Crystal Structure and Physical Properties of two Polymorphs of Ropivacaine HCl

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ABSTRACT: The crystal structure of two polymorphs of ropivacaine HCl have been determined, as well as their relative stability up to 100°C. A geometric restriction for a solid-state transition between the two polymorphs has been identified. The packing density along the H-bonded chains form the basis for a model explaining the kinetic crystallization of the metastable form. The difference in stability and physicochemical properties between the two polymorphs can be attributed to the difference in crystal structure.
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INTRODUCTION

Pharmaceutical drug substances often crystallize in different crystal modifications, a phenomenon generally referred to as polymorphism. This may also include cocrystallization with a variety of solvents in varying amounts. Different crystal modifications have different physicochemical properties, such as solubility and stability, due to the differences in crystal structure. These properties can have a significant impact on process development and product performance. Thus, solid-state characterization and the search for various crystal modifications are essential parts of drug development.[1–3]

Marketed products in most cases are formulated using the most stable modification in order to minimize the risk of transformation from metastable modifications to more stable ones with an unwanted and concurrent change of properties.[4]

When discussing the relative stability of polymorphs, it is important to distinguish between kinetic and thermodynamic stability. The relative thermodynamic stability depends on temperature, pressure, and composition. Those parameters determine which crystal structure is the most stable. On the other hand, kinetic stability is related to time and activation energies and can be affected by a multitude of factors that are difficult to control.

Among all the different techniques available for characterization of crystal modifications, X-ray diffraction, and especially single crystal X-ray diffraction, plays a central role. This technique provides structural information about unit cell parameters, atom positions, molecular conformation, and packing. In addition, different types of molecular interactions, such as hydrogen bonding patterns and $\pi-\pi$ stacking, can be identified. From the bonding properties of polymorphs, correlations between crystal structure and thermodynamic stability may be identified.

The purpose of this study is to investigate differences in crystal structure of polymorphs in relation to their physical properties. Consequently, we report here the crystal structures

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and thermodynamic properties of two polymorphs of the anaesthetic ropivacaine HCl, attempting to illustrate correlations between crystal structures and physical properties.

EXPERIMENTAL

Materials

The ropivacaine HCl system comprises of one monohydrate crystal modification, Form A (not studied here) and two anhydrate polymorphs, Form B and C. The substance is commercially produced as the monohydrate and can be crystallized from a 1:1 mixture of ethanol and water.[5] The hydrate was supplied by AstraZeneca Bulk Production. The chemical purity was better than 99.5%. The hydrate was converted into the anhydrate polymorphs as described below.

Single Crystals

For crystal structure determination good quality crystals of the anhydrate Form B were produced by dissolving 0.22 g of the monohydrate in 2.3 g of *N*,*N*-dimethylformamide. Slow evaporation at about 108°C gave crystalline needles after approximately 1 week.

Crystals of anhydrate Form C for crystal structure determination were produced by dissolving 0.47 g of the monohydrate in a mixture of 2.5 g of water and 0.05 g of glycerol. Slow evaporation at 92°C produced needle/rod-shaped crystals after about 1 week.

Bulk Crystallization

Larger amounts of Form B for physical characterization were produced by suspending Form C (produced from 10 g of monohydrate) with seeds of Form B in 50 mL of 2-propanol, allowing slow evaporation of the last 2-propanol. The phase identity was verified by X-ray powder diffraction.

Larger amounts of Form C for physical characterization were produced by dissolving 10 g of the monohydrate in 50 g of methanol under stirring and heating to boiling. Before boiling, a clear solution was formed. The methanol was rapidly evaporated under a stream of nitrogen gas producing rapid crystallization. The heat was turned off and the agglomerates formed were crushed with a spatula. Again, the phase identity was verified by X-ray powder diffraction.

Single Crystal X-Ray Diffraction

Diffraction data of suitable single crystals was collected on a Bruker-Nonius KappaCCD diffractometer using Mo Kα radiation. Structural models containing the Cl atoms and most of the other non-H atoms were obtained using direct methods [SHELXS97].[10] The remaining non-H atoms and the H atoms were located in subsequent difference-Fourier syntheses. The structures were refined on F^2 using anisotropic thermal parameters for all non-H atoms [SHELXL97].[11] A riding model was applied for the hydrogen atoms. Table 3 lists the crystallographic data and the results of the structure determination.

