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CRYSTAL POLYMORPHISM OF LOCAL ANAESTHETIC DRUGS
Part I: Pramocaine base in comparison with pramocaine hydrochloride

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Abstract

Crystal polymorphs of pramocaine hydrochloride (PRCNC) and pramocaine (PRCN) free base were produced and characterized by means of thermomicroscopy, differential scanning calorimetry (DSC), FTIR- and FT-Raman-spectroscopy as well as X-ray-powder diffractometry. The relative thermodynamic stabilities of all forms were determined and are represented in semi-schematic energy/temperature diagrams. PRCN, which is a viscous liquid at room temperature and insoluble in water, was found to exist in two different crystal forms with the melting points 23.5°C (mod. I°) and 12.5°C (mod. II). The water-soluble PRCNC crystallizes in three different crystal modifications. Mod. II° is the thermodynamically stable form at room temperature and is present in commercial products. This form is obtained by crystallization from solvents and transforms on heating at about 95°C into the high temperature form mod. I which melts at 171.0°C. Both compounds show conformational polymorphism with forms of low kinetic stability.

Keywords: conformational polymorphism, crystal forms, local anaesthetics, pramocaine, pramocaine hydrochloride, pramoxine, thermal analysis

Introduction

Local anaesthetic compounds produce a reversible loss of sensation by preventing or diminishing the conduction of sensory nerve impulses near to the site of their application [1].

These compounds have common structural features, basically a hydrophilic end, which is mostly a tertiary or secondary amine and an aromatic group at the hydrophobic end. The amine portion and the aromatic residue are most frequently connected by an ester or amide bridge. The pharmacological and pharmacokinetic properties are essentially determined by this type of linkage and by the hydrophobic substituents of the amine moiety and the substitution of the aromatic group. All synthetic local anaesthetic compounds have one or more aliphatic chains. Thus conformational flexibility can be regarded as a general feature of these molecules. Moreover, the mole-

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cules are elongated, particularly those which have aliphatic substituents at the para-amino or para-oxy position of the benzene ring. Local anaesthetic drugs are bases and used in a salt form, in general the hydrochloride salt.

The fact that a great selection of local anaesthetic drugs with common structural features is available caused us to perform a systematic investigation of the solid state properties of these compounds. Many local anaesthetic compounds have been reported to exist in different crystal forms [2–8], but most of these studies are more phenomenological in nature and do not consider structural aspects of the crystal forms. Their solid state properties may be regarded as of minor importance for drug formulation and bioavailability issues, since they are most frequently used as aqueous solutions. However, the compounds represent an intriguing selection of structures for the development of structure-property relationship which requires first of all reliable experimental data before computational chemists can develop suitable models. From the structural features of local anaesthetics it can be expected that conformational polymorphism is dominant within this set of compounds.

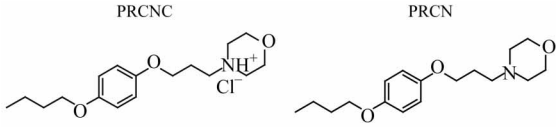

Fig. 1 Molecular formula of pramocaine hydrochloride (PRCNC) and pramocaine base (PRCN)

In the present study the results of solid-state investigations of pramocaine hydrochloride (PRCNC, pramoxine hydrochloride) and its free base (PRCN, 4-[3-(4-butoxyphenoxy)propyl]morpholinhydrochlorid) are presented. Pramocaine was developed in 1959 [9] and is used (as hydrochloride-salt) in suppositories and ointment formulations (e.g. Almay®, Pramegel®) against pruritis and anorectal inflammations. The compound (Fig. 1) belongs to the uncommon ether type and is official in the US Pharmacopoeia XXV. Thermal analytical methods, vibrational spectroscopy and powder-X-ray diffractometry as well as water vapour sorption studies were performed in order to characterize the different solid forms [10].

