Thermochimica Acta, 15 (1989) 37–45
Elsevier Science Publishers B.V., Amsterdam – Printed in The Netherlands

NIFLUMIC ACID–MORNIFLUMATE PHASE DIAGRAM: I. STUDY OF THE COMPONENTS

J.J. PINVIDIC, A. GONTHIER-VASSAL and H. SZWARC

Laboratoire de Chimie-Physique des Matérieux Amorphes (URA D 1104, CNRS), Université Paris-Sud, Bât. 490, 91405 Orsay (France)

R. CEOLIN

Laboratoire de Chimie Physique, Faculté de Pharmacie, 2 bis, Boulevard Tonnellé, 37042 Tours, Cedex (France)

P. TOFFOLI

Laboratoire Chimie Minérale, Faculté de Pharmacie, 5, rue J.B. Clément, 92296 Chatenay-Malabry, Cedex (France)

J.M. TEULON and C. GUECHOT

Laboratoire UPSA, 128, rue Danton, 92502 Rueil-Malmaison (France)

(Received 8 February 1989)

ABSTRACT

Niflumic acid and morniflumate have been studied using X-ray diffraction, DTA, DSC and TG techniques. Their solubilities in various solvents at 296 K have also been determined. Neither niflumic acid nor morniflumate significantly decompose at temperatures less than 476 K. They melt at 476 K ($\Delta_{\mathrm{fus}}H = 38$ kJ mol^{-1}) and 351 K ($\Delta_{\mathrm{fus}}H = 38$ kJ mol^{-1}) respectively. The heat capacities for the solid and liquid phases of both compounds have been determined in the 100–500 K range. The sublimation pressure for niflumic acid may be neglected. The two species easily form glasses. Only niflumic acid recrystallizes at 298 K. All these data will be used in a future study of the phase diagram of these compounds.

INTRODUCTION

Niflumates are a major series of non-steroidian anti-inflammatory analgesics that derive from 2-phenylaminonicotinic acid. Among them, niflumic acid * (INN) [1] and its β-morpholino ethyl-ester, morniflumate (INN) [2], are widely used in human therapeutics.

---

* 2-[3-(trifluoromethyl)-phenyl]amino-3-pyridinecarboxylic acid.

0040-6031/89/$03.50 © 1989 Elsevier Science Publishers B.V.

The corresponding binary phase diagram will be investigated in order to define the conditions of existence and formation of the intermediate compound obtained with a 2 : 1 molar ratio between niflumic acid and morniflumate. Before describing the niflumic acid–morniflumate phase diagram, some crystal, thermal and solubility studies on the two components will be presented.

TECHNICAL

The X-ray powder diffraction patterns were obtained with an Enraf–Nonius FR 552 Guinier camera (114.59 mm-diameter) using Cu $K\alpha_1$ radiation = 1.5405 Å (50 kV, 20 mA, 1 h).

The DTA curves and calorimetric measurements were obtained using FP 84 and FP 85 cells of a Mettler FP 800 thermal analyser connected to an Epson HX 20 computer, the DSC cell of a Du Pont 990 thermal analyser, and a Perkin–Elmer DSC 2C apparatus equipped with a thermal analysis data station TADS-3600. The DSC capsules were filled under a nitrogen atmosphere inside a glove box. The C_p calculations were performed by means of an IBM-PC computer.

The microbalance of a Du Pont 990 thermal analyser was used for the TG and the samples were weighed with 0.01-mg sensitive microbalances.

CRYSTAL DATA

The crystal structures of the compounds have been determined by Krishna Murthy and Vijayan [3] for niflumic acid and by Toffoli et al. [4] for morniflumate. Table 1 summarizes the information on the unit cells.

X-ray diffraction powder patterns are given in Table 2; they may be used to identify these compounds because, in both cases, the experimental d values are in good agreement with the distances calculated using the unit cell parameters.

DTA AND TGA STUDIES

Niflumic acid

When an airtight sealed capsule containing niflumic acid is heated, the corresponding DTA curve (Fig. 1, curve A) exhibits only a melting endothermic peak which begins at 476 K (FP 85 Mettler, heating rate: 10 K min^{-1}).

