THE CRYSTAL POLYMORPHS OF METAZACHLOR
Identification and thermodynamic stability[*]

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Abstract

Five crystal polymorphs of the herbicide metazachlor (MTZC) were characterized by means of hot stage microscopy, differential scanning calorimetry, IR- and Raman spectroscopy as well as X-ray powder diffractometry. Modification (mod.) I, II and III° can be crystallized from solvents and the melt, respectively, whereas the unstable mod. IV and V crystallize exclusively from the super-cooled melt. Based on the results of thermal analysis and solvent mediated transformation studies, the thermodynamic relationships among the polymorphic phases of metazachlor were evaluated and displayed in a semi-schematic energy/temperature-diagram. At room temperature, mod. III° (T_{fus} =76°C, $\Delta_{fus}H_{III}$ =26.6 kJ mol^{-1}) is the thermodynamically stable form, followed by mod. II (T_{fus} =80°C, $\Delta_{fus}H_{II}$ =23.0 kJ mol^{-1}) and mod. I (T_{fus} =83°C, $\Delta_{fus}H_{II}$ =19.7 kJ mol^{-1}). These forms are enantiotropically related showing thermodynamic transition points at ~55°C ($T_{trs,\ III/II}$), ~60°C ($T_{trs,\ III/I}$) and ~63°C ($T_{trs,\ II/I}$). Thus mod. I is the thermodynamically stable form above 63°C, mod. III° below 55°C and mod. II in a small window between these temperatures. Mod. IV (T_{fus} =72–74°C, $\Delta_{fus}H_{II}$ =18.7 kJ mol^{-1}) and mod. V (T_{fus} =65°C) are monotropically related to each other as well as to all other forms. The metastable mod. I and II show a high kinetic stability. They crystallize from solvents, and thus these forms can be present in commercial samples. Since metazachlor is used as an aqueous suspension, the use of the metastable forms is not advisable because of a potential transformation to mod. III°. This may result in problematic formulations, due to caking and aggregation.

Keywords: crystal polymorphism, herbicide, IR spectroscopy, metazachlor, Raman spectroscopy, solvent mediated transformation, thermal analysis, thermodynamics, X-ray powder diffraction

Introduction

Metazachlor (MTZC, 2-chloro-N-(2,6-dimethyl-phenyl)-N-(pyrazol-1-ylmethyl)--acetamide, Fig.1) is one of the most widely applied herbicides, selectively used against weeds in potato, rape, soybean and tobacco cultures. The compound was developed by BASF 1976 and belongs to the group of chloroacetanilide herbicides

[1, 2]. The substance is formulated and marketed as aqueous suspension (e.g. Butisan®) containing about 500 g MTZC per liter or a combination of MTZC and other herbicides such as quinmerac.
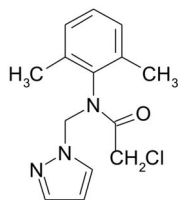

Fig. 1 Molecular structure of Metazachlor ($C_{14}H_{16}ClN_3O$, $M_r = 277.8$)

The scientific literature does not indicate the existence of crystal polymorphs of MTZC, whose melting point was specified as 81 and 82°C in the original patents [1, 3] respectively. The 'Pesticide Manual' [2] mentions a melting point of 85°C and suppliers of the substance (e.g. Riedel-de Haen AG, MTZC Pestanal®) state a melting point of 74–78°C. In 1990 BASF published a patent [4] claiming the preparation of stable MTZC suspensions by using 'monoclinic' form (named form IB), that exhibited a melting point of 76°C. The original form ('triclinic' or form IA) is said to form agglomerates in aqueous suspension formulations, which may cause a clogging of the spray-nozzles when the product is used in agriculture. However, to this date no clear data exist on the solid-state properties of this important herbicide.

The goal of this investigation was to prepare and comprehensively characterize the polymorphic forms of MTZC using a variety of analytical techniques. As the compound may be melted without decomposition, the application of thermal analytical methods was expected to be particularly successful for acquiring good thermochemical data of the solid phases. The structural aspects and the fingerprints of the polymorphic forms could be elaborated using vibrational spectroscopy and X-ray powder diffraction.

Materials and methods

Metazachlor was purchased from Riedel-de Haen/Germany (Batches 53250 and 35620 purity 99.0%). The products consist of mod. III°. The solvents used in this study were of analytical grade.