Materials and methods

Two lots of PRCNC were available: Tronothane Hydrochloride, Abbott Code 72681 and Pramoxine Hydrochloride (Sigma-Aldrich Chemie GmbH, D-Steinheim, CAS 637-58-1, EC No 211-293-1). Both products consist of mod. II°. PRCN (the base) was obtained as liquid precipitate by neutralizing an aqueous solution of PRCNC, washed with water and crystallized at about 8°C.

For thermomicroscopic investigations a Reichert Thermovar® polarisation microscope (Reichert, Vienna, A) equipped with a Kofler hot stage (Reichert, Vienna, A) was used. Low temperature microscopy was performed with a Linkam stage THMS 600 (Scientific Instruments Ltd, Waterfield Surrey, England, GB).

DSC curves were recorded with a DSC 7 (Perkin Elmer, Norwalk, Ct., USA) using the Pyris 2.0 software. Samples of approximately 2±0.0005 mg (using a UM3 ultramicrobalance, Mettler, Greifensee, CH) were weighted into Al-Pans (25 μL). Dry nitrogen was used as purge gas (purge: 20 mL min^{-1}). Low temperature DSC-curves were recorded with a DSC 7 (Perkin Elmer, Norwalk, Ct., USA), head temperature –80°C, calibrated with *n*-decane (–28°C), water (0°C) and indium 99.999% (156.6°C, 28.45 J g^{-1}).

IR-spectroscopic investigations were done with a FTIR-microscope (IR-scope I, Bruker Analytische Messtechnik GmbH, Karlsruhe, D) connected with a Bruker IFS 25 FTIR-spectrometer. The samples were fused between two ZnSe-discs and heated on a hot stage with external heat control.

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). For low temperature experiments the samples were filled in a capillary cooled in a low-temperature-cap with liquid nitrogen.

The powder X-ray diffraction patterns were obtained with a Siemens D-5000 diffractometer (Siemens AG, Karlsruhe, D) equipped with 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°2θ. Temperature-controlled experiments were done with the low temperature camera TTK (Anton Paar KG, Graz, A). The *d*-spacings ($CuK_{\alpha 1}$) were calibrated with the Silicium-NBS-standard.

Water vapour studies were performed with a SPS-11 moisture sorption analyzer (Project-Messtechnik, Ulm, D) and hygrostates with saturated salt solutions [11, 12].

Lyophilization was performed with Lyolab B, LSL Secfroid as 5%-solution at –60°C and 0.08 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). That modification which is thermodynamically stable at 20°C is marked with a '°'.

Crystallization from solvents

Various crystallization experiments from solvents such as water, ethanol, methanol, 2-propanol, acetonitrile, 1,8-dioxane and toluene as well as solvent mixtures were performed with the hydrochloride. Crystalline products always consisted of mod. II° and none of the metastable forms could be obtained in this way. From highly polar solvents the amorphous form was sometimes obtained.

Thermal analysis

Hot stage microscopy

The commercial product of the hydrochloride PRCNC consists of tabular, extremely flat crystals of mod. II°. In the polarized light the crystals appear partly isotropic or show only very weak birefringence with first order interference colours. Upon heating, the crystals transform to mod. I at about 90°C which can easily be recognized by a strong increase in birefringence. This transformation is a clear single to single crystal transformation, which means that the morphology of the original crystals is fully maintained and that the crystals do not even crack. When larger single crystals are observed, the transformation can be recognized by the expansion of a diffuse transition interface which is only noticeable by a temporary change in the interference colours. Without polarized light the transformation cannot be detected. At about 140°C the substance starts to strongly sublime to spheric discs which show spiral growth. The melting process of the high temperature form (mod. I) can be observed between 171 and 172°C. When the melt is slowly cooled, mod. I crystallizes in rays and at low cooling rates (2.5 K min^{-1}) the retransformation to mod. II° can be observed below 80°C. This retransformation (mod. I to II°) again is indicated only by a strong decrease (small crystals) or temporary change (larger crystals) in birefringence. However mod. I shows a low temperature transformation at about –27°C to mod. III, which instantly transforms back to mod. I on heating (at about –21°C). This indicates that form I and III are enantiotropically related. The transformation of mod. II° to III cannot be observed when mod. II° is cooled to –40°C without prior heating up to 90°C i.e. the prior transformation to mod. I.

