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Polymorphism in acesulfame sweetener: structure–property and stability relationships of bending and brittle crystals†

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Acesulfame is found to exist in two crystalline forms of which Form I (needles) shows bending upon mechanical stress. Crystal structures explain their mechanical response. This is the first case of aliphatic organic compounds featuring a bending phenomenon. Form I is physically more stable than Form II in ambient conditions.

Polymorphism in crystalline materials is of paramount importance to the pharmaceutical as well as the food industry.[1] Different crystalline forms of a solid compound can have different physical, chemical and mechanical properties. Thus, polymorphic behaviour of pharmaceutical or food materials must be thoroughly investigated for the successful development of a quality product. Polymorphs with different mechanical properties can have profound implications for the processing, formulation and eventually product performance.[2] In fact, control of the mechanical properties requires an improved understanding of structure–property relationships.[3] A seminal contribution by Desiraju and co-workers[4] demonstrates that organic crystals exhibit bending and shearing phenomena just as inorganic materials do[5] when mechanical stress is applied. They proposed that the sorting of visually indistinguishable polymorphs of 6-chloro-2,4-dinitroaniline is possible based on the mechanical properties.[6] Incidentally, the bending is observed in one of the crystal forms of an anticonvulsant drug, venlafaxine hydrochloride.[7] The bending/shearing phenomenon in organic crystals is attributed to the corrugated sheet or layered structure with 4 Å short axis and anisotropic interactions. However, all these compounds are broadly aromatic and this communication unveils the bending phenomenon in aliphatic cyclic compounds for the first time.

Acesulfame (6-methyl-1,2,3-oxathiazin-4(3H)-one 2,2-dioxide) is an aliphatic calorie-free sweetener and its potassium salt is widely used in food products, beverages, vitamins, table-top sweeteners, cosmetics, and in pharmaceutical formulations. The sweetening power of acesulfame is about 180 times greater than that of sucrose.[8] This study deals with the discovery of polymorphism in acesulfame and unique mechanical behaviour of one of the crystal forms. Polymorphs of acesulfame, Forms I and II, were characterized with respect to their physical and mechanical properties and thermodynamic stability relationships between the forms were established. The mechanical properties of the two forms were tied to their crystal structures.
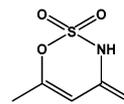
Acesulfame potassium (Ace K) was neutralized with HCl to afford a salt free acesulfame (ESI†). Good quality needle shaped crystals were obtained from ethyl acetate (EtOAc) by the evaporative crystallization of acesulfame in ambient conditions (Fig. 1a). Motivated by our interest in the mechanical properties of crystals and for curiosity, we applied stress with the help of two metallic needles on both ends of the needles, and to our surprise, they became bent (Fig. 2). However, these crystals could not be straightened back completely by a counter stress. In search of other crystal forms, these needles ($\sim$15 mg) were ground in a Retsch mixer mill for 10 s. A few drops of CH_2Cl_2 were added to the ground powder placed on a glass slide while observing under the microscope. Interestingly, few prismatic crystals were formed instantaneously (Fig. 1b). As opposed to needles, these crystals showed breakage upon mechanical stress.

The contrast in morphologies as well as mechanical properties of the crystals indicated the existence of polymorphism in acesulfame and prompted a detailed characterization of these phases. However, it was difficult to generate prismatic crystals from the bench-top solvents, CH_2Cl_2, $CHCl_3$, EtOAc and ethanol by slow evaporations, as needles were obtained all the time. Therefore, seeds were used to control the nucleation and to promote exclusive growth of the prisms.[9] With this strategy, good quality crystals (prisms) were obtained in reasonable quantities.

Thermal analysis, DSC and TGA, was carried out for needle and prismatic crystals. DSC traces of these crystalline phases were different (Fig. 3a). Needles showed one major endotherm
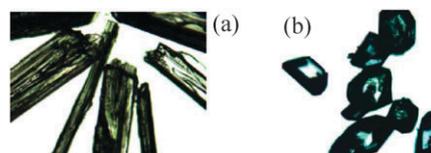
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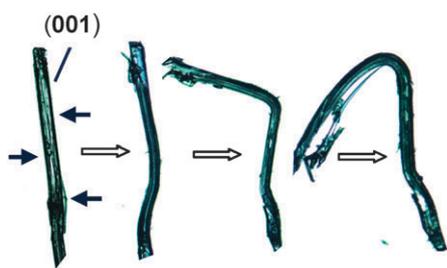
Fig. 1 Optical micrographs of (a) needle and (b) prismatic crystals.