For thermomicroscopic investigations (HTM) a Reichert Thermovar® polarization microscope (Reichert, Vienna, A) equipped with a Kofler hot stage (Reichert, Vienna, A) was used. A Kofler Hot bench (Reichert, Vienna, A) was employed for the preparation of melt film samples (by fusing the substance between a glass slide and a cover slip).

Differential scanning calorimetry (DSC) was performed with a DSC 7 (PerkinElmer, Norwalk, Ct., USA) using the Pyris 2.0 software. Approximately 1 to 3 ± 0.0005 mg sample (using a UM3 ultramicrobalance, Mettler, Greifensee, CH) were weighed into Al-Pans (25 µL). Dry nitrogen was used as the purge gas (purge: 20 mL min^{-1}). The instrument was calibrated for temperature with pure benzophe-

none (*m.p.* 48.0°C) and caffeine (*m.p.* 236.2°C) and the energy calibration was performed with pure indium (purity 99.999%, *m.p.* 156.6°C, heat of fusion 28.45 J g^{-1}).

Fourier transform infrared (FTIR) spectra were recorded with a Bruker IFS 25 spectrometer (Bruker Analytische Messtechnik GmbH, Karlsruhe, D) in the spectral range from 4000 to 400 cm^{-1} with a resolution of 2 cm^{-1} (100 scans). The samples were prepared as KBr disks using approximately 1.2 mg MTZC per 275 mg KBr. FTIR spectra of the highly unstable mod. IV were recorded by preparing melt films between two ZnSe disks using the Bruker IR microscope I (Bruker Analytische Messtechnik GmbH, Karlsruhe, D), with 15× – Cassegrain-objektives (spectral range 4000 to 600 cm^{-1}, resolution 4 cm^{-1}, 100 interferograms per spectrum).

Raman spectra were recorded with a Bruker RFS 100 Raman-spectrometer (Bruker Analytische Messtechnik GmbH, Karlsruhe, D), equipped with a Nd:YAG Laser (1064 nm) as the excitation source and a liquid-nitrogen-cooled, high sensitivity Ge-detector. The spectra were recorded in aluminum sample holders with a laser power of 100 mW (64 scans per spectrum) and a resolution of 4 cm^{-1}.

The X-ray powder diffraction patterns (XRPD) were obtained with a Siemens D-5000 diffractometer (Bruker AXS, Karlsruhe, Germany) equipped with a theta/theta goniometer, a CuK_α radiation source, a Goebel mirror (Bruker AXS, Karlsruhe, Germany), a 0.15° soller slit collimator and a scintillation counter. The patterns were recorded at a tube voltage of 40 kV and a tube current of 35 mA, applying a scan rate of 0.005° 2θ s^{-1} in the angular range of 2 to 40° 2θ.

Solvent mediated transformation (SMT) experiments were carried out by suspending the solid in a solvent (mostly water) using a glass cylinder, a magnetic stirrer and a thermostated water bath. The suspension was stirred (900 *r.p.m*) at a constant temperature and at regular intervals a few milliliters of the suspension were withdrawn, filtered and the microcrystalline solid residue was investigated by XRPD and IR- or Raman spectroscopy.

True Densities were determined with an air-comparison pycnometer (Ultrapycnometer 1000, Quantachrome Corp., Syosset, NY) using a 5 cm^3 cell with a sample size of approx. 1 g (mass accuracy ±0.0005 g). The volume was calibrated with a calibration sphere (Quantachrome Corp.) and samples were purged for 15 min with helium before each volume determination. The reported densities are based on three to four multi-run determinations (6 runs respectively) of different masses.

Results and discussion

Our experimental work on MTZC suggests the existence of five polymorphs (modifications, abbr. mod.) which we have named according to the Kofler notation using Roman numerals in the order of the melting points (i.e. the highest melting form is named mod. I). Since we proved that mod. III is the thermodynamically stable form at room temperature, we flag this form with the symbol '°'. Table 1 summarizes the most important data of the forms which are discussed in detail below.