The viscous liquid of the free base (at 25°C) crystallizes to mod. I° between 10 and 20°C when a cooling rate of about 5 K min^{-1} is applied. At faster cooling rates a second modification (mod. II) crystallizes to fine rayed spherulites. This form inhomogenously melts between 11 and 13°C to mod. I°. The melting process of mod. I° can be observed between 22 and 24°C.

Differential scanning calorimetry (DSC)

The DSC curves of PRCNC mod. II° (Fig. 2) show an endothermic phase transition at about 95°C to the high temperature form mod. I. The enthalpy of this transformation is relatively high ($\Delta_{trs}H_{II–I}$: 9.7 kJ mol^{-1}) which points at a significant change of the crystal lattice. Mod. I melts at 171.1°C ($\Delta_{fus}H_{I}$: 28.8 kJ mol^{-1}) and crystallizes on cooling (5 K min^{-1}) at about 150°C. The lower the cooling rate the more parts of the mod. I crystals retransform to mod. II° at about 70°C.

When mod. I is cooled without retransformation to mod. II° (cooling rate high) the low temperature form (mod. III) is formed (T_{trs}: –26.3°C, $\Delta_{trs}H_{I–III}$: –4.6 kJ mol^{-1}). The retransformation to mod. I occurs within a small temperature range upon heating (T_{trs}: –20.7°C, $\Delta_{trs}H_{III–I}$: –4.3 kJ mol^{-1}). When mod. I is stored at room temperature, retransformation to the stable mod. II° occurs within a few days.

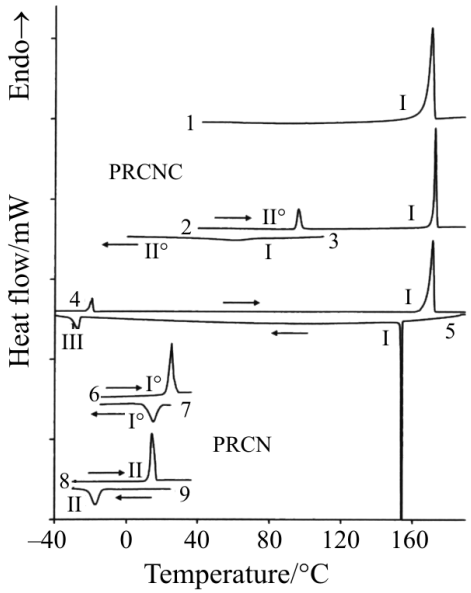

Fig. 2 DSC curves of pramocaine hydrochloride and pramocaine base. 1 – PRCNC mod. I; 2 – PRCNC mod. II° and transition to mod. I; 3 – PRCNC mod. I retransformation to mod. II° on cooling; 4 – PRCNC mod. III transformation to mod. I; 5 – PRCNC crystallization of mod. I and transformation to mod. III on cooling; 6 – PRCN mod. I° melting endotherm; 7 – PRCN mod. I° crystallization exotherm on cooling; 8 – PRCN mod. II melting endotherm; 9 – PRCN mod. II crystallization exotherm. Heating and cooling rates: 5 K min^{-1} (curve 9, 10 K min^{-1}). The roman numerals mark the modifications

PRCN mod. I° crystallizes between 10 and 20°C (cooling rate: 5 K min^{-1}) and the melting point was determined to be 23.7°C. At faster cooling rates mod. II crystallizes between –10 and –20°C, which melts at 12.3°C inhomogenously (not shown) on reheating. Fast cooling prevents the nucleation of mod. I° and at temperatures below 1°C ($\Delta_{trs}H_{II/I(calc)}$, Table 1) only mod. II can be obtained. Mixtures of PRCNC and PRCN can be identified by quantifying the heat of fusion of the melting endotherm of mod. I°. During the process of freeze-drying we received samples of PRCNC containing a small amount of PRCN, which can be easily and quantitatively identified by DSC.