The crystallographic data of the two structures have been deposited with the Cambridge Crystallographic Data Centre, CCDC Nos. 282945 and 282946 for form B and C respectively. Copies of this information can be obtained free of charge from the Director, CCDC, 12 Union Road, Cambridge CB2 1EZ, UK (fax: +44-1233-336 033; e-mail: deposit@ccdc.cam.ac.ukor www: http://www.ccdc.cam.ac.uk).

X-Ray Powder Diffraction

Powder diffractograms were obtained at room temperature between scattering angles, 2θ, of 1 to 40° using a Philips XÇPert-MPD diffractometer, giving a clear identification of the different crystal modifications. Diffractograms were compared with calculated diffractograms obtained from the single crystal structure data. Monochromatized Cu Kα radiation was employed.

Solubility Determination

The solubility was determined by equilibration of Form B and C in 1 mL of 2-propanol in 2 mL vials at 25°C in a Thermomixer Comfort from Eppendorf. The vials were shaken at 600 rpm with a 30 s pause every 5 min. The given equilibration time was between 24 and 108 h. The solvent phase was filtered through an Acrodisc 13 mm Syringe Filter with 0.45 μm GHP membrane, Pall Corporation. The saturated solution was diluted and the amount of dissolved ropivacaine HCl determined on a 1100 Liquid Chromatograph equipped with a Zorbax Eclipse XDB C8 5 μm, 150 mm, ID 4.6 mm column, all from Agilent. The eluent consisted of a mixture of acetonitrile and phosphate buffer 50 mM, pH 3.0, 25/75 v/v. Flow rate 0.7 mL/min.

Column temperature 25°C. Wavelength of detection 230 nm.

The phase identity of the remaining solid phase was determined by X-ray powder diffraction.

Solution Calorimetry

The dissolution energy was determined using a Thermal Activity Monitor (TAM) equipped with a 100 mL dissolution calorimeter at 25°C, all from Thermometric, Järfälla, Sweden. Solvents used were water, 2-propanol, and water/2-propanol, 1/1 v/v. The amount of sample used was 100 mg.

Suspension Experiment

Competitive slurry experiments between the anhydrate forms were performed as follows. About 400 mg of one form was heated to the desired experiment temperature in a closed E-flask. DMF was added while stirring, forming a slurry. After about 1 h a suitable amount of the other form was added to the slurry. The resulting slurry was mixed for one day or more, after which a fraction of the solid was captured using a Nanosep MF GHP 0.45 μm filter, Pall Corporation. The phase identity of the solid phase was determined by X-ray powder diffraction. The mixing continued until one of the forms became undetectable.

RESULTS AND DISCUSSION

Physical Properties

The solubility and heat of solution studies were carried out for the two anhydrate polymorphs. The results are summarized in Table 1. From a theoretical point of view any solvent, which does not form solvates, is suitable for determining solubility.[2] However, 2-propanol was chosen because of suitable solubility.

Table 1. The Heat of Solution in Water and the Solubility in 2-Propanol for Form B and Form C, Both at 25°C

	Form B	Form C
Heat of solution (kJ/mol)	−0.46 (0.07)	−3.30 (0.05)
Solubility (g/L)	17.8 (1.4)	29.4 (0.9)

Standard deviations are within parentheses. The heats of solution are averages of six values. The solubility data are, for Form B the average of 15 values (determined in four different experiments) and for Form C the average of 13 values (determined in three different experiments).

Table 2. Calculated Thermodynamic Differences Between the Polymorphs, Using Heat of Solution and Solubility Data. The Values Represent a Transition From Form B to Form C

Dissociation Assumed	ΔG_t (25°C) (kJ/mol)	ΔH_t (25°C) (kJ/mol)	ΔS_t (25°C) (J/mol K)
No	1.2 (1.24)	2.8	5.4
Full	2.5	2.8	1.2

The solubility data of Form B and C, in 2-propanol at 25°C, were determined to be 17.8 and 29.4 g/L, respectively. Thus, at 25°C we can regard Form B as stable and C as metastable. This significant difference in solubility does obviously have implications for other physical properties.