Fig. 2 Bending sequence in acesulfame needle crystals.

at ~122 °C (enthalpy of transition, 130.8 ± 2.6 J g^{-1}) that is attributed to a melting event. Two endotherms were observed for prisms: a minor endotherm at ~83 °C (5.4 ± 0.5 J g^{-1}) that could be interpreted as a solid–solid phase transition and a major endotherm at ~122 °C (132.4 ± 4.9 J g^{-1}) corresponding to a melting event (Fig. 3a). TGA profiles showed the absence of solvent molecules in the crystal.†

The powder X-ray diffraction patterns of these two phases were distinctly different, confirming that they are polymorphs (Fig. 3b). We classified the needle crystals that featured bending as Form I and the prisms that were brittle in nature as Form II.§ Furthermore, Raman analysis corroborates the DSC and PXRD conclusions and provides molecular insights into differences between these two solid forms.†

The acesulfame dimorphs were structurally characterized by single crystal X-ray diffraction to reveal the relationship between the structure and the mechanical property.¶ Form I crystallizes in the monoclinic, P2$_1$/c space group with two molecules of acesulfame in the asymmetric unit (Z′ = 2). The molecules adopt two different conformations.† Interestingly, the crystal structure analysis reveals that the acesulfame molecules form a layered structure. The layers were stabilized by the robust imide catemers with N–H···O synthons (d/Å, θ/°: 1.74, 169; 1.77, 156) to form one-dimensional tapes along the a-axis (Fig. 4a). These catemers were propagated in a second dimension with the support of strong and specific bifurcated C–H···O interactions to form layers. Consequently, the crystals have grown along the c-axis. The short axis of the unit cell is 7.4940 (~2 × 4 Å). The layers were stacked in an antiparallel fashion with separations of ~3.2 Å and ~3.3 Å with weak and non-specific C–H···O bonds. All the molecules in the layers were arranged in parallel to the face (001) and the bending had occurred along this plane (Fig. 4b). The face indexing of the crystal was in accordance with the bending direction and the solid-state packing.† This is not the corrugated sheet structure that is typical of some of the bending structures,[4] however, Form I is a classical case of layered crystal
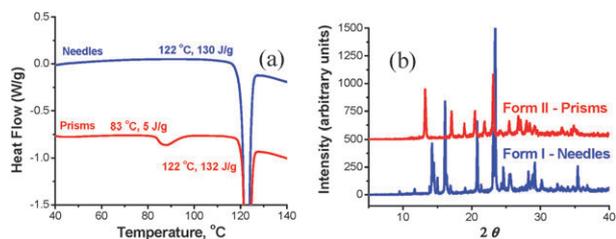

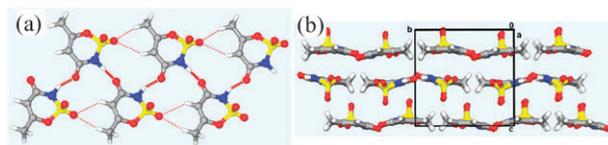**Fig. 4** (a) Crystal packing of Form I along the c axis. Note the N–H···O catemers between the two symmetry independent molecules. (b) Stacks view down the a axis and the bending which occurs in the [001] plane.

exhibiting bending. To our knowledge this is the first case of an aliphatic organic crystal that featured bending behaviour.

Form II crystallizes in the triclinic, P1̄ space group with Z′ = 1. Its conformation was similar to one of the two independent molecules of Form I.† Form II prisms could not be bent in any plane upon mechanical stress. Not surprisingly, analysis of the crystal structure revealed that it was not a layered structure. However, it was found to have the short axis of ~4 Å. In fact, it was claimed that it is a necessary but not a sufficient condition for a crystal to show shearing or bending.[4] The major interaction type was a discrete centrosymmetric N–H···O imide dimer synthon (d/Å, θ/°: 1.77, 169) (Fig. 5a).[10] A close packing was efficiently achieved in 3D by C–H···O hydrogen bonds (d/Å, θ/°: 2.49, 157; 2.65, 125; 2.67, 145; 2.68, 151) (Fig. 5b). As rationalized in the literature, brittleness appears to be because of the subtle differences in the relative strengths of the interactions in three orthogonal directions.[4] The simulated and experimental PXRD patterns for Forms I and II were perfectly matched.†

In this part, we sought to understand the stability relationships of the Forms I and II. Thermodynamic analysis of DSC data formed an excellent basis for the construction of a qualitative energy–temperature diagram (Fig. 6).[11] Physical properties of the acesulfame polymorphs are given in Table 1.

The transitions were endothermic and the melting temperature differences were small or insignificant, and hence according to heat of transition and heat of fusion rules, the polymorphs are enantiotropes (Fig. 6).[12] The PXRD pattern of Form II heating pass ~83 °C in the DSC was matched with that of Form I, which implies that the Form II had transformed to Form I. Further, heat–cool–heat studies in the DSC suggested that these enantiotropic polymorphs were non-reversible.† In general, enantiotropic transitions are thermodynamically reversible with temperature and pressure, however, they may in turn be discernible as irreversible in practical investigations.[13] In any case their free energies become equal at the transition temperature $T_p^{\text{II–I}}$.

