Journal of Thermal Analysis, Vol. 45 (1995) 1277-1284

SOLID-STATE STUDIES ON CRYSTALLINE AND GLASSY FLUTAMIDE
Thermodynamic evidence for dimorphism

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(Received September 30, 1994; in revised form January 2, 1995)

Abstract

Flutamide usually crystallizes in the orthorhombic non-centrosymmetric space group $Pna2_1$ (form I) and melts at $T_{fus}=384$ K with $\Delta_{fus}H=30$ kJ·mol^{-1}. It may be obtained in the glassy state ($T_g=272$ K) by quenching the melt. Although evidence of polymorphism could not be obtained by means of crystallography, DSC studies of the recrystallization process indicate that a metastable form (form II) occurs first and is transformed into the stable form at room temperature. ΔH for the transition I→II (2.52 kJ·mol^{-1}) is close to the difference in energy (about 2 kJ·mol^{-1}) calculated for the two possible conformers of flutamide.

Keywords: crystallography, DSC, flutamide, polymorphism

Introduction

Flutamide, 2-methyl-N[4-nitro-3-(trifluoromethyl)phenyl]propanamide, $C_{11}H_{11}F_3N_2O_3$, $M=276.22$, is a non-steroidal androgen with an effect in prostatic cancer [1].

Flutamide has been shown to crystallize in the orthorhombic non-centrosymmetric space group $Pna2_1$ [2] and the main feature of the molecular packing consists of a helicoidal network of bifurcated hydrogen-bonds C–H...O. We have also evaluated the abilities of AM1 [3] and PM3 [4] Hamiltonians to reproduce the crystalline features of flutamide. Both Hamiltonians point to two

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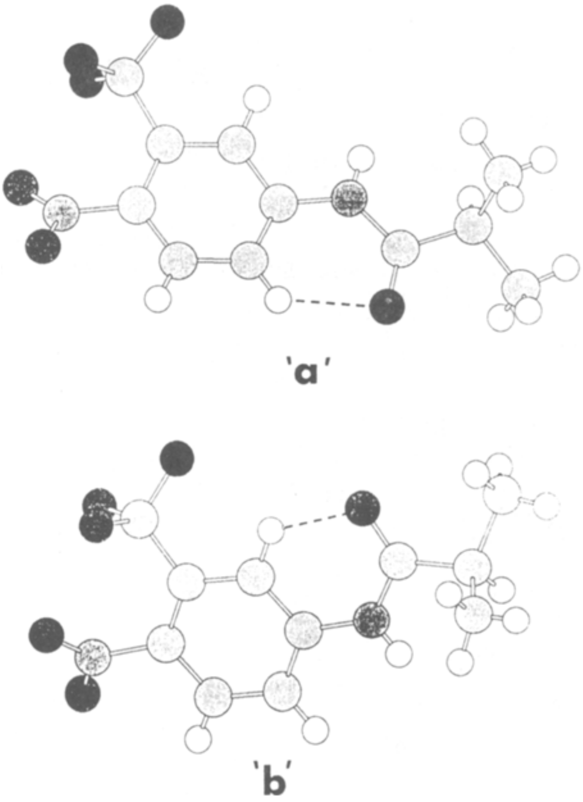

Fig. 1 Flutamide conformers: 'a' = lower-energy conformer, as found in the crystal structure [2], 'b' = higher energy conformer. Intramolecular hydrogen-bonds are denoted by dotted lines

possible conformers: a low-energy conformer 'a' and a second one 'b' (Fig. 1), higher in energy by 2.93 kJ·mol^{-1} (AM1) or 0.84 kJ·mol^{-1} (PM3).

With regard to the low value of this difference, the occurrence of polymorphism is likely.

Since conformational changes may induce polymorphism [5], which is involved in bioavailability and other pharmaceutical properties [6], we have studied flutamide powders resulting from various treatments of the starting material: crystallization from solution, compression and rapid cooling of the melt.

