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SOLID-STATE CHARACTERIZATION OF CHLOROPROCAINE HYDROCHLORIDE
Part VI. Crystal polymorphism of local anaesthetic drugs

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Chloroprocaine hydrochloride (2-CPCHC) is a local anaesthetic agent of the ester type preferentially used for epidural anaesthesia. The compound, official in the USP, was found to exist in two polymorphic crystal forms which have been characterized by thermomicroscopy, differential scanning calorimetry (DSC), pycnometry, FTIR-, FT-Raman-spectroscopy as well as X-ray powder diffractometry. Based on these data the relative thermodynamic stability of the two forms was determined and is represented in a semi-schematic energy/temperature diagram.

Mod. I° is the thermodynamically stable form at room temperature. This form is present in commercial products and can be crystallized from ethanol. Mod. II can be obtained by annealing the supercooled melt in a temperature range between 100 and 130°C. Upon heating mod. II exhibits an exothermic phase transition ($\Delta_{trs}H_{II-I}$: –5.0±0.5 kJ mol^{-1}) at about 134°C to mod. I° (melting point 175°C, $\Delta_{fus}H_I$: 46.6±0.6 kJ mol^{-1}). The exothermic transformation of mod. II to mod. I° confirms that mod. I° is thermodynamically stable in the entire temperature range (heat of transition rule) whereas mod. II is monotropically related to mod. I°, i.e. is metastable at all temperatures below its melting point. Mod. II is of low kinetic stability at room temperature and the transformation to mod. I° starts within a few minutes at room temperature. The N–H band in the infrared spectrum of mod. I° (3433 cm^{-1}) lies at significantly higher wavenumbers than that of mod. II (3413 cm^{-1}) indicating differences in the hydrogen bonding arrangement. Furthermore, the measured density of mod. I° is lower than the density of mod. II and thus both, the IR- and the density-rule are violated in this polymorphic system.

Keywords: *chloroprocaine hydrochloride, crystal forms, crystal polymorphism, local anaesthetics, monotropism, solid-state properties, thermal analysis, thermodynamic rules*

Introduction

Local anaesthetic compounds (LA) commonly are separated in two main groups, the ester type LA like tetracaine with short duration of anaesthesia and the amide type LA like lidocaine with longer duration of action. A third small group unites compounds with different molecular structures and different pharmacological profiles.

All local anaesthetics of a general formula lip-CO-hydr (*lip*=lipophilic end, mostly phenyl ring; CO=negatively charged linkage, commonly ester or amide; *hydr*=hydrophilic group, tertiary or secondary amine) are well known for the formation of polymorphs and solvates [1, 2]. The hydrophilic group is responsible for the receptor binding whereas the lipophilic and the linking group affect the duration of action [3].

The present paper deals with the solid-state characterization of chloroprocaine hydrochloride (2-CPCHC), a local anaesthetic drug of the ester type (Fig. 1), used routinely in clinical practice like tetracaine. 2-CPCHC is official in the United States Pharmacopoeia (USP) and in Canada as a local anaesthetic with a rapid onset, high efficacy, rapid metabolism and short half-life in both mother and fetus. These features make it a very appealing drug for epidural use.

Based on statistical mechanics and systematic investigations of numerous polymorphic drug substances Burger and Ramberger have formulated four thermodynamic rules, namely the heat-of-transition rule (HTR), the heat-of-fusion rule (HFR), the density rule (DR) and the infrared rule (IRR) [4], which refer to the relative stability of polymorphs. The applicability of the thermodynamic rules was proved on 113 polymorphic compounds with 228 transitions examined [5] by them. Whereas the HTR and HFR practically show no

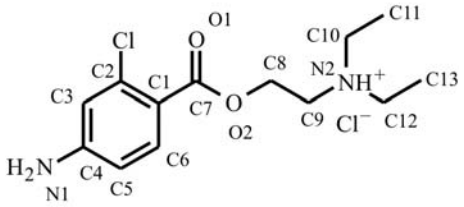

Fig. 1 Molecular structure of 2-CPCHC ($C_{13}H_{20}Cl_2N_2O_2$) with atomic numbers

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definite exceptions, the number of polymorphic systems which violate the DR and especially the IRR is growing in the last years. Burger and Ramberger have found, that all IRR exceptional compounds have one or more –CO–NH groups and since now just one polymorphic system, which certainly violates both, the IRR and the DR is known (chlorpropamide).