Table 1 Physicochemical data for metazachlor polymorphs. T_{fus} – melting point; T_{trs} – transition temperature; $\Delta_{fus}H$ – enthalpy of fusion; $\Delta_{fus}S$ – entropy of fusion; $\Delta_{trs}H$ – transition enthalpy; c.i. confidence interval (SMT – solution mediated transformation)

Modification	I	II	III°	IV	V
Designation in the literature [4]	–	IA triclinic	IB monoclinic	–	–
T_{fus}/°C					
TM	83	80	76	72–74	65
DSC (onset) ±95% c.i.	83.7±0.2	80.2±0.3	76.1±0.2	70.2±1.5	–
$\Delta_{fus}H$/kJ mol^{-1} ±95% c.i.	19.7±0.1	23.0±0.3	26.6±0.2	18.7±0.7	–
$\Delta_{fus}S$/J mol^{-1} K^{-1} ±95% c.i.	55.0±0.3	65.1±0.9	76.0±0.6	54.4±1.9	–
T_{trs}/°C	I/III°	II/I	III°/II		–
SMT-studies (exp.)	60–65	61–67	59±2		–
calculated^a/°C	58	63	55		–
$\Delta_{trs}H$/kJ mol^{-1}	–	3.3 (II→I)^b	3.6 (III°→II)^b		–
			6.9 (III°→I)^b		
			7.4 (III°→I, at 67°C)^c		
Order of thermodynamic stability at 25°C	c	b	a	d	–
density (exp.) [g cm^{-3}] at 25°C, ±95% c.i.	1.237±0.001		1.323±0.001		–
Selected IR-bands/cm^{-1}					–
ν =CH, –CH$_2$Cl	3131, 3104, 3024;	3135, 3122, 3068, 3022;	3127, 3070, 3043, 3018;	3135, 3121, 3067, 3026	
νCH$_3$, CH$_2$	2950, 2923;	2973, 2945;	2994, 2957;	2973, 2946;	
νC=O	1686	1696/86	1688	1693	

^{a}calculated according to equation 2 (k =0.005)
^{b}calculated from the enthalpy of fusion differences

Production and specification of the crystal forms

Modification I

Mod. I is the stable form at high temperatures and can be produced in gram quantities by a solvent mediated transformation of mod. III° or II in water at 66°C. The addition of some droplets of acetone accelerates this transformation. Mod. I forms pentagonal or hexagonal, tabular crystals that melt at 83°C. A few experiments showed that this form can also be crystallized from solvents such as ethanol, particularly when the solution is cooled slowly.

Modification II

This form can also be produced by a solvent mediated transformation of mod. III° or I (or a mixture of these forms) in water at a temperature of 61°C. The transformation occurs within 24 h when seeds of mod. II are added to the suspension. Preliminary crystallization experiments showed that this form can be crystallized from *n*-hexane, acetone, methanol and ethanol. The crystals of mod. II display a prismatic habit and melt at 80°C (HTM).

Modification III°

Mod.III° was present in the available commercial samples. Microscopy shows short prismatic crystals, about 40 μm in length. On heating the original crystals of mod. III, only the melting process can be observed between 74 and 76°C but no solid-solid transformation. When mod. III is seeded with mod. I, a solid-solid transformation to this form occurs about 70°C at slow heating rates (Fig. 2, insert). The equilibrium melting point was determined at 76°C, whereas the residual crystals grow to highly birefringent prisms on cooling.
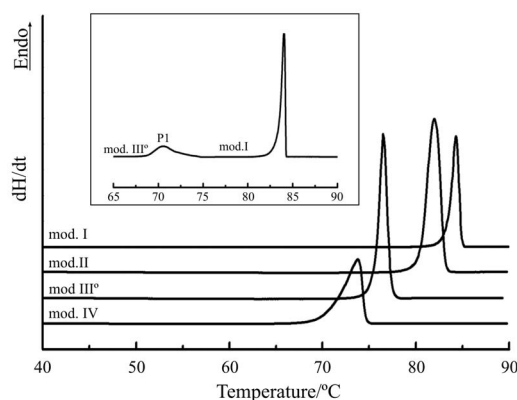

Fig. 2 DSC curves of metazachlor polymorphs (heating rate 5 K min^{-1}). The insert shows the heating curve (heating rate 0.5 K min^{-1}) of a sample of mod. III° that was seeded with mod. I

Modification IV and V

These polymorphs could only be produced from the melt on a microscopic scale (melt film preparation), preferentially below 10°C. They mostly crystallize simultaneously and easily transform to a more stable form at room temperature or on exposure to air (humidity induced transformation). This is the reason we did not succeed in getting the vibrational spectra or XRPD patterns of these two forms.