Radiocrystallographic results

As a criterion of characterization, the calculated X-ray powder diffraction profile (Fig. 2) was drawn with the computer program LAZY^{TM}, using the

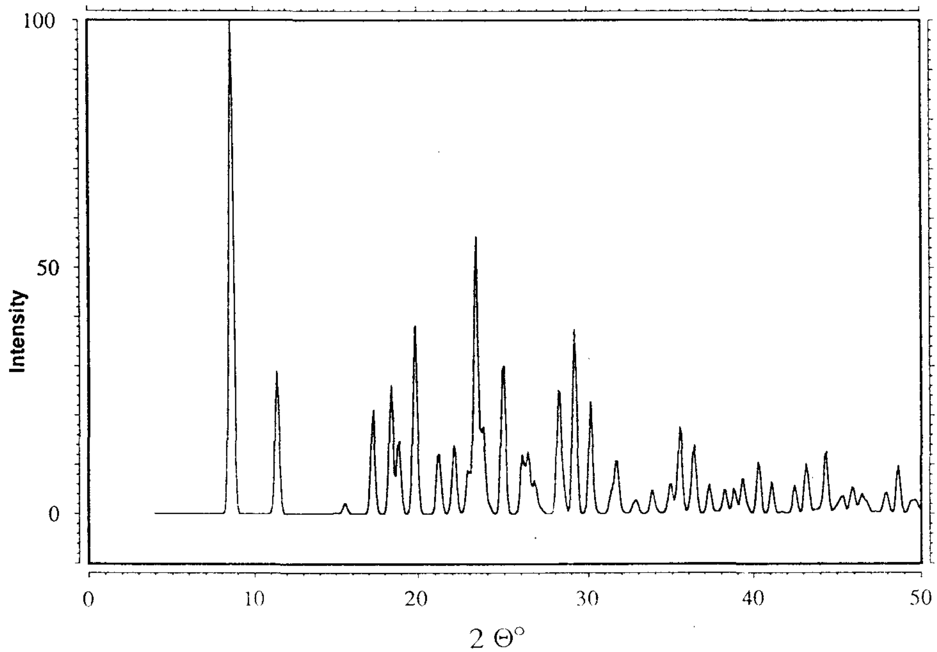

Fig. 2 Calculated X-ray powder diffraction profile for orthorhombic flutamide (a=11.856 Å, b=20.476 Å, c=4.958 Å, λ CuKα1=1.5405 Å). The Miller indices are reported in Table 1

atomic coordinates of the molecule in the orthorhombic unit cell of the known crystal structure [2].

The flutamide sample used agrees with this ideal profile because no unindexed reflection was found in its X-ray diffraction spectrum (Table 1).

Crystals were obtained by the slow evaporation at room temperature of saturated solutions in the following solvents: water, ethanol, acetone, benzene, chloroform, diethyl ether, ethyl acetate and polyethylene glycol.

The resulting crystalline batches exhibited the same X-ray diffraction spectrum as that of the starting material.

Such a spectrum was also found for a sample subjected for a few minutes to a constraint of about 10 kg·cm^{-2}.

The conclusion was drawn that no polymorphism could be revealed by these procedures.

However, on the assumption that a metastable form may occur first when, according to Tammann's hypothesis, a glass recrystallizes, thermodynamic experiments were performed by means of DSC.