Solubilites must be formulated as solubility products for salts. As a direct consequence, calculation of Gibbs free energy of dissolution from solubility data is dependent on to what degree the ion pair of the dissolved substance is dissociated. In the case of ropivacaine HCl, we may consider it as a salt consisting of the protonated ropivacaine cation, HRo^+, and the chloride anion, Cl^-. The p*K*a do give a full transfer of the free proton giving a ropivacaine cation and a chloride anion, but to what extent the "free" chloride is dissociated from the ropivacaine cation in the solvent used, is unclear.

A complete dissociation can be written:

$$HRoCl(s) \rightleftharpoons HRo^+ + Cl^- \tag{1}$$

with the dissociation constants

$$K_S^B = [HRo^+]_B[Cl^-]_B \cong c_{B^2} \quad \text{and} \qquad K_S^C = [HRo^+]_C[Cl^-]_C \cong c_{C^2} \tag{2}$$

where K_s is the solubility constant, $[HRo^+]$ is the activity of the substance cation, $[Cl^-]$ is the activity of the chloride anion, and c is the saturated concentration of the substance. The super- and subscripts B and C correspond to the solution in equilibrium with solid of Form B and C, respectively.

$$\Delta G_i^0 = -RT \ln K_S^i \tag{3}$$

where R is the general gas constant, T the absolute temperature, and i Form B or C.

The difference in dissolution Gibbs free energy equals the Gibbs free energy of transition, ΔG_t, which is inversely related to the relative stability

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Table 3. Crystallographic Data and Results of the Structure Determination of Forms B and C of Ropivacaine HCl

Parameter	Form B	Form C
Chemical formula	$C_{17}H_{27}ClN_2O$	
Formula weight	310.86	
Crystal system	Orthorhombic	Monoclinic
Space group	$P2_12_12_1$	$P2_1$
a (Å)	10.99750(10)	10.8640(4)
b(Å)	11.7565(2)	10.9000(3)
c(Å)	27.6998(5)	15.3710(7)
β (°)		97.6590(13)
V (Å^3)	3581.71(11)	1803.96(12)
ρ (calc.) (g · cm^{-3})	1.153	1.145
Formula units Z	8	4
μ (mm^{-1})	0.22	0.21
T(K)	150	100
θ (min, max)	4.55, 23.25	4.18, 22.71
Measured reflections	28778	17840
Unique reflections, R_{int}	5078, 0.062	5101, 0.078
Observed reflections ($I > 2\sigma(I)$)	4507	4810
Parameters	379	380
R_1	0.0455	0.0449
wR_2	0.117	0.1297
GooF	1.090	1.012
$\Delta\rho$ (min/max)	0.31/−0.44	0.27/−0.20

between Form B and Form C. ΔG_t can thus be formulated as:

$$\Delta G_t = \Delta G_B^0 - \Delta G_C^0 = RT \ln (c_C^2/c_B^2) = 2RT \ln (c_C/c_B) \quad (4)$$

which represents the first of two extreme cases, full dissociation.

In the other case, where no dissociation between the chloride anion and the substance cation in the dissolved substance is assumed, the situation is comparable to a nonsalt, or more specific, a noncocrystal according to

$$\text{HRoCl(S)} \rightleftharpoons \text{HRoCl(solv)} \quad (5)$$

with the dissociation constants

$$K_S^B = [\text{HRoCl}]_B \cong c_B \quad \text{and} \quad K_S^C = [\text{HRoCl}]_C \cong c_C \quad (6)$$

In this extreme case, representing no ionic dissociation, the difference in Gibbs free energy of form B and C can be formulated as:

$$\Delta G_t = \Delta G_B^0 - \Delta G_C^0 \cong RT \ln (c_C/c_B) \quad (7)$$

Thus, when calculating the difference in Gibbs free energy of dissolution between two polymorphs of a salt, the degree of dissociation must also be determined in the specific solvent used. However, useful information can be extracted by evaluation of the two limiting cases. As seen from Eqs. (4) and (7), the difference in the calculated Gibbs free energy is a factor of 2. Obviously this factor is different for different salts or cocrystals depending on their composition.

This difference corresponds to 1.2 or 2.5 kJ/mole more negative value of Gibbs free energy, ΔG_f, for the stable Form B than in the metastable Form C, corresponding to none or full ionic dissolution, respectively.

