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COMPARISON OF EXPERIMENTAL METHODS AND THEORETICAL CALCULATIONS ON CRYSTAL ENERGIES OF 'ISOENERGETIC' POLYMORPHS OF CIMETIDINE

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Abstract

The thermodynamic energy relationship between two crystal modifications of cimetidine was investigated and compared with differences in their processing properties with respect to transformation from one modification to the other.

The crystal energies of the two modifications A and D were found to be almost identical and therefore the polymorphs are regarded as virtually isoenergetic crystals. This statement is based on DSC measurements of the melting points and of the enthalpies of fusion for the two crystal forms, which enable the calculation of the Gibbs free energy functions. Furthermore, the statement is supported by measurements of the enthalpies of solution in two different solvents. Both DSC and solution experiments reveal a slightly higher stability of the D modification with respect to the A form. In addition, tribomechanical treatment also indicates modification D to be the more stable one, as well as the higher density of the D form. No transformation during DSC at low heating rate was found which could be used in a stability consideration.

As the explicit crystal structures of the two modifications are resolved, it was possible to calculate crystal energies theoretically as well. The theoretical results showed a remarkable difference in the crystal energies at zero degree Kelvin. Furthermore, they were just contradicting experimental findings by stating A being more stable than D. Possible reasons for this discrepancy and the feasibility of today's calculation methods with respect to prediction of stability properties are discussed.

Keywords: crystal modifications, DSC, Gibbs free energy function, molecular modelling, solution calorimetry

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Introduction

Quantitative thermodynamic stability relationships between the polymorphic crystal modifications of drug substances and other substances in the solid state can be important with respect to their physical properties e.g. processing of the material during manufacture of drug dosage forms and long-term storage. The main concern hereby is transformation from one modification to another by stresses applied during processing such as heat, moisture, shear stress, pressures and combinations thereof. Different crystal modifications in many cases show different physical properties to a great extent, a fact widely affecting processing properties as well as properties of the finished product in terms of performance of any solid state drug product. The instability of a crystal modification may cause problems in the whole course from production of the dry substance, tableting, storage of the drug product to the bioavailability in the final administering.

Histamin-antagonist cimetidine was chosen as a model substance, because crystal structures of two of its modifications named A and D have already been resolved and reported in the literature by Hädicke *et al*. [1] and Párkányi *et al*. [2], (Table 1). The two modifications are conformational polymorphs, in crystal modification A molecules having an intramolecular hydrogen bond whereas in modification D all hydrogen bonds are intermolecular. In spite of different bonding and tilting properties of the molecules in the solid state, surprisingly the thermodynamical stability of these two crystal modifications could not be distinguished from each other experimentally in a first study and therefore the two modifications had been regarded isoenergetic within the tolerance of the used DSC method [3]. When the same crystal modifications of cimetidine were investigated with respect to manufacture of solid dosage drug formulations, however, great differences had been found in properties and performance during processing and tableting by Bauer-Brandl [3].

Table 1 Explicit crystal structure data of modifications A and D of cimetidine

Cimetidine	A	D
Space group	monoclinic, $P2_1/c$	monoclinic, $P2_1/c$
	a=682.1 pm	a=728.3 pm
	b=1881.8 pm	b=1080.8 pm
	c=1037.4 pm	c=1828.1 pm
Angle	β=106.42°	β=118.8°
Volume unit cell	$V=1.2772\cdot10^9$ pm^3	$V=1.2684\cdot10^9$ pm^3
Reference	[1]	[2]

The objective of the present study was to investigate the thermodynamic stability relationship between these two modifications in more detail using high precision DSC method and high precision solution calorimetry.

Two polymorphs which are isoenergetic in a strict sense do not exist. The energetic situation of polymorphs and the regions of stability depend on temperature and pressure as is described by the Gibbs free energy functions. The pressure depend-

ency is not widely investigated even though it is of great practical and scientific importance. Restricting the disussion to the temperature, the Gibbs free energy functions $\Delta G_{s,i}$ with S for solid state and i=A or D have to be compared within the temperature range where the two polymorphs exist.

An isoenergetic situation in a strict sense can only exist for enantiotropically related polymorphs and only at one single sharp temperature, the so-called thermodynamic transition temperature $T_{trs,AD}$, the temperature at which the Gibbs functions are identical by definition.