All forms can be crystallized from the melt in microscopic film preparations as described in the next section.

Hot stage microscopy of melt film preparations

The supercooled melt of MTZC (film preparation) crystallizes within 36 h (at 20°C) to mod. I, II and III°, and these can be differentiated by their appearance (under polarized light) as well as by their transformation and melting behavior. At temperatures between 4 and 10°C also mod. IV and V crystallize as microcrystalline aggregates (grainy appearance) with weak interference colors (grey, white) besides mod. I and II. When such a sample is warmed to room temperature, mod. IV transforms slowly to mod. III° whereas mod. V quickly transforms to mod. I. From the supercooled melt mod. I grows as spherulites but just below the melting point seeds of mod. I grow to well shaped five- or six-sided plates. Mod. II crystallizes to broad colorful rays with contraction fissures whereas mod. III° mostly arises by a solid–solid transformation via mod. II and I. The differentiation between mod. IV and V is only possible by their melting and transformation behavior. The melting point of the very unstable mod. V could only be observed by placing the preparation on the preheated hot stage close to its melting temperature (65°C). Since mod. IV shows a higher kinetic stability than mod. V, its melting point can easily be observed between 72 and 74°C when the freshly prepared samples are heated with high heating rates. The equilibrium melting points of all forms are listed in Table 1.

Differential scanning calorimetry

The melting endotherms and enthalpies of fusions of samples of mod. I, II and III° could be determined directly at heating rates of 5 K min^{-1} (Fig. 2). The determined thermochemical data are listed in Table 1. The enthalpies of fusion of mod. I, II and III° increase with decreasing melting point, which indicates an enantiotropic relationship between these forms. In contrast to the melt film preparations on glass slides, mod. IV could be obtained as a single phase in an aluminum sample pan. The DSC-curve (Fig. 2) shows one broad melting endotherm, whith an enthalpy value lower than that of the other forms. Because of the instability of mod. V, we were not able to obtain the corresponding data for this form.

When mod. III° is mixed with small amounts of mod. I and heated at a low rate (0.5 K min^{-1}) an endothermic transition to the high temperature form (mod. I) could be observed at 67°C with an enthalpy value of 7.4 kJ mol^{-1} (Fig. 2, insert, P1). However, mixtures (1:1) of the pairs mod. I/II and II/III did not show any transformations events on heating or cooling, which suggests a high kinetic stability of the metastable forms II and III.

FT-IR- and Raman-spectroscopy

The FT-IR spectra of mod. I, II and III° could be prepared and recorded as KBr-disks (Fig. 3). A low quality spectrum of Mod. IV (not shown) was obtained from a melt film preparation between two zinc selenide disks using the IR-microscope. Form V was too unstable to get an IR-spectrum in this way. Due to the clear differences, each form can be well identified and assigned by its IR-spectrum. The frequencies of some
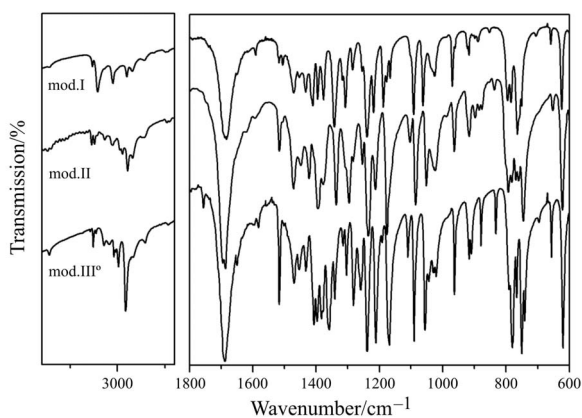
Fig. 3 FT-IR-spectra of metazachlor modifications I, II and III°

characteristic bands of the different forms are given in Table 1. As the MTZC molecule has no strong hydrogen bond donor, the differences in the solid-state IR-spectra can be attributed to weak interactions (e.g. C–H…N/O/Cl, π-π) and conformational differences. This becomes particularly evident by the distinct C–H stretching frequencies of the alkyl and the aromatic groups. The position of carbonyl band is also affected by the packing and conformational differences. The νC=O band of mod. II is clearly split, which could be an indication of two different conformations in the crystal structure of this form.