In our systematic investigations on the solid-state properties of 26 local anaesthetic drugs with examined 29 phase transitions the IRR was violated in 9 cases (31%). Thus within this class of active compounds the number of IRR exceptions is relatively high (Burger and Ramberger estimated 10% of molecular compounds being exceptions of the IRR).

In the present study for the first time the formation and the physical properties of 2-CPCHC polymorphic crystal forms are described by thermal analytical methods, vibrational spectroscopy, powder X-ray diffraction and water vapour sorption analysis evaluating their relative thermodynamic and kinetic stabilities and examining their compliance to the thermodynamic rules.

Experimental

Materials

2-CPCHC 'Chloroprocain-HCl Leuna CP 12b' Pl-G 771/54 (LeunaVEB Leuna-Werke Walter Ulbricht) from the drug store of the Institute of Pharmacy, Dept. of Pharmaceutical Technology, University of Innsbruck, was available for this study. All solvents and chemicals used in this study were of p.a. ('pro analysis') quality.

Methods

Hot-stage-microscopy

The thermal behavior of the solid-state forms was observed using an Olympus BH-2 polarizing microscope (Olympus Optical Co., Ltd.) equipped with a Kofler hot stage (Reichert, Vienna, A) and linked with a digital camera (Olympus DP50, Olympus Optical Co., Ltd.) using AnalySIS® Image Processing software.

Differential scanning calorimetry (DSC)

DSC curves were recorded with a DSC 7 system (Perkin-Elmer, Norwalk, Ct., USA) using the Pyris 2.0 software. Samples of approximately 2 mg (masses controlled to ±0.0005 mg using a UM3 ultramicrobalance, Mettler, Greifensee, CH) were weighed into Al-Pans (25 μL) with perforated cover. Dry nitrogen was used as purge gas (purge: 20 mL min^{-1}), calibrated with caffeine (236.4°C) and indium 99.999% (156.6°C, 28.45 J g^{-1}).

Pycnometry

Volume- and density-determination with Ultrapycnometer 1000 (Quantachrome Corp., Syosset, NY, USA) with helium purge, sample masses 2–3 g, calibration volume 1.0725 mL.

Infrared spectroscopy

Fourier transform infrared (FTIR) spectra were acquired on a Bruker IFS 25 spectrometer (Bruker Analytische Messtechnik GmbH, Karlsruhe, D). Spectra over a range of 4000 to 400 cm^{-1} with a resolution of 2 cm^{-1} (50 scans) were recorded on KBr tablets (approximately 2 mg 2-CPCHC per 3000 mg KBr). For temperature-controlled FTIR spectra the samples were prepared on ZnSe disks using a heating device (Bruker) and the Bruker IR microscope I (Bruker Analytische Messtechnik GmbH, Karlsruhe, D), with 15×-Cassegrain-objectives (spectral range 4000 to 600 cm^{-1}, resolution 4 cm^{-1}, 100 interferograms per spectrum).

Raman spectroscopy

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 excitation source and a liquid-nitrogen-cooled, high-sensitivity Ge-detector. The spectra were recorded in aluminium sample holders at a laser power of 300 mW (64 scans per spectrum).

Powder X-ray diffractometry (PXRD)

The X-ray diffraction patterns were obtained using a Siemens D-5000 diffractometer (Siemens AG, Karlsruhe, D) equipped with a theta/theta goniometer, a Goebel mirror (Bruker AXS, Karlsruhe, D), 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° in 2θ. Temperature- and moisture-controlled experiments were done with a low-temperature camera TTK (Anton Paar KG, Graz, A) and a SYCOS-H humidity control system (Asynco, Karlsruhe, D).