In a mere practical sense, 'isoenergetic' polymorphs do exist if the Gibbs free energy functions cannot be distinguished because the experimental error of the data set available is too large compared to the difference between the Gibbs functions [4]. In such a situation the differentiation between monotropy and enantiotropy is impossible, and as a consequence also the stability regions of the polymorphs cannot be assigned. The higher the precision of the thermodynamic data set used in calculation of the Gibbs function, the smaller are the differences of the Gibbs functions which can just be differentiated. Small differences in Gibbs free energy, namely $\Delta\Delta G_{A,D}=\Delta G_{S,A}-\Delta G_{S,D}$, moreover, indicate the absence of considerable driving force for a polymorphic transition. If a transformation could be observed, it would clearly demonstrate the stability relation for the two polymorphs, but only at this given temperature. It is not easy to yield the data sets with the accuracy necessary for the calculation of the Gibbs functions of the two polymorphs, namely the melting point, the enthalpy of fusion and for closer approximation the molar heat capacities of the polymorphs and of their liquid phase as well. In many cases, and in particular if a stable polymorph – stable at room temperature – is heated in a DSC or in any of the instruments of applied physical chemistry such as hot-stage IR or Raman spectroscopy, the 'transition temperatures' of polymorphs reported in the literature are not the thermodynamic transition temperatures $T_{trs,AD}$ but temperatures below the lower melting point of the polymorphs and above the effective thermodynamic transition temperature, for which a transformation is observed kinetically [5–8]. The explanation for the kinetically observed transformation is easy: at the thermodynamic equilibrium no transformation is possible, however far above this equilibrium the driving force becomes the determining property overruling kinetic obstacles.

A serious problem while gaining the data is the instability of crystal modifications – with respect to chemical and/or physicochemical instability – making determination of the melting point and heat of fusion impossible or too difficult to achieve with a reasonable precision. In such cases alternative procedures have to be undertaken. A high standard in the precision of the determination of the thermodynamic data even for instable substances has been reached by the development of the purity method by DSC and the necessary temperature and caloric calibrations in Novartis Services AG [9]. A great number of polymorphic and pseudopolymorphic substances have been investigated since 1968 in the laboratory for Applied Physical Chemistry by the group of Marti and coworkers. Only one of the systems investigated with solubility measurements and Gibbs free energy functions was in an experimental sense 'isoenergetic' which means that within the experimental error limits both polymorphs have the same Gibbs functions, the same solubilities in any solvent, the same vapour pressure and therefore also the same solubility rate under equal particle size distributions and the same bioavailability.

Modifications of nearly equal crystal energies have already been reported in the literature, and in some cases referred to as 'isoenergetic' as by Carstensen and coworkers [10], although these authors found a difference in DSC peak maxima of about 4 K for two modifications of ranitidine hydrochloride. Ranitidine hydrochloride is known to be rather unstable at elevated temperatures near its melting point, both thermally and in the presence of oxygen. Therefore the high precision of the experimental thermodynamic data which is necessary to make the statement of 'isoenergetic' crystal modifications cannot be achieved under normal laboratory conditions. In their case, however, the difference in crystal enthalpies measured by solution calorimetry was not significantly different at room temperature, the means of the enthalpies of dissolution only being 0.6 kJ mol^{-1} apart from each other. In their measurements the standard deviations were rather big, but unfortunately information on experimental details such as the calibration procedures applied, sample sizes and sample concentrations, and equilibration time are not given, conditions that would possibly also affect the accuracy of the measurements.

In the present paper, theoretical calculations on the basis of the resolved crystal structures [1, 2], given in Cambridge Structural Data Base, were performed and the reliability of these methods regarding prediction of material properties shall be discussed. The situation today in the theoretical calculation of stable polymorphs only on the basis of molecular structures of organic substances by computational chemistry is such that the calculated and over an energetic selection proposed possible polymorphs are always 'isoenergetic'. The main reason so far is the precision of the data obtained by calculation, which are in comparison to the level necessary for a discrimination of the polymorphs of cimetidine in particular, not sufficient. The further development of the molecular modelling is an interesting scientific task. One has certainly to stress here that with an integration of experimental results into these calculations already valuable information is gained, however, the complex relationships of solid state polymorphs as a function of temperature over the whole stability region of the solid forms is at present out of the quantitative range of crystal modelling.

Material and methods

The two modifications of cimetidine under investigation, named A and D after Hegedüs and Görög [11], were prepared in pure form according to published protocols (Prodic-Kojic *et al*. [12] and Bauer-Brandl [3]). The polymorphs were characterised by thermomicroscopy (hot stage microscope, Reichert AG, Vienna), X-ray powder diffraction (Stoe, Darmstadt, Germany), and IR spectroscopy (Perkin Elmer 841, Norwalk, CT, USA) as described elsewhere [3].