The FT-Raman-spectra of the modifications are also easy to distinguish (Fig. 4) over almost the entire spectral range. The C–H-stretching vibrations close to 3000 cm^{-1} again indicate the differences in the electronic environment of the alkyl-chains and the aromatic groups. Moreover the lattice phonon vibrations in the range between 50 and 200 cm^{-1} (Fig. 5) clearly display the different crystal lattice types of mod. I, II and III°.
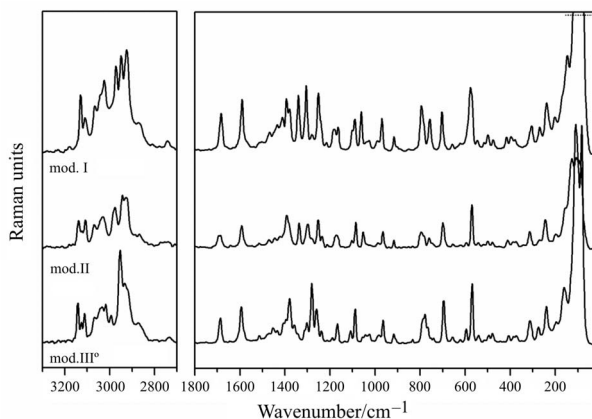

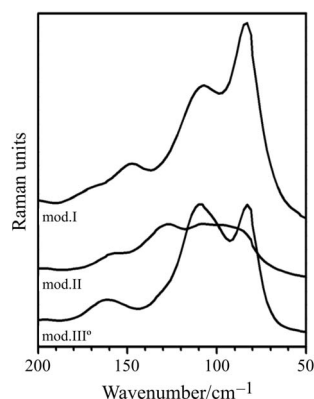**Fig. 4** FT-Raman-spectra of metazachlor modifications I, II and III°

Fig. 5 FT-Raman phonon-spectra of the metazachlor modifications I, II and III°

Powder X-ray diffractometry

X-ray powder patterns could only be obtained for mod. I, II and III° (Fig. 6). The forms can be easily discriminated by their diffraction patterns, particularly by the peaks between 6° and 15° 2Θ (mod. I: 8.77°, 10.95°, 11.30°, 13.64° 2Θ; mod. II: 8.14°, 8.43°, 13.44°, 14.49° 2Θ and mod. III°: 9.89°, 12.23°, 12.97°, 13.21° 2Θ).
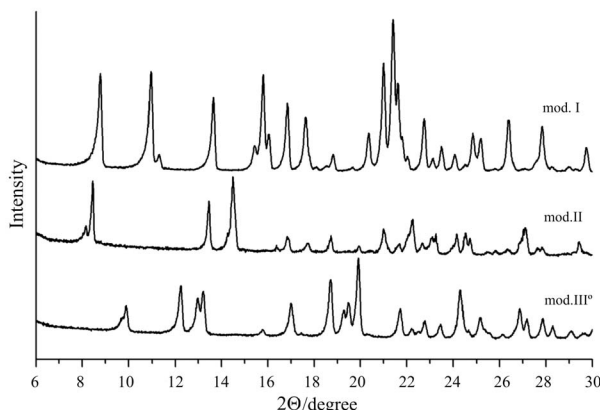

Fig. 6 X-ray powder diffraction patterns of the metazachlor modifications I, II and III°

Pycnometry

The true densities of mod. I and mod. III° were determined by helium pycnometry. The obtained values are 1.237 g cm^{-3}±0.001 and 1.323 g cm^{-3}±0.001 for mod. I and III°, respectively. The difference in relative density is 7%, which is very high for polymorphic pairs. However, it can be expected from the density rule [5, 6] that the thermodynamically stable polymorph (mod. III°) has the highest density. This rule should hold in particular for this molecule, since it contains no functional groups that are able to form

strong interactions. Here, close packing, i.e. a maximum of weak interactions, can be expected to determine the thermodynamic stability of the individual forms.