The heat of solution was determined in water, 2-propanol, and in a mixture of water:2-propanol, 1:1. Of those three, water gave reproducible results, hence the results from aqueous dissolution are presented here. Although the heat of solution, ΔH_s, is affected by the degree of dissociation, as discussed for solubility, this does not affect the difference in heat of solution between the polymorphs, since they obtain the same degree of dissociation after dissolution in any solvent used.[6]

Both anhydrate forms gave an exothermic dissolution in water, but the heat of solution is about 2.8 kJ/mole more exothermic for the meta-

stable anhydrate, Form C, than for the stable anhydrate, Form B, at 25°C (Tab. 1). This indicates that the lattice energy, which we here choose to express in terms of an enthalpy of formation, ΔH_f, is about 2.8 kJ/mole lower for the stable Form B ($\Delta H_f < 0$ for both forms). Most likely, this is a consequence of the binding energy being higher in the stable crystal Form B.

The difference in Gibbs free energy, ΔG_t, between two polymorphs represents the difference in thermodynamic stability and originates from the difference in their crystal structure. ΔG_t depends on the enthalpy, ΔH_t, and the entropy, ΔS_t, according to the well-known relation $\Delta G = \Delta H - T\Delta S$, where T is the absolute temperature. Also ΔH_t and ΔS_t originate from the differences in crystal structure. From the values of ΔG_t and ΔH_t the entropy contribution ($T\Delta S$) to ΔG_t is calculated to either 1.6 or 0.4 kJ/mole, none or full ionic dissociation assumed in solution. Thus, the stabilization of Form B by 2.8 kJ/mole, arising from its lower enthalpy, is partly compensated for (between 1.6 and 0.4 kJ/mole) by its lower entropy at 25°C.

Suspension experiments show that Form B is more stable than Form C at room temperature and at 100°C. Consequently, at least up to 100°C Form B should be regarded as the stable form and Form C as the metastable one.

The transition temperature, T_t is the point where the enthalpy and entropy difference cancel each other out giving $\Delta G_t = 0$. Calculation of the transition temperature from the solubility and heat of solution, according to Gu and Grant,[7] gives T_t between 255°C and 2046°C (255°C assuming none, and 2046°C assuming full dissociation in solution), in both cases with Form B as the stable form below this temperature. This estimation supports the postulation that Form B can be regarded as stable and Form C as metastable up to at least 100°C.

As shown above, Form B is thermodynamically stable and Form C metastable. However, the metastable anhydrate, Form C, may be regarded as kinetically strongly favored under the conditions used for crystallization. When evaporating the solvent (2-propanol) from a saturated slurry of form B, form C precipitated despite the availability of seeds of form B. A stepwise, slow evaporation to give time for a re-equilibration of the slurry, i.e., dissolution of the newly formed Form C and crystal growth of Form B, was necessary in order to produce a pure sample of the stable anhydrate (Form B).

Crystal Structures

Both anhydrous polymorphs contain chains of ropivacaine cations, HRo^+, connected by Cl^- anions via hydrogen bonds. The H-bonding is achieved by exploitation of the amide proton from one ropivacaine cation binding to Cl^-, which in turn binds to the protonated tertiary amine group of a neighboring molecule. See Figures 2, 4, and 5.

The only difference between the two polymorphs is the packing of the chains yielding a higher symmetry and higher density in Form B. No significant π-π stacking is inferred by the structures.

As a comparison, in the monohydrate of ropivacaine HCl (Form A), a different type of chains is formed.[5] In the hydrate, chains are formed by water molecules bridging the carbonyl-oxygen atom of one cation to the amide proton of another. The Cl^- ions are not part of the chains, but instead bind to the water of crystallization via H-bonds (Fig. 2).

In both anhydrate forms, the unit cell contains two independent molecules, α and β, in the asymmetric unit (Fig. 3). Consequently, two ropivacaine cations with different conformations are present in the structures. In Form C each conformation forms a separate chain, so that two types of chains, $-\alpha-Cl-\alpha-Cl^-\ldots$ and $-\beta-Cl-\beta-Cl^-\ldots$ are formed. These chains pack in an alternating fashion along the unit cell *c*-axis (Fig. 5). In Form B the conformational units are mixed to an $-\alpha-Cl-\beta-Cl-\alpha-$chain. Application of the three 2_1-axes on this chain yields four chains packed along the *c*-axis (Fig. 4).