Thermogravimetry

The TG-investigations (not shown) confirm the microscopic observation that no solvent is released during heating the forms. Due to the high vapor pressure of the hydrochloride (sublimation) the mass of the substance starts to decrease above 100°C (accelerating process).

Table 1 Physicochemical data of the crystal forms of pramocaine hydrochloride and pramocaine base. T_{trs} – transition temperature (experimental, thermodynamic), T_{fus} – melting point; $\Delta_{fus}H$ – enthalpy of fusion; $\Delta_{trs}H$ – transition enthalpy; c.i. confidence interval; $_{(calc)}$ calculated [14]

Compound	Pramocaine hydrochloride			Pramocaine base	
Modification	mod. I	mod. II°	mod. III	mod. I°	mod. II
Production	Heating mod. II° above 90°C	Crystallization from solvents	Cooling mod. I below –27°C	Slowly cooling the melt	Cooling the melt below –10°C
T_{fus}/°C	171.1±0.9	$145_{(calc)}$	$132_{(calc)}$	23.7±0.2	12.3±1.0
$\Delta_{fus}H$/kJ mol^{-1} ±95%-c.i.	28.8±0.6	$38.5_{(calc)}$	~$33_{(calc)}$	24.6±0.6	25.5±1.6
T_{trs}/°C experimental	69 (I/II°) –27 (I/III)	95 (II°/I)	–21 (III/I)		
T_{trs}/°C thermodynamic	82±13 (I/II°) –24±3 (I/III)	82±13 (II°/I)	–24±3 (III/I)		$1_{(calc)}$ (II/I°)
$\Delta_{trs}H$/kJ mol^{-1} ±95%-c.i.		9.7±0.2 (II° to I)	4.3±0.1 (III to I)		$1_{(calc)}$ (II to I°)
Order of stability at 20°C	2	1	3	1	2
Temperature range where forms are thermodyn. stable/°C	82 to 171	<82	unstable at all temp.	1 to 24	<1

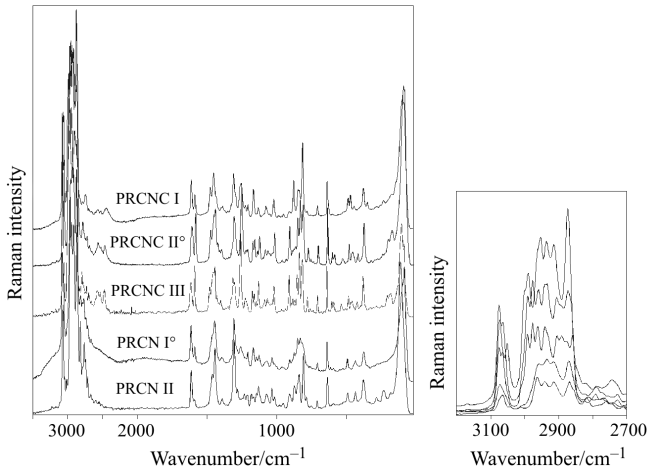

Fig. 3 Raman-spectra of pramocaine hydrochloride and pramocaine base modifications. The stable forms and PRCNC mode. I were recorded at 20°C, PRCNC mod. III and PRCN mod. II at –40°C. The right graph shows the range of C–H stretching vibrations in detail

FTIR- and Raman-spectroscopy

Similar to other cases of conformational polymorphism the FTIR (not shown) and Raman-spectra of the different crystal forms are very similar (Fig. 3). The most striking differences lie in the range of the C-H stretching vibrations of the alkyl chains (3080 to 3040 cm^{-1}, Raman), the C–O stretching vibrations of the aryl-alkyl-ether (1250 to 1260 cm^{-1}, FTIR) and the lattice vibrations (200 to 50 cm^{-1}, Raman). Except the C–H stretching vibrations band shifts of less than 5 cm^{-1} can be observed in the individual spectra. The stable forms were recorded at 20°C, the high temperature form of PRCNC was recorded after melting and recrystallization in a capillary. The low temperature forms were measured in a capillary using a liquid nitrogen cooling accessory. In spite of the high reproducibility of the FTIR- and Raman-spectra which allows the clear identification of these crystal forms the method of first choice for a clear distinction is XRPD.