Water vapor sorption analysis

The moisture sorption isotherms were acquired using a SPS-11 moisture sorption analyzer (MD Messtechnik, Ulm, D). The measurement cycles were started at 0% relative humidity (RH) and increased in 10% steps up to 90% RH and back to 0% RH. The equilibrium condition for each step was set to a mass constance of ±0.007% over 40 min. The temperature was 25±0.1°C.

Lyophilization

Freeze-drying was performed with a Lyolab B, LSL (Secfroid Lyophilisator Inula, Wien, A) equipped with vacuum pump 2400 A (Alcatel Cit, Annecy Cedex, F). The frozen aqueous solutions (5%) were dried at a pressure of 0.05 mbar.

Results and discussion

The crystal forms are named according to the Kofler notation using roman numerals in the order of the melting points (*i.e.* the form with the highest melting point is called mod. I). The modification which is thermodynamically stable at 20°C is marked with a superscript zero.

Preparation of the polymorphic crystal phases

Mod. I°, the thermodynamically stable form at room temperature, is present in commercial products and crystallises from all organic solvents tested in this study, such as ethanol, methanol, ethylacetate, 2-propanol, acetone, *n*-butanol, toluol, $CHCl_3$, etc. and from the melt at temperatures above 130°C.

Mod. II crystallises from the supercooled melt below the experimental transition temperature ($T_{trs,2\text{-}CPCHC}$=134°C), according to Ostwald's Rule of Stages [6]. Fast crystallisation occurs on annealing the supercooled melt at 100 to 120°C.

Characterization of the polymorphic crystal phases

Hot-stage microscopy

The commercial product consists of fine (100 to 200 μm length), highly birefringent needles of the stable form mod. I°. On heating the crystals start to sublime intensely above 140°C characteristically shaped like dendrites (Fig. 2a) increasing until the temperature reaches the melting point. Needles and sublimates melt at about 175°C which coincides with the melting points given in the literature (173–178 [7], 176–178 [8]). Mod. I° scarcely crystallizes from the melt after seeding as highly birefringent stems and plates (Fig. 2b).