If we define a hydrogen-bond *direction* in the different chains in forms B and C as

amide → chloride → tertiary amine

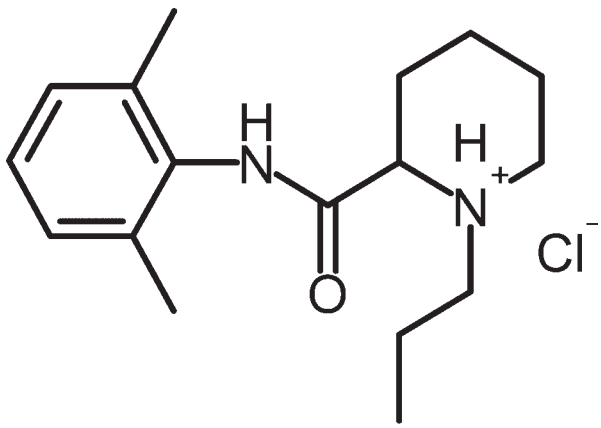

Figure 1. Molecular structure of ropivacaine HCl.

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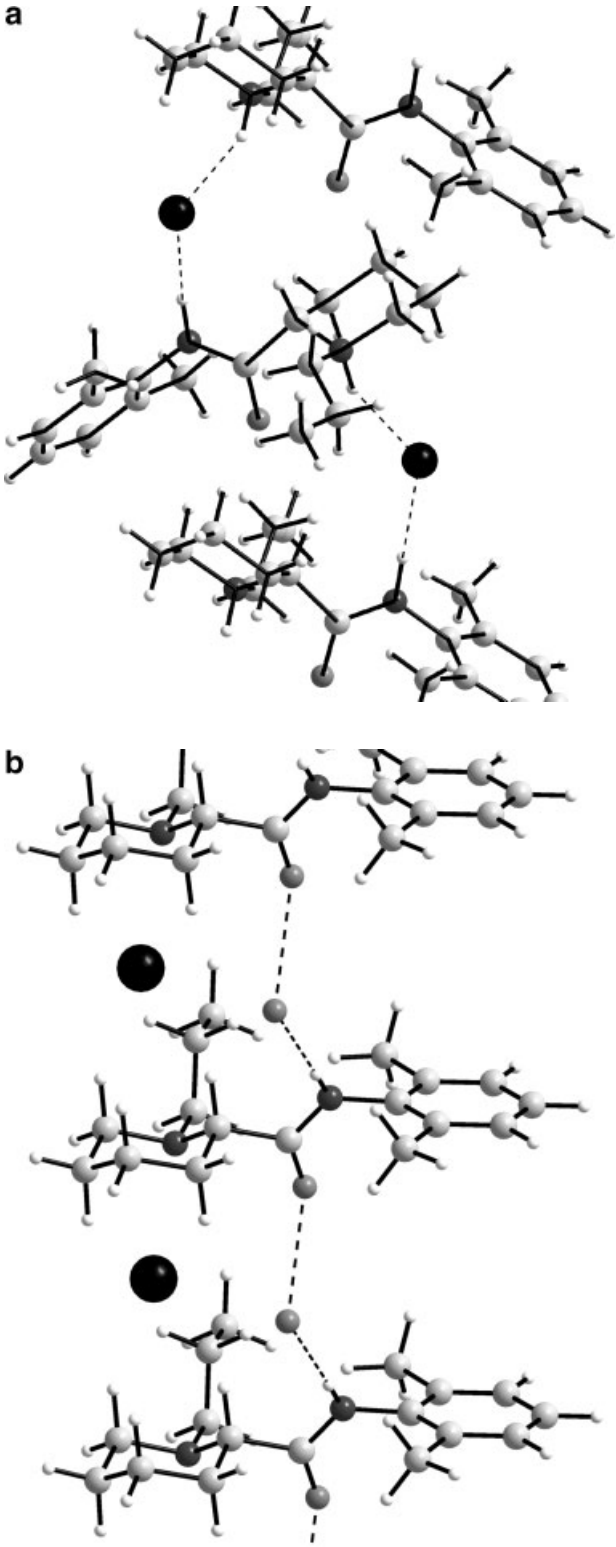