The transition temperatures observed in DSC could be of kinetic origin and slurry transformation studies[14] are a practical way to determine the thermodynamic stabilities of different solid forms. The PXRD and DSC analysis of the
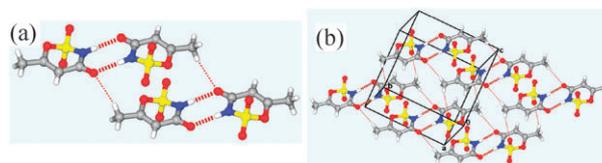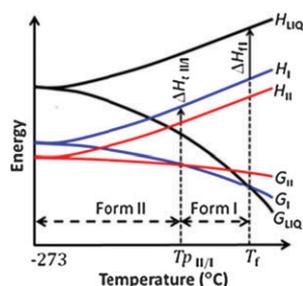

Fig. 3 Acesulfame (a) DSC traces and (b) PXRD patterns for Forms I and II.

Fig. 5 Acesulfame Form II. (a) Centrosymmetric N–H···O dimer synthon, and (b) the effective close packing via C–H···O interactions.

Fig. 6 Energy–temperature diagram of an enantiotropic dimorphic system: G, free energy; H, enthalpy; T_p, transition temperature; T_f, melting temperature.

Table 1 Physical properties of acesulfame, Forms I and II

Modification	Form I	Form II
M.p. (°C) DSC onset temp.	122.27 ± 0.13^a	—
Enthalpy of transition/J g^{-1}	—	82.57 ± 0.57^a
Calculated density/g cm^{-3}	1.643	1.755
Packing co-efficient C_{k*}	67.8	72.7
True density/g cm^{-3}	1.6154 ± 0.0021^b	1.7097 ± 0.0094^b
Stability at 22 °C	Stable	Metastable
Lattice energies/kcal mol^{-1}	−28.25	−29.83

^{a} $n = 3$ determinations. ^{b} $n = 10$ determinations, true densities of Forms I and II are significantly different (T-test, $p < 0.05$).

product phase from slurry studies (at room temperature (RT) of about 22 °C) indicated that the Form II had transformed to Form I. This result confirmed that the Form I is thermodynamically more stable than the Form II in ambient conditions and the transition temperature could be at or below RT. Thus, adequate attention must be paid with respect to evaluating the physical stabilities of enantiotropic polymorphs at storage conditions.†

The calculated densities and packing fractions were obtained from the single crystal structures at −123 °C and true densities for these forms were measured using a pychnometer at RT (Table 1). The calculated density of Form II was higher than that of Form I, which is in line with the close packing observed in Form II. Lattice energy calculations further indicated that the Form II had lower free energy (~ 1.6 kcal mol^{-1}) compared to Form I at −123 °C, and therefore, Form II is thermodynamically stable at −123 °C.† In fact, the stability order has changed somewhere between −123 °C and RT as indicated by equilibrium slurry studies. However, the density of Form II was higher than that of Form I at ambient temperature. As cautioned in the literature, the density rule can deviate for solids with $Z' \neq 1$ which is the case for Form I.[15]

In conclusion, the two polymorphic forms of acesulfame sweetener were discovered and unequivocally characterized. One of these aliphatic polymorphs showed bending (Form I) and the other was brittle (Form II) in nature. The bending phenomenon in Form I is very well correlated to the layered structure. Forms I and II were enantiotropically related. Form I is thermodynamically more stable than Form II in ambient conditions. Future prospects are to investigate the influence of mechanical properties (bending/brittle) on the powder compaction or tableting behaviour.

Notes and references

§ Baseline physical characterization of neutral acesulfame shown to be Form I.

¶ Crystallographic data for the acesulfame dimorphs ($C_4H_5NO_4S$, $M = 163.15$, Kappa CCD, −123 °C). Form I: monoclinic, $a = 7.4940(15)$, $b = 11.784(2)$, $c = 15.238(3)$ Å, $\beta = 101.36(3)°$, $V = 1319.3(4)$ Å^3, $D = 1.643$ g cm^{-3}, space group = $P2_1/c$, $Z = 8$, μ(Mo-Kα) = 0.443 mm^{-1}, size 0.22 ×0.18 × 0.13 mm. 9845 total reflections of which 5031 were independent, 4024 observed [$I > 2\sigma(I)$]. Refinement against F^2 with 183 parameters, R1 [$I > 2\sigma(I)$] = 0.0432, wR2 = 0.1433. Form II: triclinic, $a = 6.3310(2)$, $b = 7.4720(3)$, $c = 7.7150(15)$ Å, $\alpha = 62.5460(15)$, $\beta = 73.1710(18)°$, $\gamma = 77.874(2)°$, $V = 308.73(2)$ Å^3, $D = 1.755$ g cm^{-3}, space group = $P\bar{1}$, $Z = 2$, μ(Mo-Kα) = 0.473 mm^{-1}, size 0.28 ×0.26 × 0.18 mm. 1307 total reflections of which 1307 were independent, 1256 observed [$I > 2\sigma(I)$]. Refinement against F^2 with 91 parameters, R1 [$I > 2\sigma(I)$] = 0.0313, wR2 = 0.0910.

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