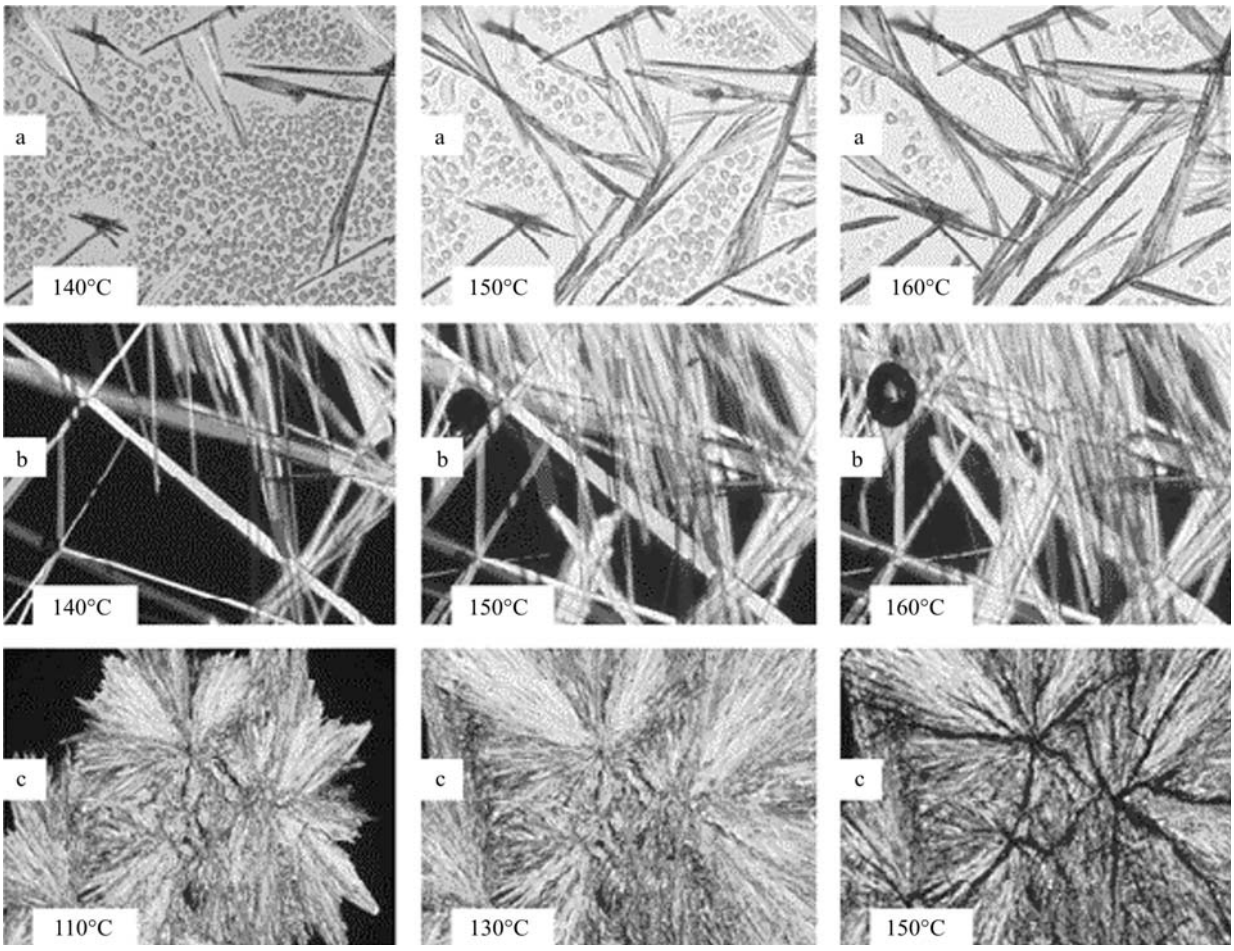

Fig. 2 Micrographs of 2-CPCHC crystal phases: a – sublimation of mod. I°, b – crystal film of mod. I° growing above 140°C, c – crystal film of mod. II growing between 110 and 130°C, transforming to the monotropically related mod. I° at 134°C

Mod. II crystallises from the supercooled melt in capillary spherulites (Fig. 2c), which slowly transform to mod. I° on heating above 130°C. The transformation mostly starts from the middle of the spherulites, where dark stems of mod. I° grow over the spherulites of mod. II.

Differential scanning calorimetry

Figure 3 shows the DSC curves of the 2-CPCHC polymorphic crystal forms and in Table 1 the thermophysical data are summarized. The stable mod. I° exhibits an endothermic melting peak with an onset of 175.1°C with a fusion enthalpy of 46.6 kJ mol^{-1}. On cooling the melt using a cooling rate of 5 to 10 K min^{-1} the unstable mod. II crystallizes between 120 and 100°C. Mod. II exothermally transforms to mod. I° at 134°C (DSC onset) with a transition enthalpy of –5 kJ mol^{-1}.

Thermogravimetry did not show significant amounts of residual solvents (<0.05%).

Pycnometry

The density of mod. I° was measured to be 1.188±0.009 g cm^{-3} whereas the unstable mod. II shows a significantly higher density (1.288±0.014). The difference of the measured densities of the two polymorphs is rather high (8%) and additionally contradict the DR.

FTIR- and Raman-spectroscopy

Both, FTIR- (Fig. 4) and Raman-spectra (Fig. 5) show high relativity between the two crystal phases with small but well reproducible differences of the individual crystal forms. The band shifts of the polymorphs average to 3 to 6 cm^{-1}, comparable to other con-