Figure 2. Comparison of H-bonded chains of an anhydrate, here Form B, via chloride (a) and the hydrate via water (b). The water hydrogen atoms are omitted, since their positions were not determined.

it is noted that the chains are aligned in planes, parallel to the *a*- and *b*-axes, where all chains in one plane have the same H-bonding direction (Figs. 4 and 5). In Form C the H-bonding direction shifts between adjacent planes with one direction defined by the α-conformation chains and the other direction by the β-conformation chains (Fig. 5). In Form B *two* planes of chains with the same H-bonding direction alternate with *two* in the other direction and, in contrast to Form C, the individual chains are identical except for their positioning (Fig. 4).

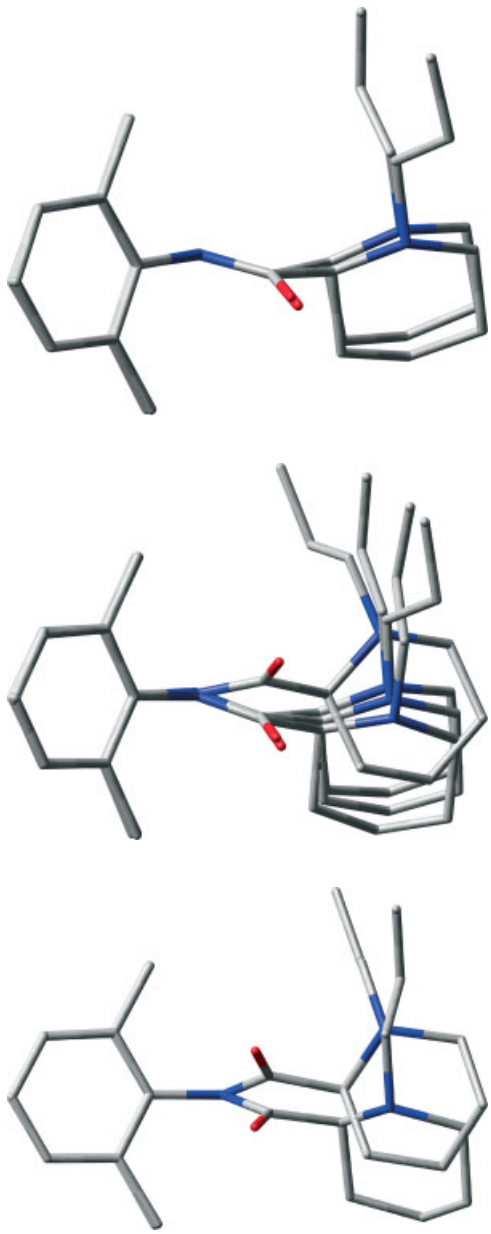

Figure 3. Superposition of conformers. Above: Form B. Middle: Form B and C. Below: Form C.