Heat flow DSC (DSC 600 TABase, WSK Messtechnik GmbH, D-Limeshain) was done using approx. 10 mg of samples at a heating rate of 0.2 K min^{-1} in air atmosphere at a pressure of 1000 hPa. Samples were pure A, pure D and a physical mixture (50/50) thereof.

Power compensating DSC (Perkin Elmer DSC 7) was performed in the laboratories of Marti in Basel. Sample masses were approx. 2.5 mg and a heating rate of 5 K min^{-1}. All DSC results were corrected for sample mass and scan speed.

Solution calorimetry both in water and in methanol was executed for A and D using a Precision Solution Calorimeter and Pre-Thermostat to the Thermal Activity

Monitor (Thermometric AB, S-Järfälla). The measuring temperature was 25°C, the mass of samples adjusted between 22 and 96 mg in glass ampoules. The reaction vessel was filled with 100 ml water or methanol of highest purity respectively, the stirrer moved at 400 rpm; samples were allowed to equilibrate for 30–40 min. Then a baseline was recorded, the reaction started by crushing an ampoule and the reaction was followed for 30–40 min. After that a second baseline was recorded. Each of these experiments was repeated once.

The stabilities of polymorphs in the presence of water was tested by storing aqueous slurries of the pure modifications and a 50/50 physical mixture respectively at ambient conditions.

The calculation of 'theoretical crystal energy' is based on calculated difference in molecular mechanics energy (affecting to one molecule) between a 'minicrystal' of A and D forms. Minicrystal in this respect means that the original unit cell (derived from Cambridge Structural Database) is multiplied to 100 molecules. After this, the crystal energy is minimized. This is necessary because the resolution in crystal structure analysis is limited by the quality of real crystals (residual up to approx. 2 Å=0.2 nm) and by the mean error of the analysis technique (ca. 0.2 Å= 0.02 nm). Cerius 2 modelling software (MSI, Version 2) was used, and a Dreiding Force Field calculation described by Mayo *et al.* [13]. Point charges were calculated using the Gasteiger method as implemented in Cerius 2 software (MSI, San Diego, CA). Minimization (conjugate method) was stopped when the RMS force was under 0.2 kJ mol^{-1}. Terms used in the force field are shown in Table 8 together with the results of form A. After the minimization of the minicrystal one molecule of the 100 was deleted from the middle of the crystal and single point energy was calculated. The same calculation procedure was done for a minicrystal of the form D (Table 9) and results compared (Table 10).

Results

DSC

Both modifications A and D showed straightforward melting behaviour with no sign of any polymorphic transition in the DSC at a low heating rate of 0.2 K min^{-1} (Fig. 1). The melting peaks, with a difference of 0.35±0.03 K between them, are regarded as extremely close to each other. They were reproducible and the difference between them is highly significant, particularly taking into account that the results were obtained using two different DSC methods in two different laboratories (Table 2). The enthalpies of fusion had been measured on instruments based on careful temperature and caloric calibration. In the laboratories of Marti and coworkers, high purity indium as the reference material for caloric calibration has been applied since 1968 and the best caloric value has been obtained by collecting all primary literature values with eliminating outlying measurements. The resulting best value of the enthalpy of fusion for the reference substance indium as a sequence of increasing number of literature data available are listed in Table 3.

A physical mixture of modifications A and D also showed no sign of transformation, but two overlapping melting peaks, the melting points being widely unaffected

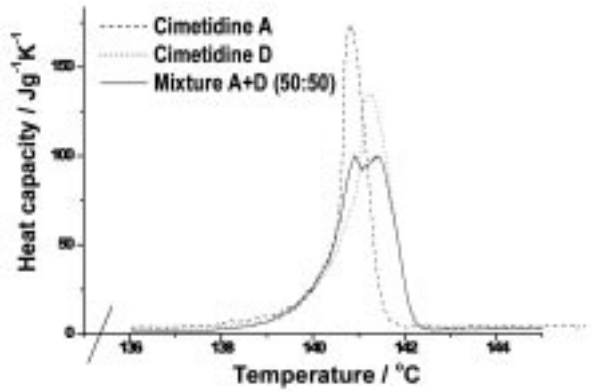

Fig. 1 DSC curves of cimetidine modifications A, D and a physical mixture thereof

compared to the pure modifications and revealing practically the same difference of the melting points as measured for pure samples of modifications A and D.

In all measurements the melting peak of modification D was found at higher temperatures than the melting peak of modification A, together with the higher enthalpy of fusion for the D modification revealing a monotropic relation. This means that the D modification is over the whole temperature range between 0 K and the melting temperature T_{fus}=140.65°C the stable form calculated with respect to the Gibbs free energy function which is the absolute criterion of the stability of polymorphs.