Powder X-ray diffractometry (XRPD)

The X-ray powder patterns are illustrated in Fig. 4 and the positions, spacings and relative intensities are listed in Table 2 and Table 3. The diffractograms of PRCNC forms show lines with constant spacings at low angles indicating strong similarities in all crystal systems. To minimize preferred orientation effects of the tabular crystals the samples were poured into the sample holder and not pressed. Thanks to the use of parallel beam optics acceptable patterns with minor orientation effects were obtained of the sample preparations with irregular surfaces. Any other preparation method re-

Table 2 Two theta positions (2θ), d-spacings (d in Å) and relative intensities (I) of the X-ray powder diffraction patterns of pramocaine hydrochloride

Pramocaine hydrochloride								
mod. I			mod. II			mod. III		
°2θ	d/Å]	I/%	°2θ	d /Å	I/%	°2θ	d /Å	I/%
2.96	**29.87**	**100.00**	**3.08**	**28.69**	**100.00**	3.05	28.99	85.77
5.95	14.85	23.45	6.20	14.25	53.38	6.15	14.35	17.20
8.94	9.88	27.47	9.31	9.49	25.59	9.27	9.53	29.01
11.95	7.40	25.68	12.44	7.11	52.23	12.38	7.14	37.34
14.97	5.91	29.77	15.59	5.68	59.04	15.51	5.71	30.97
15.75	5.62	5.94	15.79	5.61	36.90	16.12	5.49	16.27
16.55	5.35	32.11	16.11	5.50	33.98	16.48	5.32	42.14
17.81	4.98	40.23	16.39	5.40	14.45	17.32	5.12	13.76
19.43	4.56	17.04	16.97	5.22	30.71	17.66	5.02	30.08
20.17	4.41	27.36	17.82	4.98	23.60	18.02	4.92	39.72
21.34	4.16	27.28	18.43	4.81	70.97	18.49	4.79	50.64
22.06	4.03	42.06	19.53	4.54	40.83	19.82	4.48	63.04
22.70	3.91	34.05	20.23	4.39	39.28	20.63	4.30	24.34
23.57	3.77	37.16	21.20	4.19	30.40	21.20	4.19	11.13
23.78	3.74	21.68	21.93	4.05	67.43	21.78	4.08	29.99
24.08	3.69	15.89	22.18	4.00	49.58	22.09	4.02	76.55
24.89	3.57	8.69	22.82	3.89	41.41	22.37	3.97	63.13
25.89	3.44	17.40	23.18	3.83	76.89	22.65	3.92	52.63
26.18	3.40	8.90	23.90	3.72	33.14	23.09	3.85	19.07
27.12	3.28	6.43	24.18	3.68	77.29	23.56	3.77	23.87
28.45	3.14	9.97	24.69	3.60	34.56	24.22	3.67	56.46
29.05	3.07	7.11	25.27	3.52	36.15	**24.85**	**3.58**	**100.00**
30.97	2.89	6.01	25.52	3.49	26.56	25.56	3.48	13.34
31.57	2.83	5.22	26.74	3.33	25.50	27.79	3.21	9.09
32.48	2.75	8.41	28.33	3.15	19.58	29.19	3.06	14.06
33.12	2.70	5.24	28.48	3.13	28.59	29.55	3.02	13.04
33.97	2.64	4.81	29.08	3.07	18.91	30.80	2.90	9.94
34.81	2.58	5.41	29.93	2.98	17.76	31.90	2.80	12.79
			30.54	2.92	26.91	32.28	2.77	15.08
			31.30	2.86	10.30	33.14	2.70	8.50
			31.87	2.81	19.62	33.99	2.64	12.96
			32.32	2.77	12.46	35.19	2.55	8.71
			33.08	2.71	9.72	37.67	2.39	9.18
			34.11	2.63	12.55			
			35.53	2.52	8.71			
			36.16	2.48	14.67			
			38.01	2.37	9.37			
			38.89	2.31	11.44			