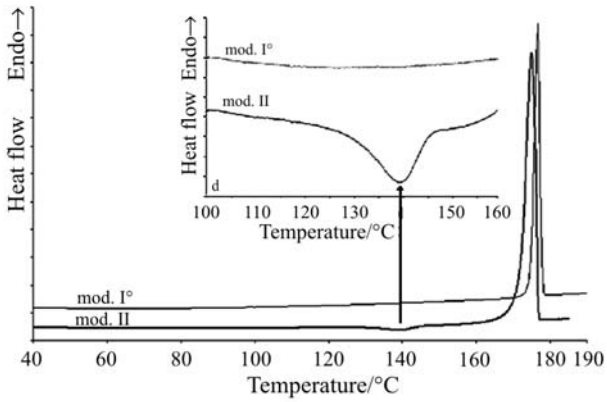

Fig. 3 DSC curves of 2-CPCHC crystal forms. d – shows the temperature range of the crystal transformation mod. II→mod. I° in detail; heating rate: 5 K min^{-1}

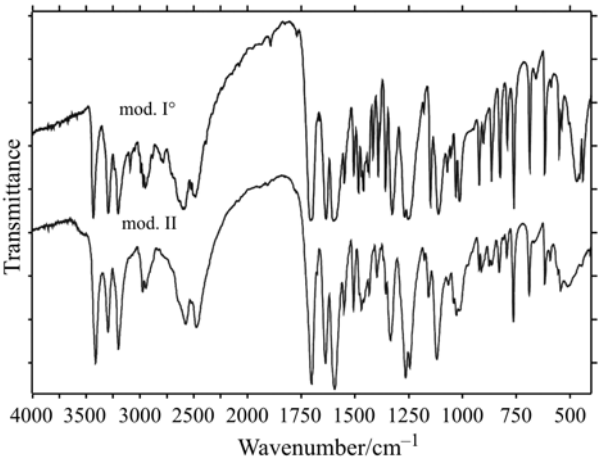

Fig. 4 FTIR spectra of 2-CPCHC crystal forms at room temperature (KBr method)

Table 1 Physicochemical data of 2-CPCHC polymorphic forms

Crystal form	2-CPCHC mod. I°	2-CPCHC mod. II
Production	commercial product, from all tested solvents	from the supercooled melt
Melting point/°C	175.1±0.4$_{DSC}$	
Enthalpy of fusion/kJ mol^{-1}±95% – c.i.	46.6±0.6	41.6$_{calc.}$
Transition temperature/°C (experimental, DSC onset)		133.9±1.2
Enthalpy of transition/kJ mol^{-1}±95% – c.i.		–5.0±0.5
Transition temperature/°C (experimental, HSM)		135±5
IR data/cm^{-1}, ν(N–HCl)	3433	3413
Order of thermodyn. stability of polymorphs at a.c.	1	2
Density/g cm^{-3}	1.188±0.009	1.288±0.014
Max. water vapor sorption at 90% RH/%*	0.2	1.0
Kinetic stability (storage, 20 to 25°C, 30 to 45% RH)	stable	<1 h

c.i. – confidence interval, *mass change in % relating to the sample mass at 0% RH, HSM – hot stage microscopy, DSC – differential scanning calorimetry, calc – calculated

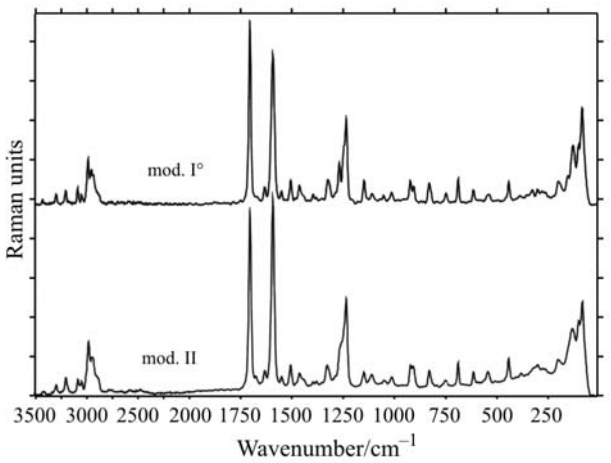

Fig. 5 FT-Raman spectra of 2-CPCHC crystal forms at room temperature

formational polymorphic LA [9–11]. The most striking differences can be realized in the range of the νNH (3440 to 3410 cm^{-1}, FTIR), the CH stretching vibrations of the alkyl chain (2980 to 2960 cm^{-1}, Raman), the valence vibrations of the carbonyl and amine group (1700 to 1600 cm^{-1}, FTIR), the molecule vibrations (1500 to 1000 cm^{-1}, FTIR) and the lattice vibrations (200 to 50 cm^{-1}, Raman). The characteristic IR absorption bands of the different forms are shown in Table 2.

