

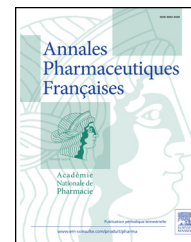


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ORIGINAL ARTICLE

The topological pressure-temperature phase diagram and crystal structures of the dimorphic system spiperone



Diagramme de phase topologique pression-température et structures cristallines du système dimorphe spipéron

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KEYWORDS

Crystal structure;
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Polymorphism;
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Summary The topological pressure-temperature phase diagram for the dimorphism of spiperone, a potent neuroleptic drug, has been constructed using literature data and improved crystal structures obtained with new crystallographic data from single-crystal X-ray diffraction at various temperatures. It is inferred that form II, which is the more dense form and exhibits the lower melting temperature, becomes the more stable phase under pressure. Under ambient conditions, form I is more stable.

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MOTS CLÉS

Structure cristalline ;
Comportement de
phase ;
Stabilité physique ;
Thermodynamique ;
Polymorphisme ;
Dilatation thermique

Résumé Le diagramme de phase topologique pression-température du dimorphisme de spiperone, un puissant neuroleptique, a été construit en utilisant des données de la littérature et de nouvelles données cristallographiques obtenues par diffraction des rayons X par un monocristal à différentes températures. Il est déduit que la forme II, qui est la plus dense et qui possède la température de fusion la moins élevée, devient la forme stable sous pression. Sous conditions ambiantes, la forme I est plus stable.

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Introduction**Literature data**

Spiperone, also known as spiroperidol, has been presented as one of the most potent neuroleptics [1]. Its chemical formula has been provided in Fig. 1. It belongs to the butyrophenone chemical class and it has been proposed for the treatment of schizophrenia [1].

The first crystal structure of the polymorphic system was determined in 1973 by Koch who found a monoclinic unit cell [1]. This structure has later been called form II [2]. Ten years later, another polymorph was found to crystallize in a different monoclinic unit cell [2]. The crystal data for the two polymorphs have been compiled in Table 1. The dimorphism was explained in terms of different conformations of the fluorophenyl-oxobutyl side chain by Azibi et al. (shown in

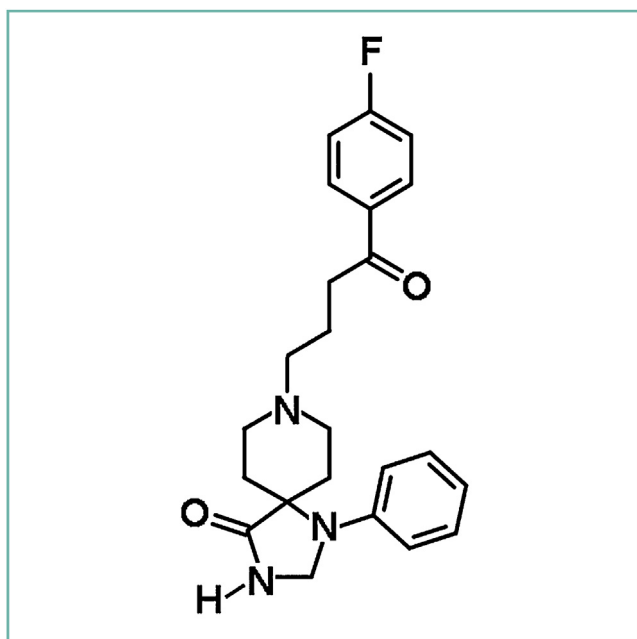


Figure 1. Chemical formula of spiperone, 8-[4-(4-fluorophenyl)-4-oxobutyl]-1-phenyl-1,3,8-triazaspiro[4.5]decan-4-one, $C_{23}H_{26}N_3O_2F$, $M = 395.47 \text{ g mol}^{-1}$.
Formule chimique de la spiperone, 8-[4-(4-fluorophenyl)-4-oxobutyl]-1-phenyl-1,3,8-triazaspiro[4,5]decan-4-one, $C_{23}H_{26}N_3O_2F$, $M = 395.47 \text{ g mol}^{-1}$.

Fig. 2) [2] with conformational versatility a widely accepted cause of molecular crystalline polymorphism [3]. In addition to the crystallographic information, Azibi et al. have also determined the temperatures and heats of fusion of the two crystalline forms by differential scanning calorimetry at a rate of 5 K min^{-1} (Table 1) [2].

In the present work, the phase relationships between the two solid forms and the other phases will be determined as a function of pressure and temperature by constructing the topological pressure-temperature phase diagram. Bakhuis-Roozeboom has formerly described the four possible types of phase diagram for a dimorphic system [4] and in the first part of the paper, the literature data in Table 1 will be used to determine to which case the phase diagram of spiperone belongs.

It has to be understood however, that the two structures have been obtained 10 years apart on different diffractometers. This will certainly have an influence on the accuracy of the difference in the specific volume between the two phases. Therefore, in the second part of the paper, new X-ray scattering data as a function of temperature will be presented of both forms measured on the same

Table 1 Crystallographic^a and calorimetric data from the literature for forms I and II of spiperone.
Données cristallographiques^a et calorimétriques pour les formes I et II de la spiperone, d'après la littérature.

	Form I [2]	Form II [1]
System	Monoclinic	Monoclinic
Space group	$P2_1/a$	$P2_1/c$
$a/\text{Å}$	12.722	18.571
$b/\text{Å}$	7.510	6.072
$c/\text{Å}$	21.910	20.681
$\beta/^\circ$	95.08	118.69
Z	4	4
$V_{\text{cell}}/\text{Å}^3$	2085.11	2045.75
$D_{\text{cal}}/\text{g cm}^{-3}$	1.260	1.284
$v/\text{cm}^3 \text{ g}^{-1}$	0.7938	0.7788
T_{fus}/K	482.9	480.1
$\Delta_{\text{fus}}H/\text{J g}^{-1}$	132.25	130.98

^a Both structures have been determined at room temperature (298 K).

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