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X-ray studies of piracetam in a wide range of temperatures

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This paper presents the results of the study of the third modification of piracetam (an ingredient of a nootropic drug) by the method of low-temperature x-ray diffraction in the range from 150 to 375 K. The dependence of the unit cell parameters on the temperature for a given compound was first obtained and its coefficients of thermal expansion were calculated. 2D and 3D figures of thermal expansion are constructed, based on this data.

Keywords: piracetam, nootropics, neurostimulants, low-temperature X-ray diffractometry, thermal expansion

1. Introduction
Polymorphism is a widespread phenomenon among pharmaceutical ingredients. Modifications of the same compound can have various properties such as density, solubility, melting point, heat capacity, biological activity, etc. In this regard, it is very important that the sample used as a medicine or its ingredient has a specific polymorphic form and is stable throughout its expiration date. Understanding the processes of phase transition and knowledge of the presence of a specific polymorphic modification, at each stage of processing all components of the pharmaceutical, and most importantly in the final product is an actual problem of the pharmaceutical industry [1]. While high-temperature studies of the conversion of piracetam have been the subject of several studies, it has not been studied at low temperatures.
Piracetam (nootropil) is a nootropic drug successfully used for the treatment of diseases with chronic cerebral vascular insufficiency, manifested in impaired of memory, attention, speech, dizziness, etc., as well as changes in cerebral circulation, during restorative therapy after comatose and sub-comatose states. Piracetam has five polymorphic modifications, two of which (IV and V) were obtained at high pressure [2]. Identification of I, II and III polymorphic forms were carried out at atmospheric pressure [3, 4]. Form I is obtained by heating the II or III forms to 400 K, followed by cooling to room temperature, and for a few hours in ambient conditions it returns to the modification II. Form II is metastable, only modification III under ambient conditions is a stable compound. In this case, piracetam can also exist as a mono- and dihydrate [5].

This work is a continuation of the systematic research of pharmaceutical ingredients. Earlier in articles [6 ± 8] we investigated the structural and thermodynamic properties of methylprednisolone aceponate, myo-inositol. The aim of this work is to study the behavior of piracetam in the low temperature region and to investigate its thermal expansion by means of low-temperature radiography. The method of high- and low-temperature radiography makes it possible to measure the coefficients of thermal expansion along any direction of the crystal structure, along the crystallographic axes (it is more interesting for us), the coefficient of volumetric expansion, the average coefficient of thermal expansion, and so on. [9]. Thermal expansion is one of the thermophysical characteristics of a substance that provides information about it in a wide range of temperatures [10].

2. The experimental part
2.1. Sample
The studied sample of piracetam (CAS: 7491-74-9) was purchased from Jiangxi Yuehua Pharmaceutical Co. (according to the passport for the reagent, the purity of the sample is at least 99.1%). An x-ray diffraction pattern of pyracetam was obtained in the 2θ range from 5 ° to 60 ° on a XRD-6000 X-ray diffractometer from Shimadzu (CuKα radiation, scanning step 0.02 °.) to identify the phase (Fig. 1). X-ray data and estimation of the impurity content in the studied substance allowed us to conclude that the researched sample is an individual crystal com-
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Table. Unit cell parameters and coefficients of thermal expansion of piracetam