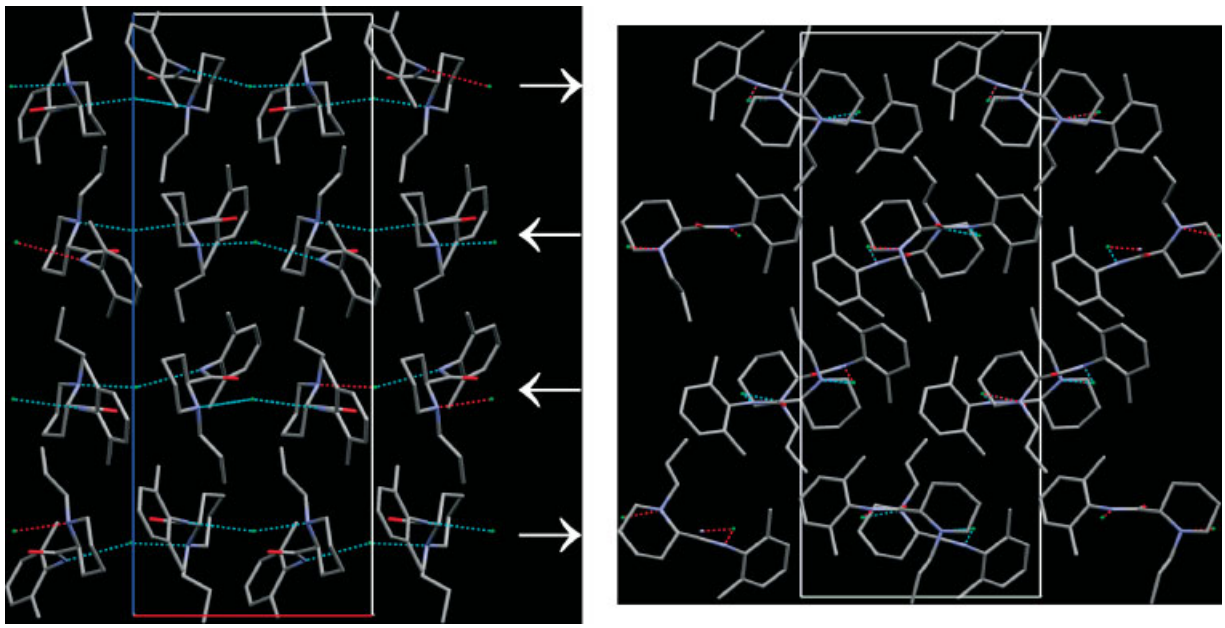

Figure 4. Form B seen Left: along *b*-axis, *a*-axis horizontal, *c*-axis vertical Right: along *a*-axis, *b*-axis horizontal, *c*-axis vertical Arrows represent H-bond direction as defined in text. Dotted lines represent H-bonding.

Between each change in H-bond direction, Form C has one layer of chains with the same H-bond direction and Form B has a double layer of chains with the same H-bond direction. Based on these H-bonding patterns, it is concluded that a solid-state transition between Form B and C, without H-bond breaking, cannot occur by a conformational change within the chains only. A transition would also require positional exchange between the chains. Because of this, the activation energy of transition most probably is relatively high. As a consequence, a solid-state transition appears complicated and less likely to occur.

Along the H-bonding *direction* (the *a*-axis in Form B and the *b*-axis in Form C) the length per molecule in Form C is about 0.9% shorter than in Form B.[9] As will be seen below, this is significant in spite of the different temperatures for which diffraction data were collected. That most probably indicates that the increased density (and stability)

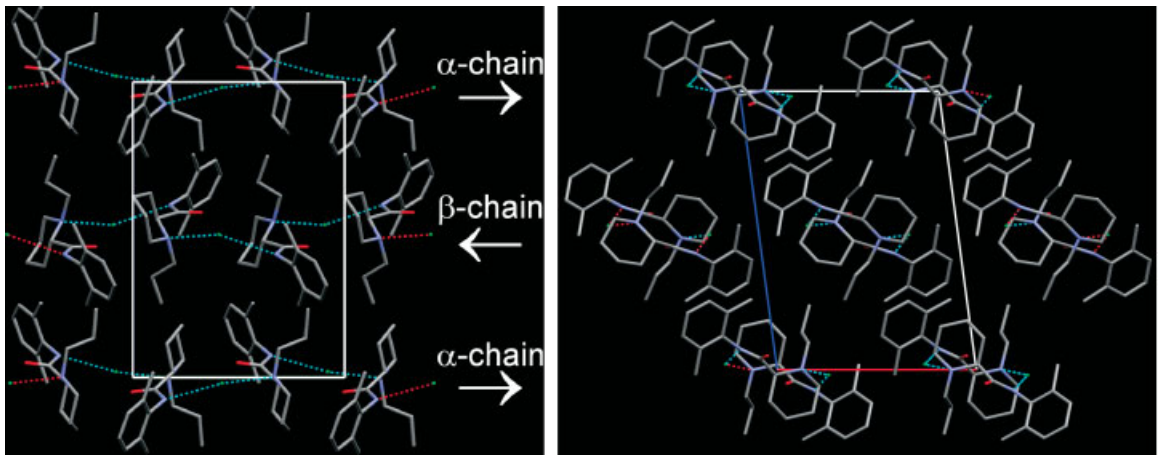

Figure 5. Form C seen Left: along *a*-axis, *b*-axis horizontal, *c*-axis vertical Right: along *b*-axis, *a*-axis horizontal, *c*-axis vertical Arrows represent H-bond direction as defined in text. Dotted lines represent H-bonding.

