherrer geometry, transmission mode) from INEL, using monochromatic Cu $K\alpha_1$ radiation ($\lambda = 1.5406$ Å), selected with an asymmetric focusing incident-beam curved quartz monochromator. The generator power was set to 1.0 kW (40 kV and 25 mA). The detector consisted of 4096 channels providing angular step of 0.029° (2) between 4° and 120°. External calibration using the $Na_2Ca_2Al_2F_{14}$ (NAC) cubic phase mixed with silver behenate was performed by means of cubic spline fittings. From that, each channel is converted in diffraction angle.

The samples were gently crushed before being introduced into Lindemann glass capillaries with 0.5 mm inner diameter, which were then rotated perpendicular to the X-ray beam direction in order to decrease as much as possible the effects of preferred orientations.

Crystal structure was determined with the reflex plus module of Materials Studio Modeling 5.5 [9]. First, the pattern was indexed by means of the peak picking option of the software package. Potential solutions for cell parameters and space group were found using the X-cell algorithm [10]. Then, a Pawley profile-fitting procedure was applied including refined cell parameters experimental profile fitting with pseudo-voigt function, zero shift and asymmetry Finger-Cox-Jephcoat function [11]. Distances, angles and torsions in the molecule were obtained *via* energy-minimization calculations with the forcite module using the Dreiding force field [12]. Then, a Monte-Carlo approach, included in the reflex plus module, was carried out in the direct space to solve the structure moving the molecule as a rigid-body and allowing the change of the chain torsion angles [13].

2.3. Thermal analysis

Differential scanning calorimetry and thermo-gravimetric analysis experiments were performed using an 822e thermal analyser, equipped with a FRS5 sensor, and a TGA 850 from Mettler-Toledo (Switzerland). The DSC and TGA experiments were carried out in the 25–300 °C temperature range at different scan rates from 2 to 100 °C min^{-1} under a constant nitrogen flow.

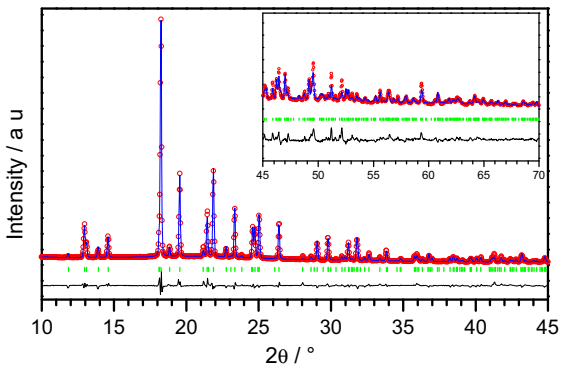

Fig. 1. Final Rietveld refinement of X-ray diffraction pattern of *p*-synephrine obtained at 294 K. Blue line: experimental pattern, empty red circles: calculated pattern, green vertical bars: peak positions, black line: residual XRPD patterns. The insert corresponds to the scale for the data between 45° and 70° magnified 15 times. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

Temperature and enthalpy calibration of the apparatus were carried out at 10 °C min^{-1}. Indium and zinc were used for temperature and enthalpy calibration. The multiple thermocouple sensor technology of the device combined with furnace and sample tau lag calibration eliminates the influence of the heating rate on temperature and heat flux measurements [14]. The tau lag was calibrated for scan rates ranging from 2 to 100 °C min^{-1}, using the procedure as described by the manufacturer. Regarding the enthalpy values, a relative standard uncertainty on the values was estimated at 5%. For all the experiments, an empty aluminium pan was used as a reference. The melting temperatures were determined at the onset of the corresponding endotherms. *p*-Synephrine samples (approximately 2.5 mg) were weighed with a microbalance sensitive to 1 μg and then introduced into a crucible with a perforated cover. The standard uncertainty on the temperatures was determined from the standard deviation, with 0.68 level of confidence, of three independent measurements performed for each scan rate.

3. Results and discussion

The crystal structure of *p*-synephrine was determined at room temperature (294 K). The title compound crystallizes in the monoclinic space group $P2_1/c$ with $a = 8.8504 \pm 0.0011$ Å, $b = 12.1166 \pm 0.0015$ Å, $c = 9.7820 \pm 0.0011$ Å, $\beta = 122.551 \pm 0.2°$, with four molecules per unit cell ($Z = 4$). Since the space group is centrosymmetric, the asymmetric unit consists of one independent molecule ($Z' = 1$). The translational mirror c (and center) is explained by the fact that the compound is a racemic compound. The agreement between observed and computed diffraction patterns is estimated by a reliability factor Rwp. The final Rietveld refinement (including Pawley refined parameters, rigid-body molecular units, torsions, preferred orientations and overall isotropic factor) converged to a final Rwp value of 6.98% (Fig. 1). From the refinement, the density Dx of solid synephrine is found to be 1.256 ± 0.001 g cm^{-3} at 294 K.

All the above results are gathered in Table S1.

Rietveld refinement allowed us to propose the crystal structure presented in Fig. 2 and the asymmetric unit with atom numbering in Fig. S1. As shown in Fig. S1, a disorder between two positions of the hydrogen atoms of the hydroxyl group (O11) and secondary amine (N8) leads to an occupancy factor of 0.5 for each. Each position makes a hydrogen bond in the crystal, as shown in Table S2.

The molecular structure is maintained through five intermolecular H-bonds (Table S2) directed along the rows $[0\bar{1}1]$ and [011] (Fig. S2). The refinement also revealed two intra-molecular