The Gibbs free energy functions have been introduced for a thorough discussion of the conditions of thermodynamic stability of crystal modifications and in order to enable a high throughput of such assessment of new active substance in the areas of drugs, agrochemicals, and additives with a substituted phenoxyacetic acid in 1974 by Marti *et al*. [17] and for sulfathiazole [4]. The benefit of the knowledge of the absolute thermodynamic relationship is the independence from kinetic experiments and kinetic obstacles. The importance of these free energy relations for crystalline

Table 2 Melting characteristics of cimetidine modifications (DSC); (medium values and absolute range from 2 different series in 2 different laboratories)

Modification	A	D
Melting point/°C	140.30±0.1	140.65±0.1
Enthalpy/kJ mol^{-1}	39.7±0.5	41.0±0.5

Table 3 Best value for the enthalpy of fusion for high purity indium (99.9995%)

Year of evaluation	$\Delta_{fus}H$± standard deviation of the mean value/J mol^{-1}	Number of primary literature data	Reference
1982	3303±10	17	[14]
March, 1998	3292±6	34	[15]
December, 1998	3288±5	46	[16]

substances and their limitations are until today not widely known and understood. Some scientists believe in relative descriptions which are also of a certain importance, but omit the absolute thermodynamic relationship which is the base for all kinetic observations.

However, discussion of thermodynamic stability and monotropy or enantiotropy in particular needs experimental data of high accuracy. Enthalpies of fusion independent of temperature are needed for a first approximation of the thermodynamic transition point $T_{trs,AD}$ of two crystal modifications, which has been introduced by Marti *et al*. [18]:

The Gibbs free energy functions of the polymorphs are given by Eq. (1) referring to the liquid or supercooled state as the reference state:

$$\Delta G_{S,i}(T) = G_{S,i}(T) - G_{lq}(T), \quad i = A, D \tag{1}$$

and

$$\Delta G_{S,i} = -\Delta_{fus}H_i\left(1 - \frac{T}{T_{fus,i}}\right) \tag{2}$$

The thermodynamic transition temperature is defined by equal values of the Gibbs free energy functions of both modificaitons and calculated according to Eq. (3) as

$$T_{trs,AD} = \frac{\Delta_{fus}H_A - \Delta_{fus}H_D}{\frac{\Delta_{fus}H_A}{T_{fus,A}} - \frac{\Delta_{fus}H_D}{T_{fus,D}}} \tag{3}$$

For enantiotropy the calculated thermodynamic transition temperature $T_{trs,AD}$ is a real value below the lower melting point of the two polymorphs whereas in the case of a monotropically related pair of crystal modifications this transition point is a virtual temperature above the melting points of the two crystal modifications.

A consideration of the monotropy-enantiotropy relation for cimetidine is presented in Table 4. These evaluations are based on the following assumptions:

The temperatures of fusion are regarded as true values with no errors. This assumption is possible because the temperature of fusion of the form D is 0.35 K

Table 4 Monotropy-enantiotropy relation for the A and D modifications of cimetidine according to Eq. (1); $T_{fus,A}$=140.30°C; $T_{fus,D}$=140.65°C

Type	Enthalpy of fusion/kJ mol^{-1}		$T_{trs,AD}$/°C	Crystal modification relationship between A and D
	A	D		
Mean from Table 2	39.7	41.0	virtual	monotropy
A+0.5 D–0.5	40.2	40.5	virtual	monotropy
A+1.0 D–1.0	40.7	40.0	121, real	enantiotropy

Table 5.1 Gibbs free energy functions of A and D modifications and their differences; mean values of enthalpy of fusion for A: 39.7; for D: 41.0 kJ mol^{-1}; $T_{fus,A}$=140.30°C; $T_{fus,D}$=140.65°C

T/°C	ΔG_A/	ΔG_D/	$\Delta\Delta G_{A,D}$/
	kJ mol^{-1}		
160	+1.89	+1.92	–0.03
140	–0.03	–0.06	+0.03
120	–1.95	–2.05	+0.10
100	–3.87	–4.03	+0.16
80	–5.79	–6.01	+0.22
60	–7.71	–7.99	+0.28
40	–9.63	–9.97	+0.34
20	–11.55	–11.95	+0.40
0	–13.47	–13.93	+0.46
–20	–15.39	–15.92	+0.53
151.7*	+1.09	+1.09	±0.00

* value of $T_{trs,AD}$

Table 5.2 Gibbs free energy functions of A and D modifications and their differences; enthalpy of fusion (type A+0.5; D–0.5) for A: 40.2; for D: 40.5 kJ mol^{-1}; $T_{fus,A}$=140.30°C; $T_{fus,D}$=140.65°C