TABLE 1

Unit cell data for niflumic acid [3] and morniflumate [4] crystals

	Niflumic acid $C_{13}H_9F_3N_2O_2$ (M.W. = 282.2)	Morniflumate $C_{19}H_{20}F_3N_3O_3$ (M.W. = 395.4)
Space group	Monoclinic $P2_1/n$	Triclinic $P\bar{1}$
a (Å)	5.111	10.123
b (Å)	15.330	9.157
c (Å)	15.479	11.707
α (deg)	90.0	114.04
β (deg)	95.5	100.55
γ (deg)	90.0	102.01
V (Å^3)	1207.2	924.7
Z	4	2
D_M	1.51	
D (mg m^{-3})	1.552	1.420

DSC measurements using the Perkin–Elmer DSC 2C apparatus gave a value for T_{fus} of 475.4 ± 0.6 K (zero-heating rate extrapolation; mean value of 5 determinations). When the sample is slowly cooled back to room temperature, a recrystallization exotherm is observed.

If such a sample is stored for 10 days at 298 K and then heated again, the ensuing thermogram shows an exothermic peak at 425 K (Fig. 1, curve B), which may be assigned to recrystallization of some liquid that remained after the previous cooling process.

Further studies using the DSC 2C apparatus are illustrated in curves A and B of Fig. 2, which show the thermograms obtained when heating rapidly quenched liquid samples (-320 K min^{-1}) without (curve A) and with

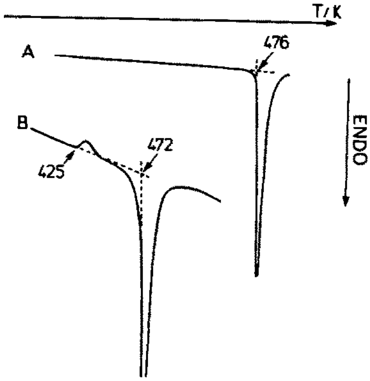

Fig. 1. Niflumic acid, DTA curves by means of Mettler FP800 T.A.: curve A, first heating at 10 K min^{-1} (full scale sensitivity $S = 100$ mV); curve B, second heating ($S = 50$ mV) after storage for 10 days at 298 K.

TABLE 2

X-ray powder diffraction data for niflumic acid and morniflumate. Intensities are estimated visually and expressed using the following symbols: w = weak, s = strong, m = medium, v = very

Niflumic acid				Morniflumate			
d_{obs} (Å)	I	d_{calc} (Å)	*hkl*	d_{obs} (Å)	I	d_{calc} (Å)	*hkl*
11.0	w	10.9	011	10.3	ms	10.2	001
7.80	vw	7.70	002	9.5	m	9.45	100
6.95	ms	6.88	012	7.98	w	7.94	010
5.48	w	5.43	022	6.63	w	6.58	$1\bar{1}0$
4.86	m	4.87 4.85	013 031	6.10	s	6.08 6.04	101 $\bar{1}\bar{1}1$
4.77	w	4.83	110	5.67	w	5.64	$0\bar{1}2$
4.73	w	4.73	$\bar{1}11$	5.50	s	5.46	$\bar{1}11$
4.29	w	4.27 4.265	$\bar{1}12$ 023	5.21	w	5.20 5.18	011 $\bar{1}02$
4.21	vs	4.24 4.17	120 $\bar{1}21$	5.12	w	5.10 5.09	002 $\bar{1}\bar{1}2$
3.96	vw	3.93	112	4.80	s	4.77	$\bar{2}10$
3.86	m	3.85	004	4.74	vw	4.72	200
3.765	w	3.735	014	4.65	w	4.63	$1\bar{1}2$
3.712	vw	3.719	041	4.48	ms	4.46	$0\bar{2}1$
3.623	w	3.622	033	4.38	ms	4.36	$\bar{2}11$
3.594	ms	3.594	122	4.23	m	4.22	$0\bar{2}2$
3.477	m	3.460	131	4.15	mw	4.15 4.14	$\bar{1}20$ $\bar{2}02$
3.379	w	3.368	113				
3.173	vw	3.154	$\bar{1}14$	3.98	vs	3.98 3.97	$\bar{2}\bar{1}1$ 020
3.081	ms	3.076	034				
				3.82	ms	3.81	$\bar{1}\bar{1}3$
				3.74	vs	3.734 3.727	$\bar{1}\bar{2}2$ $\bar{1}\bar{2}1$
				3.60	mw	3.599 3.592	012 210
				3.56	vw	3.557	$\bar{1}03$
				3.51	w	3.506	$0\bar{2}3$
				3.45	w	3.447	$\bar{1}21$
				3.32	s	3.321	$\bar{1}\bar{2}3$
				3.27	vw	3.263 3.262	$\bar{3}11$ $\bar{2}03$