Thermodynamic and kinetic stability of the modifications

The existence of five polymorphic forms means that we have to deal with $(n–1)n/2=10$ ($n=5$) polymorphic pairs, which can be either enantiotropically or monotropically related. Since we were able to determine the melting points and enthalpies of fusion (Table 1) of mod. I, II, III°, and IV, we can apply the heat of fusion rule [5] to solve the thermodynamic relationship between these forms. Accordingly, mod.I (highest melting point) is enantiotropically related to mod. II and III because these forms melt at lower temperatures but have a higher enthalpy of fusion. Concerning the pair mod. I/III°, this relationship is also confirmed by the endothermic transition of mod. III° to mod. I at about 70°C in DSC-experiments (Fig. 2 and Table 1). According to the heat of transition rule [5] such an endothermic transition from a lower melting form to a higher melting form on heating provides an unambiguous proof of enantiotropism. Mod. II and III° must also be enantiotropically related as well, because mod. III° shows a lower melting point but a higher heat of fusion. In comparison, mod. IV must be monotropically related to mod. I, II and III°, as its melting point and enthalpy of fusion is lower. Due to the lack of data we cannot apply any of the thermodynamic rules to mod. V. However we can conclude from the extremely low kinetic stability that mod. V is the least stable form over the entire temperature range and thus monotropically related to all the other forms.

The measured thermochemical data allow us to construct a semi-schematic energy/temperature diagram (Fig. 7) according to Burger and Ramberger [5, 6], where the relative thermodynamic stabilities of the different forms can be visualized in the temperature range between 0 K and their melting points.

As discussed above, mod. I, II and III° are enantiotropically related, which means that there exist three transition points (intersection of the G-isobars in Fig. 7, marked with black spots). In the DSC experiments we could only determine the experimental transition temperature of mod. III° to mod. I at 70°C. Since solid–solid transitions are kinetically controlled, the true (thermodynamic) transition point must be lower than this temperature. Moreover, from the possible intersections in the semi-schematic energy/temperature diagram we can conclude that the transition points must increase in the order III°/II, III/I and II/I. In order to verify this and to determine the thermodynamic transition temperatures of these pairs more precisely, solution mediated transformation experiments [7] were performed. Mixtures of polymorphic pairs were suspended in the solvent and the suspensions were stirred at different temperatures. Table 2 summarizes the results of these experiments. Below 60°C all mixtures resulted in pure mod. III° whereas mod. II was obtained at 61°C and mod. I at temperatures of 65°C and higher. From these results and the thermoanalytical results we can unambiguously draw the conclusion that mod. III° is thermodynamically stable below 60°C, whereas mod. I is the stable form at temperatures above 63°C. However, in the small temperature window between 61 and 63°C,
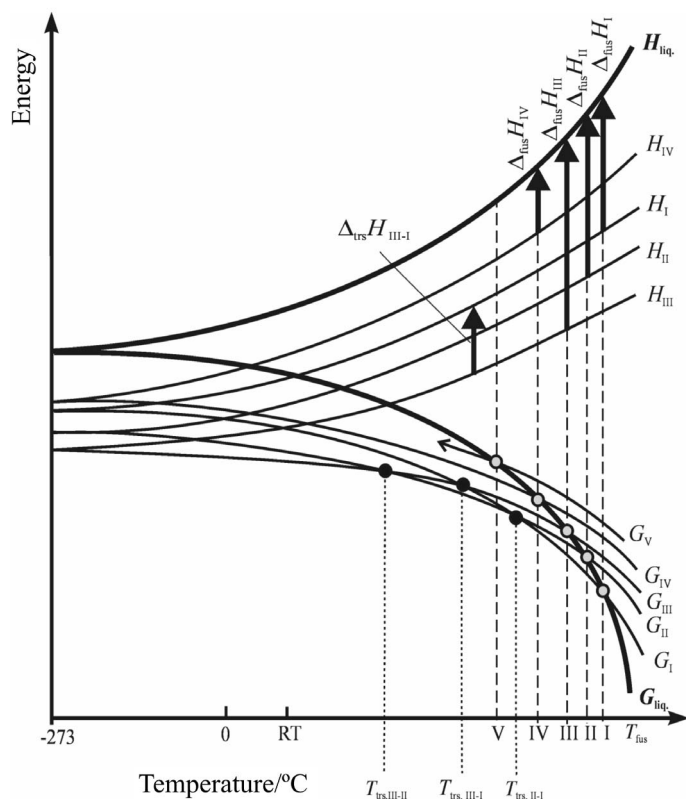
Fig. 7 Semi-schematic energy/temperature diagram of metazachlor polymorphs (I, II, III°, IV and V). T_{fus} – melting point, G – Gibbs free energy, H – enthalpy, ΔH_f – enthalpy of fusion, T_{trs} – transition point, $\Delta_{trs}H$ – transition enthalpy, liq – liquid phase (melt). The bold vertical arrows sign the experimentally measured enthalpies