T/°C	ΔG_A/	ΔG_D/	$\Delta\Delta G_{A,D}$/
	kJ mol^{-1}		
160	+1.92	+1.89	+0.02
140	–0.03	–0.06	+0.03
120	–1.97	–2.02	+0.05
100	–3.92	–3.98	+0.06
80	–5.86	–5.94	+0.07
60	–7.81	–7.89	+0.08
40	–9.75	–9.85	+0.10
20	–11.70	–11.81	+0.11
0	–13.64	–13.76	+0.12
–20	–15.58	–15.72	+0.14
193.0*	+5.12	+5.12	±0.00

* value of $T_{trs,AD}$

Table 5.3 Gibbs free energy functions of A and D modifications and their differences; enthalpy of fusion (type A+1.0; D–1.0) for A: 40.7; for D: 40.0 kJ mol^{-1}; $T_{fus,A}$=140.30°C; $T_{fus,D}$=140.65°C

T/°C	ΔG_A/	ΔG_D/	$\Delta\Delta G_{A,D}$/
	kJ mol^{-1}		
160	+1.94	+1.87	+0.07
140	–0.03	–0.06	+0.03
120	–2.00	–2.00	+0.00
100	–3.97	–3.93	–0.04
80	–5.94	–5.86	–0.07
60	–7.90	–7.80	–0.11
40	–9.87	–9.73	–0.14
20	–11.84	–11.66	–0.18
0	–13.81	–13.59	–0.22
–20	–15.78	–15.53	–0.25
121.4*	–1.86	–1.86	±0.00

* value of $T_{trs,AD}$

higher than the value for the A form. Even if a rather small absolute shift of the melting points would exist after the temperature is corrected, both of the melting points would be affected in the same way. However, the enthalpies of fusion are considered as error affected. Therefore 3 cases are collected in Table 4:

- $\Delta_{fus}H$ according to the mean values from Table 2
- $\Delta_{fus}H$ shifted by 0.5 kJ mol^{-1}, namely increased for the A form and decreased for the D form
- $\Delta_{fus}H$ shifted by 1 kJ mol^{-1} in the same way as in case 2.

The Gibbs free energy functions calculated according to Eq. (2) as well as the difference of these functions, namely $\Delta\Delta G_{A,D} = \Delta G_{S,A} - \Delta G_{S,D}$ are presented in Tables 5.1 to 5.3 under the same assumptions as applied in Table 4. The Gibbs free energy functions are presented in Fig. 2 for the mean values of the temperature of fusion and the heat of fusion. The functions are revealing the two crystal modifications as monotropically related, however, the differences in energies are extremely small, namely about 30 J mol^{-1} in the melting region and about 400 J mol^{-1} at room temperature.

Solution calorimetry

Solution calorimetry at room temperature (25°C) also showed reproducible and distinct difference between the two modifications.

The results of the dissolution measurements in water and in methanol for modification A are shown in Table 6 and for modification D in Table 7. The enthalpies of

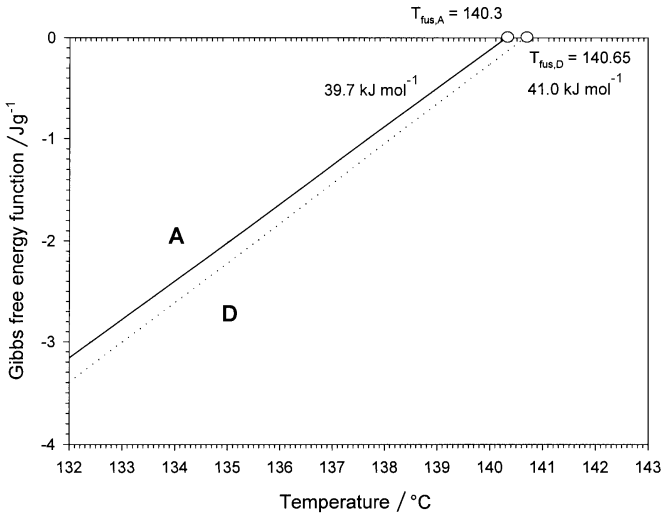

Fig. 2 Gibbs free energy functions of the crystal modifications A and D

dissolution are collected in Fig. 3 as well as the differences obtained for the crystal forms and for the two solvents. The differences of the enthalpy of dissolution at 25°C between the two crystal modifications are practically equal in water and in methanol as is expected due to the fact that all the solvent effects are eliminated. However, this is only valid if the concentrations of cimetidine in solution are practically identical. Therefore, the result with a considerable lower concentration for the A modification in water (Table 6, 2nd row) is not taken into account.