Table 3 Two theta positions (2θ), d-spacings (d in Å) and relative intensities (I) of the X-ray powder diffraction patterns of pramocaine base modifications

Pramocaine base					
mod. I			mod. II		
°2θ	d/Å	I/%	°2θ	d/Å	I/%
4.78	**18.48**	**100.00**	**2.55**	**34.62**	**100.00**
8.33	10.61	10.35	5.10	17.33	64.76
9.58	9.22	6.99	7.65	11.55	53.44
12.53	7.06	8.11	10.20	8.66	2.83
15.06	5.88	19.18	12.76	6.93	3.10
15.80	5.61	6.05	15.33	5.78	12.00
18.32	4.84	14.05	18.53	4.78	23.03
18.54	4.78	31.17	19.30	4.60	4.93
18.80	4.72	15.95	19.99	4.44	9.69
19.63	4.52	90.94	20.35	4.36	16.25
20.55	4.32	9.75	21.56	4.10	11.46
21.72	4.09	89.15	22.46	3.95	3.12
22.54	3.94	6.04	23.19	3.83	3.43
23.30	3.82	50.09	26.74	3.33	3.79
28.10	3.17	12.76	28.60	3.12	3.45
28.95	3.08	7.05	30.80	2.90	3.05
30.83	2.90	5.34			
37.56	2.39	4.21			

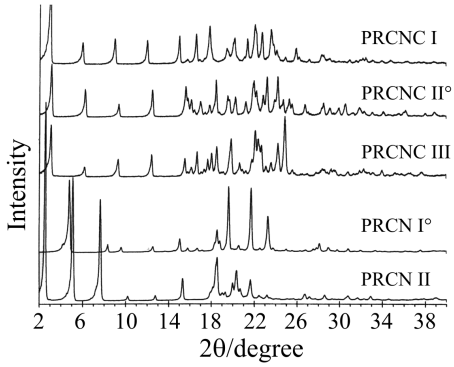

Fig. 4 X-ray powder patterns of pramocaine hydrochloride and pramocaine base modifications, stable forms recorded at 20°C, PRCNC mod. III and PRCN mod. II at –40°C, PRCNC mod. I at 40°C after heating up to 140°C, relative intensities see Table 2 and Table 3

sulted in patterns where the lines with constant spacing dominate. From this behavior we may assume, that the PRCNC modifications form layer structures.

The XRPD pattern of PRCN mod. II shows also prominent peaks with constant spacings, whereas the pattern of mod. I° suggests a distinct crystal structure.

The transformation behavior between the crystal forms of both compounds was also confirmed by variable temperature XRPD. The diffractogram of PRCNC mod. I was recorded at 40°C after heating mod. II° up to 140°C.

Moisture sorption

Also the moisture sorption behaviour of the hydrochloride and the base were routinely examined at 25°C in order to check for the existence of hydrates and the affinity to water. The critical relative humidity (deliquescence) of the hydrochloride was observed between 80 and 90% relative humidity. At 92% r.h. (saturated KNO_3 solution) the liquefied hydrochloride approaches an equilibrium at a water content of 42% after 7 days (static atmosphere). The water uptake of the liquid free base occurs continuously with increasing relative humidity up to 70% r.h. (about 1% water). At 92% r.h. an equilibrium moisture content of 4% was determined.

Thermodynamic stability of the modifications

Table 1 summarizes the most important physicochemical data of the modifications of PRCNC and PRCN. Based on these data, semi-schematic energy/temperature-diagrams [13] were constructed (Fig. 5) in order to display the thermodynamic relationship of the polymorphs at different temperatures. Figure 6 shows the transformation pathways between the polymorphs and the melt under experimental conditions (thermomicroscopy).