Table 2 Conditions and results of the solution mediated transformation experiments of metazachlor modifications

Temperature/°C	Initial mixture of polymorphs (mod.)	Time/h	Resulting form/mod.
25	I/II/III°	72	III°
40	I/III°	18	III°
57	II/III°	24	III°
60	I/III°	15	III°
61	II/III°	48	II
65	I/III°	12	I
67	I/II	36	I

mod. II must be the stable form. By following the Gibbs free energy curve in Fig. 7, starting with mod. III° at 0 K and moving towards higher temperatures it becomes clear that the thermodynamically stable form (i.e. that with the lowest free energy) changes in the order III°, II, I.

We additionally calculated the transition points from the melting points and enthalpy of fusion by applying the following equation [8, 9],

$$T_{trs} = \frac{\Delta_{fus}H_2 - \Delta_{fus}H_1 + (C_{p,liq} - C_{p,1})(T_{fus,1} - T_{fus,2})}{\dfrac{\Delta_{fus}H_2}{T_{fus,2}} - \dfrac{\Delta_{fus}H_1}{T_{fus,1}} + (C_{p,liq} - C_{p,1})\ln\left(\dfrac{T_{fus,1}}{T_{fus,2}}\right)} \tag{1}$$

where T_{trs} is the thermodynamic transition point (K), T_{fus} the melting point (K), $\Delta_{fus}H$ the heat of fusion (kJ mol^{-1}) and C_p the heat capacity in J mol^{-1} K^{-1}. The indices 1 and 2 stand for the higher and lower melting form respectively. As the heat capacities of the melt ($C_{p,liq}$) and the higher melting form ($C_{p,1}$) are not known, the correction term $k\Delta_{fus}H_1$ was used for the expression $C_{p,liq} - C_{p,1}$ which then gives:

$$T_{trs} = \frac{\Delta_{fus}H_2 - \Delta_{fus}H_1 + k\,\Delta_{fus}H_1(T_{fus,1} - T_{fus,2})}{\dfrac{\Delta_{fus}H_2}{T_{fus,2}} - \dfrac{\Delta_{fus}H_1}{T_{fus,1}} + k\,\Delta_{fus}H_1\ln\left(\dfrac{T_{fus,1}}{T_{fus,2}}\right)} \tag{2}$$

A value of 0.005 was used for the factor k, which was empirically determined and allows a good approximation of the heat capacity differences in the majority of cases [10]. Using this equation we calculated values of 55, 58 and 63°C for the pairs II/III°, I/III° and I/II respectively, which matches very well with the experimentally determined transition temperature ranges (Tables 1 and 2).

Conclusions

Metazachlor represents a very interesting example of crystal polymorphism showing at least five different modifications. Two of these (mod. IV and V) are of no practical importance, since they are highly unstable. However, the kinetic stability of the metastable forms mod. II and I is very high and since these forms may also crystallize from solvents, commercially available metazachlor products may consist of either one of these forms or mod. III°. This is also the reason why the literature states different melting points. The data clearly show that mod. III°, II and I are enantiotropically related and that mod. I is the stable form above 63°C, mod. III° below 55°C and mod. II in a small window between these temperatures. These temperatures lie exactly in the range where crystallizations from solvents are performed and therefore, depending on the solvent and the crystallization conditions, any of these forms or mixtures may arise. Since the substance is formulated as an aqueous suspension, the presence and use of one of the metastable forms is risky, and may result in unemployable formulations because of caking and segregation when the stable form crystallizes at storage conditions.

Owing to the thermal stability of metazachlor, a clear characterization of the polymorphs and their thermodynamic stability is possible by applying mainly thermal analytical methods. From the molecular structure and the observed vibrational spectra we may assume that this system can be attributed to conformational polymorphism [11].

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