The N–H stretching vibration (FTIR) of the stable form (mod. I°) lies at distinctly higher wavenumbers (3433 cm^{-1}) than that of the metastable mod. II (3413 cm^{-1}). This observation violates the IRR and suggests that intermolecular hydrogen-bonding to the N1 amino-function does not play an important role in the molecular arrangements of the crystal forms. Burger and Ramberger showed that all exceptions of the IRR have at least one CO–NH group, which is not the case in 2-CPCHC. But it is reasonable that the vinyl moiety which separates the CO and the NH group in the 2-CPCHC molecule causes the same structural behaviour. 31% of our systematically examined LA did not fullfill the IRR, which is a relatively high number of IRR exceptions, whereas Burger and Ramberger expected 10% exceptions of the IRR.

The lattice vibrations in the region below 200 cm^{-1} (Raman) clearly reflect the different crystal lattices of the polymorphic forms.

Table 2 Characteristic infrared frequencies and assignments for 2-CPCHC polymorphs

2-CPCHC mod. I°/cm^{-1}	2-CPCHC mod. II/cm^{-1}	Assignment
3433 (s)	3413 (s)	ν(N–H$^+$)
2999 (w)	2995 (w)	ν(C–H)
2624 (m)	2617 (m)	
1679 (s)	1677 (s)	ν(C=O)
1590 (s)	1598 (s)	ν(C–N)
1464 (w)	1449 (w)	molecular vibrations (fingerprint)
1252 (s)	1246 (s)	
1024 (m)	1020 (m)	
750 (w)	755 (w)	rocking vibrations of alkyl chains
572 (w)	569 (w)	

(s) – strong (>70% T), (m) – medium (40–70% T), (w) – weak (<40% T)

SSNMR-spectroscopy

As mod. II transforms to mod. I° at the high spinning rates during the measurement time, no spectra of the unstable mod. II could be obtained. 1H-, 13C- and 15N-spectra of the stable form mod. I° indicate a single molecule in the asymmetric unit.

Powder X-ray diffractometry (PXRD)

The X-ray powder patterns of the polymorphs are illustrated in Fig. 6 and the positions and relative intensities are listed in Table 3. The PXRD method, showing distinctly different peaks between the two polymorphs at small angles 2θ is the best method for a clear and fast identification of the polymorphs or mixtures of them. Mod. II additionally shows peaks of the mod. I° pattern due to phase transformation during the X-ray measurement.

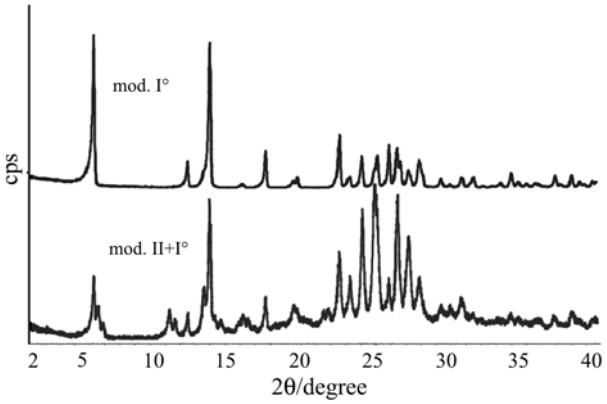

Fig. 6 Powder X-ray diffraction patterns of 2-CPCHC crystal forms

Thermodynamic and kinetic stability of PRCHC solid-state forms

Table 1 summarizes the most important thermodynamic data of the 2-CPCHC polymorphs as well as the wavenumbers of the νNH IR-modes (intermolecular hydrogen bondings), the measured density and water vapour sorption data. The thermodynamic relationship of the PRCHC solid-state forms of both compounds is displayed in the semi-schematic energy/temperature-