(curve B) annealing at 301.5 K: a glass transition is clearly visible at $T_g = 303$ K (10 K min^{-1}) in both cases. Recrystallization follows at about 340 K and occurs in two steps.

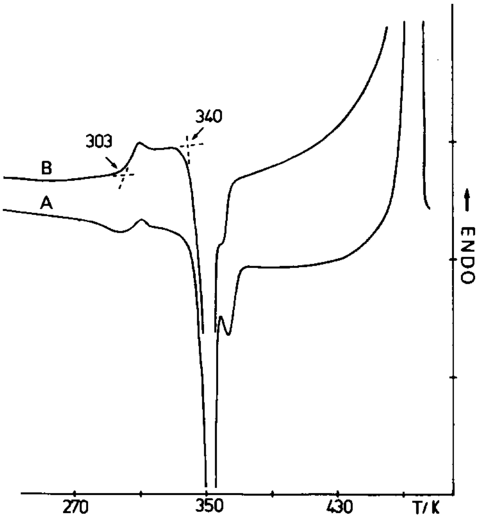

Fig. 2. Niflumic acid, DSC curves by means of Perkin–Elmer DSC 2C. Heating (10 K min^{-1}) of a rapidly quenched liquid sample (5.67 mg) without (curve A) and with (curve B) annealing at 301.5 K. Y-axis unit = 0.20 mW.

The C_p increment between the glass and the metastable liquid is about 0.2 J K^{-1} g^{-1} (56 J K^{-1} mol^{-1}). ΔH measurements show that crystallization is not complete as a $\Delta_{\text{fus}}H$ value of 114 J g^{-1} (32,2 kJ mol^{-1}) is found from

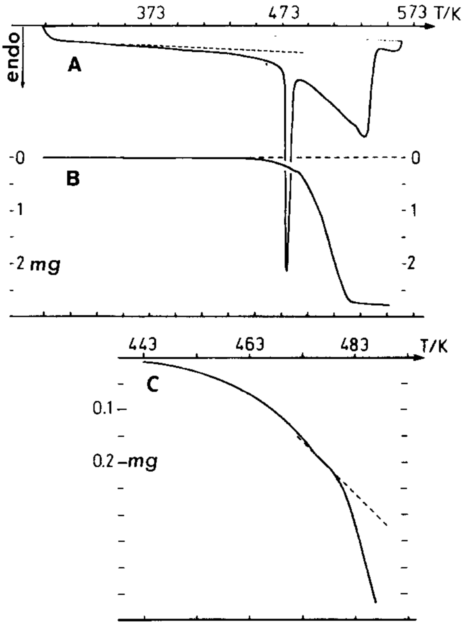

Fig. 3. Niflumic acid, DTA and TG curves by means of Du Pont 990 T.A. Heating (10 K min^{-1}) in open containers: curve A, DTA, 3.70 mg; curve B, TG, 2.75 mg; curve C, details of curve B with change in the slope of the curve at melting.

the melting endotherm that follows the recrystallization effect instead of a value of $\Delta_{\text{fus}}H = 130$ J g^{-1} (36.8 kJ mol^{-1}), which is derived from the melting peak of the crystalline sample. This could be related to some thermal decomposition of the product in the melt.

TG analysis with a sample in a closed container with a 0.2-mm diameter aperture shows a weight loss that is perceptible only from 483 K, i.e. after melting, and is completed by about 673 K.

DTA curves obtained from samples in open containers show (Fig. 3, curve A) results that differ from the preceding ones (see Fig. 1, curve A): from 373 K, an increasing endothermic departure from the base line is observed; it is still increasing after the melting, observed at 476 K.