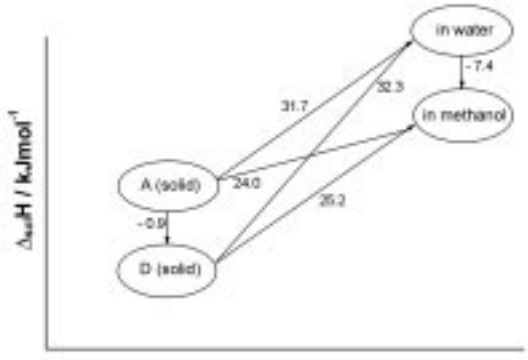

Fig. 3 Enthalpy of dissolution and differences thereof: cimetidine modifications A and D

The difference in enthalpies yielded from solution measurements corresponds to the enthalpy necessary to transform one modification into the other. A common problem hereby is the fact, that a small difference of two big quantities is calculated.

The average values given in Tables 6 and 7 calculate the transition enthalpy for modification A to D to

$$\Delta_{trs}H_{A\rightarrow D,\,H_2O} = \Delta_{sol}H_{A,\,H_2O} - \Delta_{sol}H_{D,\,H_2O} = 31.7 - 32.3 = -0.6\pm0.4 \text{ kJ mol}^{-1}$$

and

$$\Delta_{trs}H_{A\rightarrow D,\,MeOH} = \Delta_{sol}H_{A,\,MeOH} - \Delta_{sol}H_{D,\,MeOH} = 24.0 - 25.2 = -1.2\pm0.4 \text{ kJ mol}^{-1}$$

The mean value for the enthalpy of transition in both of the solvents is

$$\Delta_{trs}H_{A,D} = -0.9\pm0.4 \text{ kJ mol}^{-1}$$

which is a rather small value.

Table 6 Solution calorimetry of form A in water and methanol at room temperature (25°C)

Solvent	Mass of cimetidine A/		Q_{react}/J	ΔH/kJ mol^{-1}	
	g	mmol			average
Water	0.0941471	0.3731	11.804	31.67	31.7
	(0.0221087)	0.0876	2.665	(30.53)	
Methanol	0.0662080	0.2624	6.230	23.78	24.0
	0.0685388	0.2716	6.547	24.14	

Table 7 Solution calorimetry of form D in water and methanol at room temperature (25°C)

Solvent	Mass of cimetidine D/		Q_{react}/J	ΔH/kJ mol^{-1}	
	g	mmol			average
Water	0.0955902	0.3788	12.189	32.20	32.3
	0.0517301	0.2050	6.629	32.39	
Methanol	0.0730582	0.2895	7.259	25.11	25.2
	0.0815796	0.3233	8.137	25.20	

The dissolution experiments would also indicate that the D modification is the stable crystal modification at 25°C under the assumption that the difference of the entropies of modifications A and D is zero.

Molecular modelling

In Table 8 the energy decomposition for the A modification after the deletion of one cimetidine molecule is expressed as the so-called crystal energy ΔA.

The same procedure was done for a 'minicrystal' of the modification D, and the result is expressed as ΔD in Table 9.

The total energies of the full crystals and after deletion of one molecule are theoretically calculated and are not to be considered; only the change in the proportion of the forces may be used. The difference between A and D after deleting one molecule is the calculation of highest interest: Theoretical crystal energy of A and D, however, showed differences of 6.2 kJ mol^{-1} (Table 10), indicating the crystal modification A to be considerably more stable than the crystal modification D.

Table 8 Calculated energy decomposition (cimetidine A) in kJ mol^{-1}

		Minicrystal	After deletion of 1 molecule	ΔA
Valence terms	bonds	408.2	404.0	4.3
	angles	9622.5	9522.2	100.3
	torsions	1053.0	1042.2	10.8
	inversions	42.8	42.3	0.5
Nonbond terms	van der Waals	–3448.6	–3333.1	–115.5
	electrostatic	–4728.5	–4661.7	–66.8
	hydrogen bonds	–2793.0	–2743.3	–49.7
Total energy		156.3	272.4	–116.1

Table 9 Calculated energy decomposition (cimetidine D) in kJ mol^{-1}

		Minicrystal	After deletion of 1 molecule	ΔD
Valence terms	bonds	309.1	305.9	3.2
	angles	9156.0	9060.6	95.4
	torsions	1004.1	993.7	10.4
	inversions	8.7	8.6	0.1
Nonbond terms	van der Waals	–3253.0	–3148.9	–104.1
	electrostatic	–3680.9	–3628.0	–52.9
	hydrogen bonds	–2991.0	–2929.0	–62.0
Total energy		553.0	662.8	–109.9