Table 1 X-ray powder diffraction pattern for orthorombic flutamide

2Θ	d_{obs}	d_{cal}	I_{obs}	I_{cal}	hkl
8.61		10.26		23	110
8.63	10.21	10.24	vvS	100	020
11.41	7.76	7.749	m	35	120
14.93	5.94	5.928	w	<1	200
15.55	5.70	5.694	w	3	210
17.27	5.136	5.130	S	24	220
18.40	4.818	4.819	m	7	011
18.87	4.704	4.700	S	19	140
19.82		4.476		19	230
19.87	4.469	4.464	vS	32	111
21.26	4.178	4.176	mw	16	121
22.14	4.014	4.011	mw	18	031
22.90		3.880		1	310
22.93	3.880	3.874	w	10	240
23.37	3.806	3.803	vS	49	201
23.39		3.800		20	131
23.87	3.743	3.739	S	21	211
24.95	3.566	3.565	S	39	221
26.09	3.411	3.413	mw	13	060
26.43	3.373	3.369	mw	15	250
26.81	3.324	3.322	w	8	231
28.24	3.162	3.157	m	31	051
28.51	3.135	3.128	w	8	340
29.20	3.056	3.056	S	28	311
29.23		3.053		9	241
29.25		3.051		9	151
30.18	2.962	2.958	m	26	321
31.39	2.846	2.847	w	2	420
31.76	2.816	2.815	mw	13	331
32.92	2.724	2.719	vw	3	430
33.85	–	2.646	–	6	341
34.95	2.569	2.565	w	7	440
35.53	2.527	2.525	m	17	411
36.36		2.468		3	421
36.39	2.469	2.467	mw	6	351
36.43	2.460	2.464	w	6	171

Table 1 Continued

2Θ	d_{obs}	d_{cal}	I_{obs}	I_{cal}	*hkl*
37.28	2.412	2.410	w	5	112
37.29		2.409		2	022
38.27	2.354	2.350	w	5	280
38.80	2.316	2.319	w	5	271
39.30	2.291	2.291	w	3	361
40.33	2.236	2.234	mw	9	190
41.13	2.194	2.193	w	8	142
42.45		2.218		2	511
42.52	2.125	2.124	w	2	371
42.52		2.124		1	290
42.54		2.123	w	2	281

Θ(°), Bragg angle; d_{obs} (Å), interplanar distances measured from spectra on films obtained with an Enraf-Nonius FR552 camera (λCuKα1 = 1.5405 Å, 50 kV, 20 mA); d_{cal} (Å), interplanar distances calculated from unit-cell parameters a=11.856, b=20.476 and c=4.958 Å; I_{obs}, observed intensity, visually estimed (vw=very weak, w=weak, m=medium, S=strong); I_{cal}, calculated intensity in arbituary units (I(020)=100); *hkl*, Miller indices.

Thermodynamic results

The crystalline powders obtained as described above exhibited the same thermal behaviour (Fig. 3). On cooling from 298 K down to 200 K, no thermal effect was observed that would have indicated the transition into a low-temperature stable form. On heating from 200 K up to 400 K at 10 deg·min^{-1}, melting of the orthorhombic species was observed at 384 K (onset temperature) (curve A, Fig. 3) with an enthalpy of fusion $\Delta_{fus}H$= +30(1) kJ·mol^{-1} (average value from 14 runs) and an entropy of fusion $\Delta_{fus}S$= +0.31 kJ·mol^{-1}·deg^{-1}.

When the melt was cooled from 400 K down to 200 K at –20 deg·min^{-1}, no recrystallization was observed. On heating again (curve B, Fig. 3), a glass transition was recorded (Fig. 3, insert B1) in the range 268–276 K (midpoint 272 K), with a specific heat increment, ΔC_p, of about 11 kJ·mol^{-1}·deg^{-1}. This was followed by recrystallization of the metastable liquid at 312 K (onset temperature). It can be observed (Fig. 3, insert B2) that the recrystallization process occurs in two steps: a rapid one (sharp exothermal effect) and a slow one, which is complete at 357 K. By summation between 304 and 357 K, the enthalpy of crystallization, $\Delta_{cryst}H$, was found to be –27 kJ·mol^{-1}.

The difference between the enthalpy of crystallization and the enthalpy of fusion yields a value of 39 J·mol^{-1}·deg^{-1} for the average specific heat (C_p) of crystalline flutamide in the range 320–384 K.