Table 3 Most important two theta positions (°2θ), *d*-spacings (*d*) and relative intensities (*I*) of the powder X-ray diffraction patterns of 2-CPCHC polymorphs

2-CPCHC I°			2-CPCHC II		
2θ/degree	*d*/Å	*I*/%	2θ/degree	*d*/Å	*I*/%
6.264	14.0985	100.00	6.227	14.1813	42.06
			6.529	13.5265	25.32
			6.854	12.8856	13.96
			11.304	7.8215	23.22
12.546	7.0496	18.19	12.528	7.0598	19.83
			13.618	6.4971	38.23
14.045	6.3005	94.86	14.002	6.3195	96.36
17.799	4.9793	24.95	17.753	4.9919	31.75
22.748	3.9058	35.36	22.705	3.9132	61.64
26.068	3.4155	28.82	25.081	3.5475	100.00
28.105	3.1723	17.57	28.070	3.1763	45.03

diagram [12] in Fig. 7 along with a scheme showing the possible transition pathways between the forms. Since mod. II transforms exothermally to mod. I°, the two polymorphs are monotropically related (heat of transition rule [13]) and thus mod. I° is the thermodynamically stable form in the entire temperature range. Mod. II, which is obtained by recrystallisation from the melt, transforms to the stable mod. I° within a few hours (confirmed by DSC and PXRD). In contrast to other metastable crystal forms of ester type LA (Oxybuprocaine HCl, Tetracaine HCl [14], Salicaine HCl [15]) 2-CPCHC mod. II has a low kinetic stability comparable to those LA where the metastable crystal form only is achievable from the supercooled melt (Pramocaine HCl, Falicaine HCl [16], Dyclonine HCl [17]), too.

Moisture sorption

Even though 2-CPCHC is a less hygroscopic compound and forms no hydrate under moisture conditions, the polymorphic forms can be differentiated by sensitive moisture sorption analysis. Figure 8 shows the moisture sorption isotherms of the two polymorphs, which can be used as a very helpful method to differentiate and identify polymorphic crystal phases or rank the polymorphic forms by their relative thermodynamic stability (with regard to surface area and crystallinity). Mod. I°, the thermodynamically and kinetically stable form, adsorbs a very small amount of water at 90% RH (Table 1), whereas the metastable mod. II shows a fivefold higher value. Additionally, the sorption isotherms of mod. II show strong hysteresis at relative humidities above 50% RH, which may indicate an incorporation of water into the crystal lattice.