<table>
<thead>
<tr>
<th>T (K)</th>
<th>a (nm)</th>
<th>b (nm)</th>
<th>c (nm)</th>
<th>β (°)</th>
<th>V (nm³)</th>
<th>ρ (g·cm⁻³)</th>
</tr>
</thead>
<tbody>
<tr>
<td>150</td>
<td>0.6494(7)</td>
<td>0.6407(4)</td>
<td>1.6307(18)</td>
<td>92.14(8)</td>
<td>0.6781(7)</td>
<td>1.392</td>
</tr>
<tr>
<td>175</td>
<td>0.6498(5)</td>
<td>0.6411(3)</td>
<td>1.6337(14)</td>
<td>92.18(6)</td>
<td>0.6801(6)</td>
<td>1.388</td>
</tr>
<tr>
<td>200</td>
<td>0.6501(4)</td>
<td>0.6413(3)</td>
<td>1.6357(11)</td>
<td>92.17(5)</td>
<td>0.6814(5)</td>
<td>1.385</td>
</tr>
<tr>
<td>225</td>
<td>0.6507(3)</td>
<td>0.6417(2)</td>
<td>1.6378(9)</td>
<td>92.16(4)</td>
<td>0.6833(3)</td>
<td>1.381</td>
</tr>
<tr>
<td>250</td>
<td>0.6509(3)</td>
<td>0.6420(2)</td>
<td>1.6404(8)</td>
<td>92.16(3)</td>
<td>0.6850(3)</td>
<td>1.378</td>
</tr>
<tr>
<td>275</td>
<td>0.6517(3)</td>
<td>0.6426(2)</td>
<td>1.6428(8)</td>
<td>92.13(3)</td>
<td>0.6875(3)</td>
<td>1.373</td>
</tr>
<tr>
<td>300</td>
<td>0.6519(3)</td>
<td>0.6432(2)</td>
<td>1.6459(8)</td>
<td>92.12(4)</td>
<td>0.6896(3)</td>
<td>1.369</td>
</tr>
<tr>
<td>325</td>
<td>0.6524(3)</td>
<td>0.6439(2)</td>
<td>1.6499(7)</td>
<td>92.07(3)</td>
<td>0.6926(4)</td>
<td>1.363</td>
</tr>
<tr>
<td>350</td>
<td>0.6529(4)</td>
<td>0.6443(3)</td>
<td>1.6570(11)</td>
<td>92.02(5)</td>
<td>0.6966(4)</td>
<td>1.355</td>
</tr>
<tr>
<td>375</td>
<td>0.6529(5)</td>
<td>0.6453(4)</td>
<td>1.6605(15)</td>
<td>92.04(6)</td>
<td>0.6992(6)</td>
<td>1.350</td>
</tr>
<tr>
<td>α·10⁵ (K⁻¹)</td>
<td>2.57</td>
<td>3.09</td>
<td>7.80</td>
<td>-0.70</td>
<td>13.50</td>
<td></td>
</tr>
</tbody>
</table>

Fig. 1. X-ray of piracetam
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2.2. Apparatus and measurement technique

To study the thermal expansion of piracetam in the temperature range from 150 to 375 K, a powder diffractometer XRD-6000 Shimadzu (CuKα radiation, reflection photography θ-2θ) with a scanning step of 0.02° in the range from 5 to 60° and a low temperature attachment TTK-450 Anton Paar were used. The result of the experiment is a series of radiographs obtained at certain temperatures with scanning step 25 K (increments). X-ray diffraction was performed using the XRAY software [11].

The quantitative characteristic of thermal expansion is the coefficient of thermal expansion, calculated as follows:

\[ \alpha_a = \left( \frac{1}{a} \right) \cdot \left( \frac{d}{dT} \right), \]

\( a \) is the unit cell parameter, \( T \) is the temperature.

Fig. 2. Temperature dependences of the unit cell parameters
Fig. 3. 2D figures of thermal expansion of piracetam
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3. Results and discussion

The unit cell parameters and the coefficients of thermal expansion of the investigated sample of piracetam are presented in the table. The temperature dependence of the unit cell parameters is shown in Fig. 2. The dependencies are described by the following polynomials:

\[
\begin{align*}
\alpha &= 1.6751515 \cdot 10^{-4} \cdot T + 6.468727273 \ (150 \leq T \leq 375 \, \text{K}) \\
\beta &= 1.9854545 \cdot 10^{-4} \cdot T + 6.37398181818 \ (150 \leq T \leq 375 \, \text{K}) \\
\gamma &= 12.8242424 \cdot 10^{-4} \cdot T + 16.09776363636 \ (150 \leq T \leq 375 \, \text{K}) \\
\delta &= -6.4319297 \cdot 10^{-4} \cdot T + 92.28658585455 \ (150 \leq T \leq 375 \, \text{K}) \\
V &= 9.28 \cdot 10^{-2} \cdot T + 662.98 \ (150 \leq T \leq 375 \, \text{K}).
\end{align*}
\]

The behavior of the parameters of a unit cell with increasing temperature corresponds to the most characteristic behavior of monoclinic elementary cells. Thermal expansion of piracetam is anisotropic, and its coefficient of thermal expansion depends on temperature. The anisotropy of thermal expansion is demonstrated most clearly by the 2D and 3D figures of thermal expansion shown in Fig. 3 and 4.

It was discovered that the crystal structure of the piracetam expanded along all three crystallographic axes, but the greatest thermal deformation was observed for the crystallographic axis c. In addition, as the temperature is raised, a decrease in the monoclinic angle is observed, which is characteristic of crystals with a monoclinic syngony.

Temperature dependence of the crystal density was calculated using the temperature dependence of the volume of a unit cell of piracetam. The density of pyracetam (\( \rho = 1.369 \, \text{g/cm}^3 \)) was previously estimated in [2], our results agree well with this value.

4. Conclusion

The overall aim of this work was to study a piracetam sample at low temperatures using powder X-ray diffraction for the presence or absence of low-temperature phase transitions, and to study the thermal expansion of this compound and the calculation of its coefficients.

Acknowledgements

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References