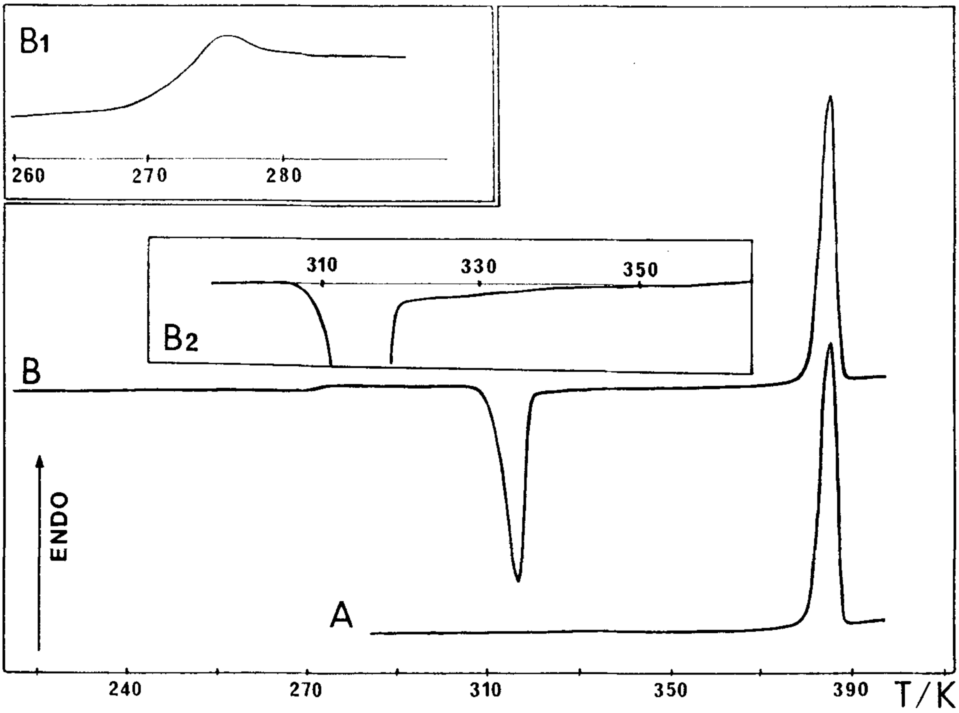

Fig. 3 DSC curves for A) crystalline flutamide, B) glassy flutamide (B1: glass transition, B2: recrystallization). Heating rate: 10 deg·min^{-1}, sample mass: 7.59(2) mg, Perkin Elmer DSC-2C differential scanning calorimeter equipped with TADS-3600 data station

Discussion

To check whether the process of recrystallization of glassy flutamide is due to polymorphism, we attempted to separate the two exothermal effects.

When a 14.17 mg sample of glassy flutamide was heated at 2.5 deg·min^{-1}, curve A in Fig. 4 was recorded. This indicates unambiguously that a second effect (area abc) takes place. It corresponds to an enthalpy of about −2.52 kJ·mol^{-1}. The same glassy sample was heated again at the same rate up to ~318 K, the temperature of point 'b', and quenched at 270 K. On heating back, the main recrystallization peak was not observed. The only peak to be recorded (area a'b'c' in Fig. 4B) corresponds to the slow exothermal effect, but the corresponding enthalpy, −1.25 kJ·mol^{-1}, is half that previously measured.

This difference may be explained as follows: both effects occur at about the same temperature and the second effect is about twice as slow as the first one is, as can be seen in Fig. 4.