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in Form B cannot be attributed to molecular packing in the H-bonding direction.

In the *bc*-plane of Form B (*ac*-plane in Form C), *perpendicular* to the H-bonding direction, the hydrogen bond chains are weakly interacting (van der Waals-type of interaction). In this plane the area per H-bond chain is about 2.3 % larger in Form C than in Form B, as calculated from the relevant unit cell axes and angles (Tab. 3)[9] and compensating for the temperature expansion of Form C between 100 and 150 K using the data in Figure 6. The denser packing of the chains in Form B is sufficient to compensate for the lower packing density along the H-bonded chains.

The fact that the packing is denser between the chains in Form B, but denser along the chains in Form C, may give a hint to the reason why the metastable Form C is kinetically favored at crystallization from solution. The crystallization process most probably begins with the formation of H-bonded chains. During this process, a denser packing along the H-bonded chain is probably energetically more favorable. When the three-dimensional crystal structure is propagated by secondary interactions of these H-bonded chains, it is likely to be kinetically favorable to keep the denser packing along the chains.

Different single crystals of Form C were analyzed at different temperatures during structure evaluation. This gives information about the unit cell change for Form C as a function of temperature (Fig. 6). In Figure 6, the length of each axis at a certain temperature is compared to the value at 100K. It is obvious that the unit cell axis along the H-bonded chains (the *b*-axis) is fairly constant between 100 and 300 K, whereas the *c*-axis, which corresponds to the direction of the propyl chains, changes significantly. This is what

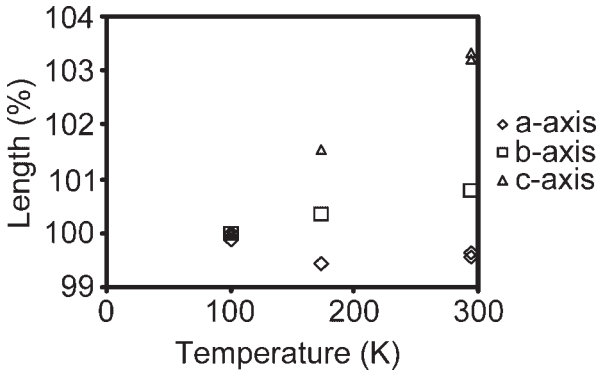

Figure 6. Unit cell axis length change versus temperature for Form C.

should be expected since thermal expansion is much larger in directions where chemical bonding is weak.[8] As the temperature increases, the packing along the *c*-axis becomes less dense and gradually less important for the total energy of the crystals. Thus, Form B becomes less and less stable relative to Form C and at a certain point of temperature the Gibbs energy is the same for the two forms. This is the phase transition temperature, and beyond this a phase transformation from the low-temperature Form B (thermodynamically stable below the transition temperature) to the high-temperature Form C (thermodynamically stable above the transition temperature) is envisaged.

From these data it is obvious that the denser packing within the H-bonded chains of Form C is significant, although data for Form B and C were collected at 150 and 100 K, respectively.

CONCLUSIONS

The crystal structure and relative stabilities of two polymorphs of the anhydrate of ropivacaine HCl have been determined. One polymorph is shown to be stable and the other metastable up to at least 100°C. However, the metastable form is observed to be kinetically strongly favored during crystallization. The structural data have been used to rationalize some of this physical behavior.

The crystal structure of both polymorphs consists of H-bonded chains that are packed in a hexagonal pattern by dispersion forces. By defining a H-bond direction it is shown that there is a geometrical restriction for a solid-state transition between the two polymorphs. A transition demands a positional exchange of H-bonded chains.

The packing is denser along the H-bonded chains for the metastable form but denser between the chains for the stable form. A model where the crystallization begins with formation of H-bonded chains rationalizes the kinetic crystallization of the metastable form.

It has been pointed out that when calculating the Gibbs free energy differences from the solubility of a salt or another cocrystal, the degree of dissociation of the components in solution greatly influence the interpretation of thermodynamic data.

A deeper knowledge into the formation of different polymorphs could be gained by spectroscopic studies of association in solution or theoretical modeling.

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