TG performed with the same conditions shows (Fig. 3, curve B) that this endothermic departure has to be connected with some sublimation and, after melting, with the boiling of niflumic acid.

Consequently, the endotherm at 476 K has to be considered as corresponding to the solid + liquid + vapour triple point.

Curve C, Fig. 3, shows details of curve B, Fig. 3, near melting which is revealed by a change in the slope of the weight loss curve versus T. During melting, the weight loss rate is near 0.1 mg min^{-1} at 476 K, with a heating rate of 10 K min^{-1}.

Morniflumate

On heating a morniflumate sample in a closed container, DTA shows (Fig. 4, curve A) a shouldered melting endotherm that begins at 345 K (for a 10 K min^{-1} heating rate).

By using low heating rates (0.3 and 1 K min^{-1}), two separated endotherms can be observed (Fig. 4, curve C: an invariant-like weak one that begins at 343.4 K (0.3 K min^{-1}) or at 344.6 K (1 K min^{-1}) and a liquidus-like one, the maximum of which is at 348.8 K (0.3 K min^{-1}) or at 350.5 K (1 K min^{-1}).

When cooled at room temperature, the samples remain in the liquid state: no recrystallization occurs in two months. However, seeding with crystalline morniflumate induces a slow recrystallization that may also be started with water traces without observable hydrolysis. By rapidly quenching (-320 K min^{-1}) molten morniflumate, a glassy phase is obtained as indicated by a glass transition visible on curves A and B of Fig. 5.

By annealing the sample at 246 K, a subsequent enthalpic relaxation is observed around T_g (compare curves A and B, Fig. 5) but no recrystallization occurs.

The existence of two exotherms could suggest polymorphism. Thus, a sample was simultaneously studied by DTA and by visual observation under a microscope: a liquid phase appeared at 344 K and melting was complete at 350 K. This result shows that no allotropic modification is involved and

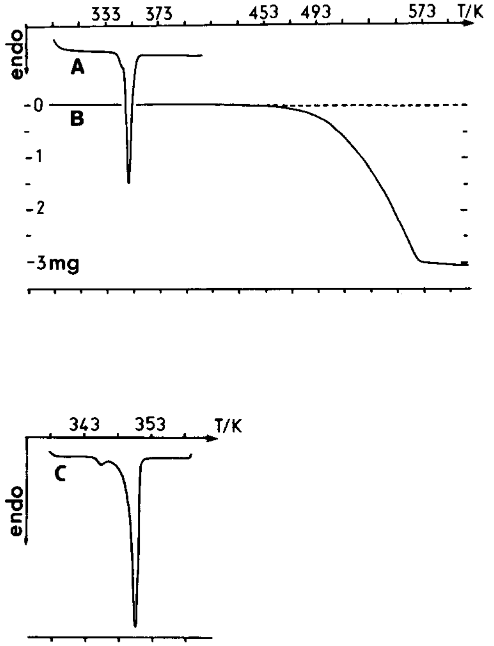

Fig. 4. Morniflumate, DTA and TG curves by means of Du Pont 990 T.A.: curve A, DTA at 10 K min^{-1}, sample (6.6 mg) in closed pan; curve B, TG at 10 K min^{-1} (3.33 mg); curve C, DTA at 1 K min^{-1} (5.3 mg).

means that the peak at 344 K corresponds to a (probably eutectic) invariant equilibrium and that the peak at 350 K is a liquidus-like one.

As the purity of morniflumate is better than 99.5%, the 344 K eutectic equilibrium may be considered as degenerated on the morniflumate. Therefore the melting temperature of this compound must not be measured at the onset of the 350 K peak. It probably lies between 349 and 352 K, which correspond to the temperatures of the maxima obtained with heating rates of 0.3 and 10 K min^{-1}, respectively.