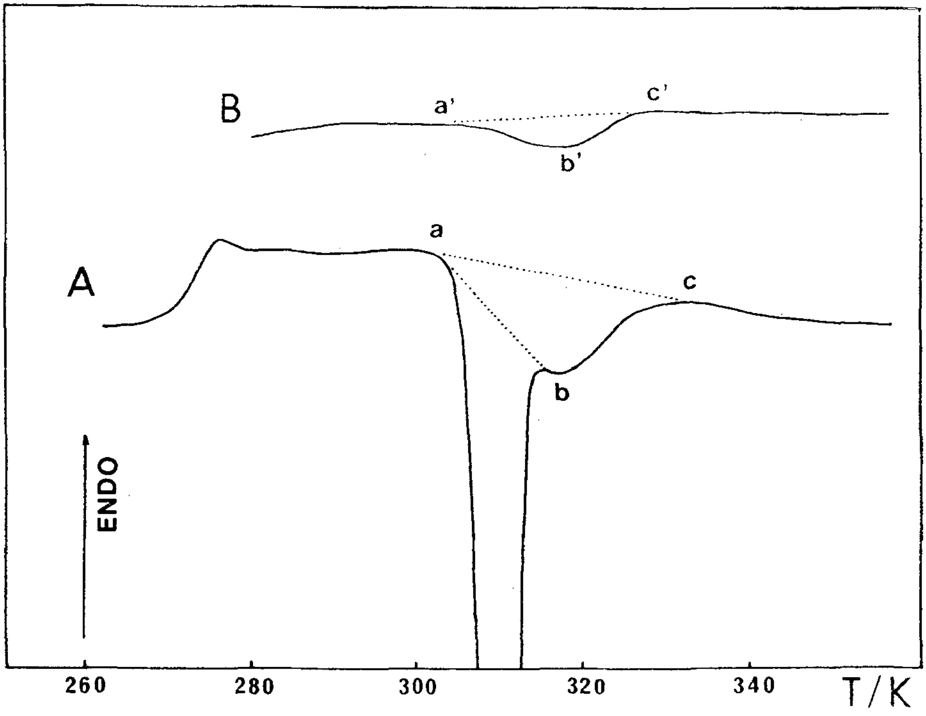

Fig. 4 DSC curves exhibiting the two thermal effects of the recrystallization process. Heating rate: 2.5 deg·min^{-1}, sample mass: 14.17(4) mg. A: On heating the glassy phase, B: after heating up to point b and cooling down to 270 K, only the second thermal event (a'b'c') is observed

These results may be understood through the existence of a new modification, form II, which crystallizes from the metastable liquid and transforms, as soon as it is formed at room temperature, into the usual stable orthorhombic modification, form I.

The enthalpy of the transition II → I (–2.52 kJ·mol^{-1}) is close to the energy difference calculated for conformers 'a' and 'b' (0.84 or 2.93 kJ·mol^{-1}). Therefore, glass formation could be related to the presence in the molten state of embryos of the less stable conformer 'b', for which we have shown [2] that steric hindrance due to CF_3 groups prevents it from long-range ordering by means of bifurcated intermolecular hydrogen-bonds C–H...O.

Conclusions

The methods used to look for polymorphs resulted in thermodynamic evidence of a new modification of crystalline flutamide. However, form II has been shown to transform spontaneously into form I, much too quickly for X-ray diffraction experiments on form II to be possible.

The glass transition at T_g=272 K roughly conforms to the Tammann rule, according to which T_g/K=2/3 T_{fus}/K.

However, glass formation in the range 250–310 K seems to be a very common feature of hydrogen-bonded networks. For instance, glass transitions have been found for a number of such compounds in the same range: glucose (290 K [7], 311 K [8]), niflumic acid (303 K [8]), morniflumate (245 K [8]), stiripentol (253 K [10]), D-sorbitol (270 K [11]) and indomethacine (310 K [12]).

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Zusammenfassung — Flutamid kristallisiert in der rhombischen nicht-zentrosymmetrischen Raumgruppe Pna2_1 (Form I) und schmilzt bei T_{fus}=384 K mit $\Delta_{fus}H$=30 kJ/mol. Durch Abschrecken der Schmelze kann es im Glaszustand (T_g=272 K) erhalten werden. Obwohl kristallografisch kein Beweis für Polymorfismus erhalten werden konnte, zeigen DSC-Unter- suchungen des Rekristallisationsprozesses, daß zuerst eine metastabile Form (Form II) vorkommt, die dann bei Raumtemperatur in die stabile Form übergeht. ΔH für den Übergang I →II liegt mit 2.52 kJ/mol nahe der für die beiden möglichen Konformere von Flutamid berechneten Energiedifferenz (etwa 2 kJ/mol).