Table 10 Calculated energy differences of cimetidine A and D in kJ mol^{-1}

		ΔA	ΔD	ΔA–ΔD
Valence terms	bonds	4.3	3.2	1.1
	angles	100.3	95.4	4.9
	torsions	10.8	10.4	0.4
	inversions	0.4	0.1	0.3
Σ		115.8	109.1	6.7
Nonbond terms	van der Waals	–115.5	–104.1	–11.4
	electrostatic	–66.8	–52.9	–13.9
	hydrogen bonds	–49.7	–62.0	12.3
Σ		–232.0	–219.0	–13.0
Total energy		–116.1	–109.9	–6.2

Discussion

In a previous paper [3] the two modifications A and D were regarded 'isoenergetic' within the accuracy of the DSC method used there.

In the present study, measurements with low heating rates showed no sign of transformation which would imply a monotropic pair. The absence of transformation of a modification during the experiments is no proof for monotropy because the unstable form could be metastable as any transition is a kinetically controlled process. Therefore, concluding from the absence of transition that the polymorph studied is stable, could be a fallacy. In general, on the basis of a data set for a linear or non-linear Gibbs free energy function for the polymorphs studied, kinetic experiments on the stability of polymorphs are easily structured and performed in an optimum way.

Restricting to cimetidine and to the polymorphs A and D thereof, the melting points found can be relied on in the absolute sense and also in the difference between the two forms of 0.35 K based on results from two laboratories. A further proof of a difference of this value is given in Fig. 1 revealed for a mixture of the two polymorphs. The difference of the melting points is in this experiment unaffected by the temperature calibration of the instrument. The small difference in melting points alone indicates that the modifications may be 'isoenergetic'. Expecting enthalpies of fusion for the two polymorphs also being very close to each other would lead to a $\Delta\Delta G_{A,D}$ in the melting point region which is also rather small. Therefore, even in a 1:1 physical mixture, practically no driving force for a transformation is existing. In such a case precise determination of the enthalpies of fusion seems possible. The robustness of caloric calibration of the instrument used is demonstrated in Table 3 with a shift of the reference value for indium over 16 years of only 0.5% and a standard deviation of the mean of only 0.15%. All the literature values published are within a span of about 25%. With such a big range of reference values in calibration an enthalpy of fusion for any organic substance can vary up to 3 kJ mol^{-1}. Together with the possible errors for the temperature of fusion for any inorganic substance given by errors of calibration and of the measurements due to the reference material, the reference value, the sample handling and sample stabilities under the experimental conditions chosen, the Gibbs functions calculated can be meaningless and far from reality. Under such laboratory conditions, the only opportunity to study the transformation of polymorphs over a certain temperature interval are kinetic experiments, however, a laborious alternative.

The results in Table 4 are revealing that cimetidine polymorphs A and D are monotropically related. However, adding errors to the enthalpy of fusions in a statistically not very probable direction, namely for A with +1 kJ mol^{-1} and for D with –1 kJ mol^{-1} the system gets enantiotropical. The same considerations are presented quantitatively in the Tables 5.1. to 5.3. showing for the mean values of the temperatures of fusion and enthalpy of fusion monotropy for A and D. The $\Delta\Delta G_{A,D}$ value for the mean data at 120°C is –100 J mol^{-1} and for 20°C it is –400 J mol^{-1} (molecular mass of cimetidine = 252.34). The other two data sets (Tables 5.2 and Table 5.3) have even lower $\Delta\Delta G_{A,D}$ values. The Gibbs free energy function reveal the quantitative fact that it is not easy to transform the unstable A modification into the more stable D form and it is not surprising that no transformations in the solid state have been observed so far.

The difference of the enthalpy of fusion for 140°C is $\Delta_{trs}H_{A,D}$=–1.3±0.5 kJ mol^{-1} and is regarded identical (within the error limits) with the difference of the enthalpy of dissolution of –0.9±0.4 kJ mol^{-1} at 25°C. This finding implies that the difference of the molar heat capacities of A and D, namely $\Delta\Delta C_{p,A,D}$ is practically zero. This result supports the monotropy of the two modifications because the higher approximation of the Gibbs function (Eq. (11) in [18]) is reduced to a practically identical function.