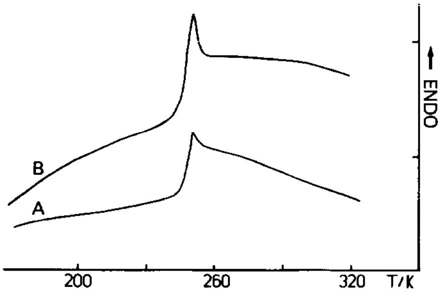

Fig. 5. Morniflumate, DSC curves by means of Perkin–Elmer DSC 2C. Heating (10 K min^{-1}) of the rapidly quenched liquid sample (5.67 mg) without (curve A) and with (curve B) annealing at 246 K. Y-axis unit = 0.75 mW.

TG measurements show that weight loss does not occur at temperatures less than 476 K (Fig. 4, curve B). This weight loss is not due to vaporization of morniflumate, but to its pyrolysis.

CALORIMETRIC MEASUREMENTS

Enthalpies of fusion

The melting enthalpies $\Delta_{fus}H$ for niflumic acid and morniflumate have been determined by DTA measurements with sample masses ranging from 10 to 18 mg and by DSC experiments with 1.3–4.0 mg samples.

The results are recorded in Table 3 where each value corresponds to the average of 5 determinations.

Specific heats

The C_p values were derived from DSC measurements for both compounds. Table 3 gives interpolated formulae for C_p in different temperature intervals: they have been determined as average mathematical expressions from 3 runs on one sample of each compound.

Furthermore, the C_p values obtained at 483 and 499 K for liquid niflumic acid are 598 and 655 J mol^{-1} respectively.

No peak was observed on heating crystalline samples from 110 or 140 K. Therefore, no low temperature polymorph of these compounds is observed.

TABLE 3

Melting enthalpies and specific heats for niflumic acid and morniflumate. The standard deviations for C_p values are always less than 12%

	DTA			DSC		
	T_{fus} (K)	$\Delta_{fus}H$ (kJ mol^{-1})	$\Delta_{fus}S$ (J K^{-1} mol^{-1})	T_{fus} (K)	$\Delta_{fus}H$ (kJ mol^{-1})	$\Delta_{fus}S$ (J K^{-1} mol^{-1})
Niflumic acid	476	38 ± 2	80	475 ± 0.6	36.8 ± 0.5	77
Morniflumate	352	38 ± 2	80	350 ± 0.6	34.5 ± 0.5	101

	T interval (K)	C_p (J K^{-1} mol^{-1})
Solid niflumic acid	140–465	$0.9\,T + 20$
Solid morniflumate	110–340	$1.2\,T + 83$
Liquid morniflumate	356–439	$1.4\,T + 142$

TABLE 4

Solubilities (mg ml^{-1}) of niflumic acid and morniflumate in various solvents at 296 ± 1 K

	Niflumic acid	Morniflumate
Methanol	58 ± 2	36 ± 2
Ethanol	30 ± 2	44 ± 2
Ethyl oxide	125 ± 5	40 ± 2
Acetone	> 400	95 ± 2
Chloroform	1.5 ± 0.05	
Water		< 0.5

SOLUBILITY MEASUREMENTS

The solubilities of both compounds in various solvents were measured at 296 ± 1 K.

A solvent was slowly added by 0.10-ml increments to a known quantity of product. The solution was observed under transverse light against a dark background. The final concentration at which solid traces were still visible and the first at which no trace remained were determined.

Solubility (in mg ml^{-1} solvent) was derived from the mean of the above two concentrations. Table 4 gives the solubilities of niflumic acid and morniflumate in various solvents.

CONCLUSION

Some physico-chemical data were determined for niflumic acid and morniflumate. These data will be used in a future study of their binary phase diagram. As no significant decomposition of these compounds has been observed at temperatures less than 476 K, the co-melt method may be used. Nevertheless, the possible formation of binary glasses will limit the validity of this method in some concentration ranges where precipitation from common solvents will have to be chosen as the method used.

REFERENCES

1 U.S. pat. 3,415,834.

2 U.S. pat. 3,708,481.

3 H.M. Krishna Murthy and M. Vijayan, Acta Crystallogr., Sect. B, 35 (1979) 262–263.

4 P. Toffoli, M. Coquillay, N. Rodier, R. Ceolin, J.M. Teulon and C. Guechot, Acta Crystallogr., Sect. C, 44 (1988) 547–550.