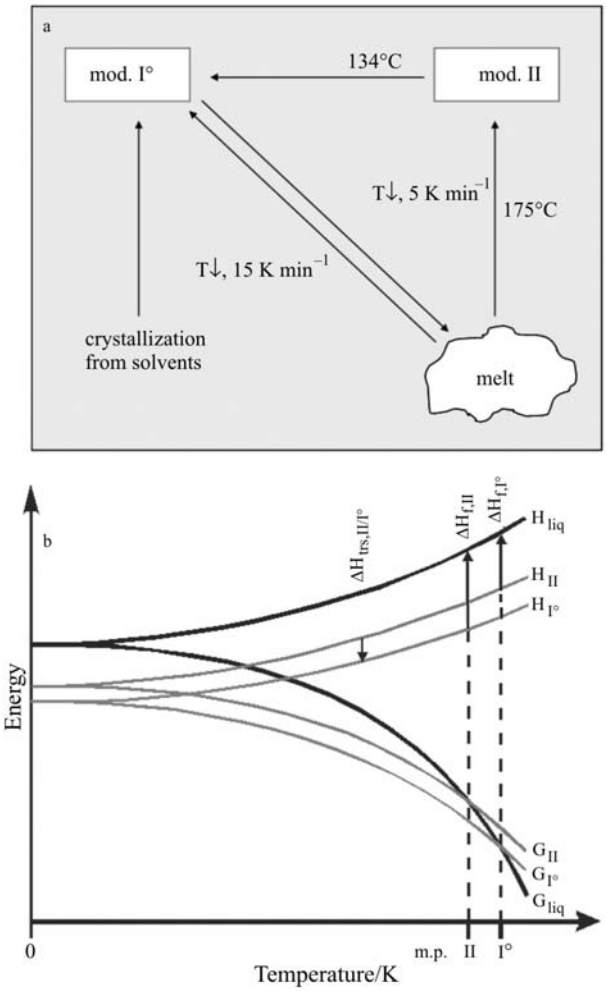

Fig. 7 Flow chart of 2-CPCHC crystal forms and melt with transformation temperatures under a – ambient pressure conditions and b – semischematic energy/temperature-diagram of the polymorphs; *H* – enthalpy, *G* – Gibbs free energy, ΔH_f – heat of fusion, ΔH_{trs} – heat of transition, *liq* – liquid phase (melt); thermal data from DSC

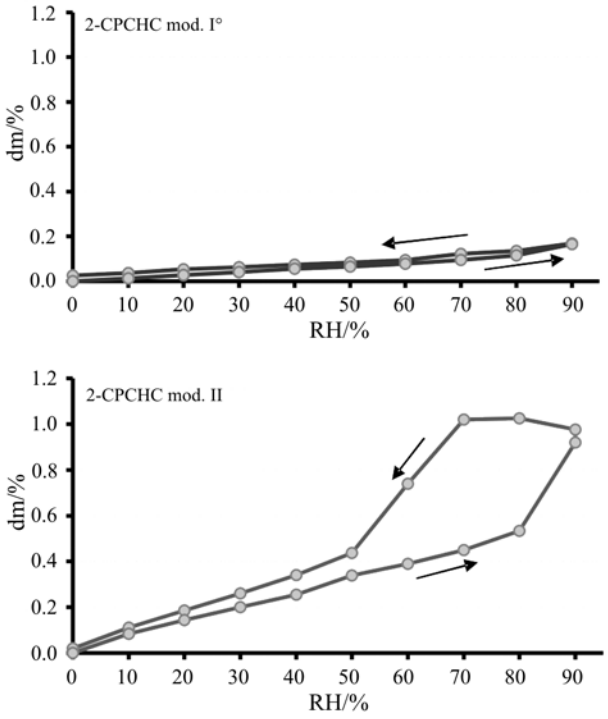

Fig. 8 Moisture sorption isotherms of 2-CPCHC crystal forms at 25°C; the mass change is corrected for the minimum mass value at 0% RH. The measurement cycle started at 0%

Conclusions

Chloroprocaine hydrochloride crystallizes in at least two crystal forms. Mod. I° is the stable form and present in commercial products. Mod. II crystallizes from the supercooled melt, is monotropically related to mod. I° and thermodynamically unstable in the entire temperature range. Mod. II exhibits a relatively low kinetic stability (a few hours) at ambient conditions.

The N–H band in the infrared spectrum of mod. I° (3433 cm^{-1}) lies at higher wavenumbers than that of mod. II (3413 cm^{-1}) indicating differences in the hydrogen bonding arrangement. Furthermore, the measured density of mod. I° is lower than the density of mod. II and thus both, the IRR and the DR are violated in this polymorphic system, a combination, that Burger and Ramberger found just in one case: chlorpropamide ($C_{10}H_{13}ClN_2O_3S$), which shows some structural characteristics to chloroprocaine on molecular level (substituted planar phenyl ring and side chain with rotational mobility).

Since 2-CPCHC is a drug compound with high solubility in water and a kinetically low stable polymorph (mod. II), the existence of the metastable form is probably of low practical relevance. However, as exception of both, the IRR and the DR, this drug compound represents thermodynamic characteristics of its polymorphs as it is already known for compounds with an amide structure. The results of this study may be helpful for the solution of the crystal structures of this polymorphic compound.

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