From the explicite crystal structure data (Table 1), where the theoretical density of the crystals are given in terms of the volume of the unit cells, it can be concluded that D is the more stable modification because of a higher density. The difference in density is very small (ca. 0.7%) compared to the commonly accepted limits of resolution of X-ray diffraction. Crystal structure data as well indicate that the two polymorphs A and D are rather similar to each other.

Under tribomechanical treatment, modification D is regarded most stable compared with other modifications of cimetidine because transition upon seeding occurs after intense trituration [3].

In an aqueous slurry of modifications A and D respectively, no transformation was observed despite of a high solubility of the compound in water. Even if a physical mixture of the two modifications (50:50) was stored for a year at ambient conditions, there was no transformation observed [3]. This is another indication that the driving force for a transformation into form D is extremely low. A direct observation of a transition from the crystal modification A into D in a suspension would have to be planned on the basis of the Gibbs functions.

The theoretical calculations would just contradict the above mentioned experimental consistent results:

The conclusion of calculations is that the crystal energy of modification A (the one with the intramolecular hydrogen bond) is mainly formed by van der Waals and electrostatic forces, whereas with D hydrogen bonding has higher impact; and in total the internal energy of D is estimated to a higher value.

Calculations in the present study were made from the physical point of view by deleting one molecule from the middle of the 'minicrystal', but neither melting nor dissolution takes place there. This fact may also explain the difference between theoretical and experimental results. Another aspect is the fact that the 'minicrystals' may be of too small dimensions because they only comprise of 100 molecules, so that the central molecule would only have about 2 neighbours in each direction and the forces may be effective over longer distances. This is probably not the main point as it holds for both modifications and forces will be extremely small.

Similar contradictory results regarding theoretical crystal energy determinations as described above was reported for other polymorphic drug substances by Osborn and York [19]. For modifications of both paracetamol and carbamazepine they found calculated differences of crystal energies of about 8 kJ mol^{-1}, which is in the same range as was found by calculations of cimetidine in the present study. Their experimental results indicate smaller differences than theoretically calculated for both substances (1.2 and 0.6 kJ mol^{-1}, respectively). In the case of paracetamol, the difference and therefore the stability relationship, is reversed by the calculation with respect to the experiments, the same phenomenon as was found in the present study.

Osborn and York attributed this discrepancy of theoretical and experimental results to a lack of sensitivity of the molecular modelling method.

Reasons for such contradictory results may be that the calculations are at present not capable of solving complex solid state problems as expressed by the Gibbs functions: they only consider 0 K and cannot describe the temperature relation of stability of two crystal structures. However, the experimental findings of the stability regions of polymorphs obtained by various methods such as thermodynamic data by DSC and dissolution experiments, by partial pressure measurements or observations in the hot-stage microspcope or IR or Raman spectroscopy, or in the case of hydrates and solvates using thermobalance e.g. together with FT-IR are until now the state of the art.

Conclusions

Crystal structure data as well as thermodynamic data for the two modifications A and D of cimetidine are rather similar to each other and therefore the Gibbs free energy functions calculated quantitatively according to Marti [4] are also closely related.

This fact is already indicated by the two melting points being as close as $T_{fus,A}$=140.30°C and $T_{fus,D}$=140.65°C. The practically isoenergetic situation of the two modifications could be solved by DSC measurements in two independent laboratories and are supported by two facts: (i) applying the highest possible precision in DSC and dissolution experiments, and (ii) combining all the available results to a quantitative result supported by qualitative ones.

The two modifications of cimetidine are not isoenergetic in a strict sense, but they are monotropically related, the D modification being the stable crystal structure over the whole temperature range of existence in the solid state.

Anyhow, no transformation of the instable A modification into the D modification could be observed neither in the DSC experiment nor as an aqueous slurry.

The explanation for this fact is given by the Gibbs free energy functions.

The differences of the Gibbs free energy functions are extremely small, namely $\Delta\Delta G_{A,D}$=–100 J mol^{-1} at 120°C and $\Delta\Delta G_{A,D}$=–400 J mol^{-1} at 20°C. Therefore the driving force for a transformation of the A form into the D form is so small, that such a transformation would only take place under carefully selected conditions, as the kinetic activation energy has to be overcome.

Using theoretical calculations, other polymorphic systems with differences of the melting points that are higher by a factor 10 to 100, which means 3 to 30°C and Gibbs free energy functions also showing marked differences larger by a factor of 20 to 40, which means 5 to 10 kJ mol^{-1} may be easier to study than cimetidine modifications. Carefully selected substances with well-known Gibbs free energy functions of such marked differences between their polymorphs would be a starting point for studies using molecular modelling procedures. Cimetidine modifications A and D may in the next decades be used as a model for the evaluation of the abilities of calculation methods.

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