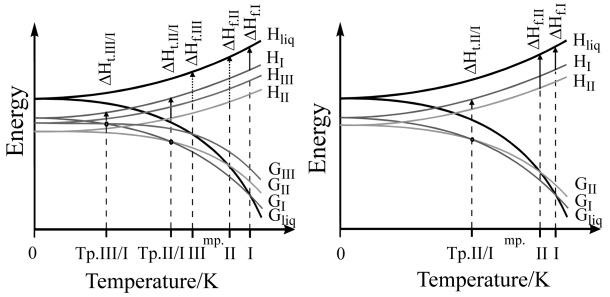

Fig. 5 Semi-schematic energy/temperature diagrams of pramocaine hydrochloride and pramocaine base crystal modifications. G – free enthalpy curve and H – enthalpy curve of the melt (liq), mod. I (I), mod. II (II) and mod. III (III); T_p – thermodynamic transition point, ΔH_f – heat of fusion; mp – melting point, dotted arrows – calculated enthalpies, arrows – measured values

According to the heat of transition rule [13] mod. III and mod. II° of the hydrochloride are enantiotropically related to mod. I and because of the lower transition enthalpy for the III/I transition compared to that of II/I, mod. III and II° are monotropically related. Mod. II° is the thermodynamically stable form below 82°C

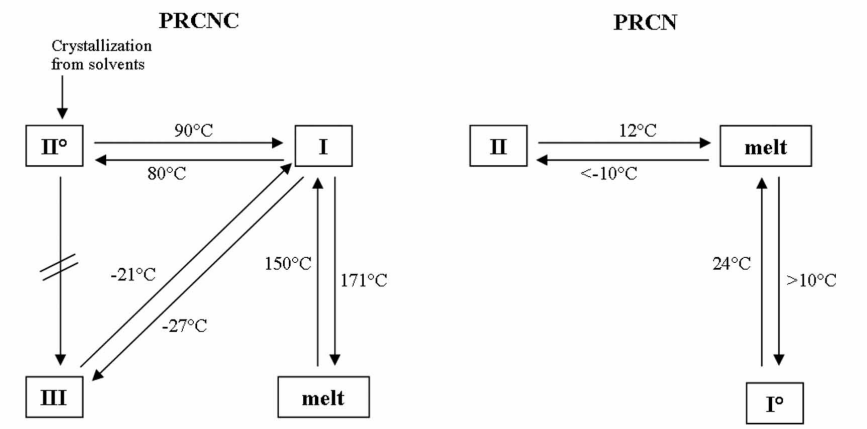

Fig. 6 Transformation scheme between the different polymorphic forms of pramocaine hydrochloride and pramocaine base (data from thermomicroscopy)

whereas mod. I is the high temperature form, i.e. the thermodynamically stable form above 82°C. Mod. III is thermodynamically unstable in the entire temperature range.

As the lower melting mod. II of the free base has the larger enthalpy of fusion (heat of transition rule [13]), the two forms must be enantiotropically related. Mod. II is thus stable in the temperature region below the thermodynamic transition point (at about 1°C), which has been calculated from the melting points and enthalpies of fusion according to Yu [14].

None of the metastable forms could be obtained by crystallization from a solvent.

Conclusions

The regular use of PRCNC as water-soluted active substance in creams and jellies is definitely not affected by the existence of the three crystal modifications. However, the thermal treatment (>80°C) of this compound can cause a transformation to mod. I which exhibits different physical properties compared to the original material. At room temperature mod. I slowly transforms to the stable mod. II° within a few days.

The method which is best qualified for the identification of the different crystal forms is the XRPD. The three forms of PRCNC show considerable similarities in their crystal structure and assumably form layer structures. As hydrogen bonding is not an issue with this molecular structure, structural differences between the crystal forms must be connected with the conformational flexibility of the molecules. This has been also performed by preliminary single crystal structure investigations of mod. II°.

The presence of traces of the free base PRCN can be proved by XRPD and quantitatively identified by the melting endotherm at 24°C in the DSC-curve.

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