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### Elastic Constants and Related Mechanical Properties of the Monoclinic Polymorph of the Carbamazepine Molecular Crystal

Himansu Mohapatra and Craig J. Eckhardt\*

*Department of Chemistry, Center for Materials Research and Analysis, University of Nebraska—Lincoln, Lincoln, Nebraska 68588-0304*

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Brillouin scattering has been used to probe the acoustic phonons of the monoclinic ( $P2_1/c$ ) polymorph of the drug carbamazepine (CBZ III). By sampling a variety of acoustic phonons, the complete elastic constant tensor has been determined for this CBZ polymorph. The diagonal elastic constants  $c_{11}$ ,  $c_{22}$ ,  $c_{33}$ ,  $c_{44}$ ,  $c_{55}$  and  $c_{66}$  are 10.89, 11.47, 11.32, 3.68, 0.85 and 2.89 GPa, respectively. The elastic constants of CBZ III are effectively governed by nondirected dispersive type interactions similar to aromatic systems with delocalized  $\pi$  bonds. The bulk modulus and linear compressibility have been calculated from the compliance matrix. The relative strength of intermolecular interactions in different directions is estimated from the linear compressibility plotted in three crystallographic planes. Cauchy's ratio, calculated from the elastic constants, suggests that many-body forces of dispersive interactions contribute significantly to the lattice anharmonicity of CBZ III.

#### Introduction

Organic compounds have the ability to crystallize in more than one crystalline form that differs in the arrangement or conformation of the molecule in the crystal lattice; this is referred to as polymorphism. The dissimilar interactions that arise from differences in arrangements of molecules cause variation in the physical properties of polymorphs.<sup>1–5</sup> Polymorphism is a major issue in drug uptake and tablet processing of pharmaceuticals.<sup>6–12</sup> This has led to a wide variety of research activities ranging from understanding crystal packing to polymorph prediction.<sup>13–27</sup> Polymorph stability and ease of formation arise from variations in intermolecular interactions. Thus, knowledge of intermolecular forces is crucial to understanding the phenomenon. A property closely related to intermolecular interactions in molecular crystals is the elasticity of the material. A complete picture of the elasticity demands accurate determination of the elements of the elastic constant tensors.

Recently, there has been considerable interest in polymorph prediction by computational methods.<sup>28–32</sup> There are fundamental issues that need to be addressed.<sup>33</sup> First, the energy differences between crystal structures obtained computationally are small compared to the accuracy of the calculation. Thus, calculatable experimental quantities that are sensitive to intermolecular forces are most useful if they can be obtained from the actual force field. Computational methods have revealed many different alternative crystal-packing arrangements within a narrow energy range that could be possible polymorphs, but only a few are experimentally observed. Furthermore, in some systems, the global-minimum structure is not the experimentally observed crystal structure. To eliminate other possibilities, factors such as growth rate, mechanical properties and morphology have been considered.<sup>28</sup> Another important issue is that the stability of crystal structures predicted computationally is discussed mostly in terms of enthalpy while the entropy contribution is ignored. The intra- and intermolecular entropy

\* Corresponding author. E-mail: [ceckhardt1@unl.edu](mailto:ceckhardt1@unl.edu).

can be derived from vibrational analysis, but most computational methods are usually restricted to the harmonic approximation.

The relative mechanical hardness and softness of a series of related polymorphs is a property of general interest, particularly for the drug processing industries.<sup>34</sup> Harder forms will have better granularity, filterability and flow properties. Further, in drug tableting, the hardness of the tablet and dosage, which depend on the amount of pressure applied during the compaction process, are related by the mechanical properties of the material.<sup>35–38</sup> Thus, it is practically useful to characterize pharmaceutical polymorphs based on their elastic properties.

A detailed understanding of the mechanical properties can also provide insight into the solid-state reactivity and phase transformations that are caused by grinding or other processing by mechanical means. The mechanism of transfer of mechanical energy from the lattice into molecular modes is a function of anharmonic coupling between phonons and molecular degrees of freedom. Luty, Ordon and Eckhardt have shown how mechanical energy applied to a crystal can be translated directly into molecular electronic modes.<sup>39,40</sup> The anharmonicity of the phonon modes is important in determining the effectiveness of this transfer as well as determinative of thermal conversion of the mechanical energy. Therefore, the elasticity of the material is an important parameter that reflects the extent of coupling of mechanical energy either to cause dissociation by effective band gap reduction and reaction or to undergo a phase transformation.

In this paper, we present the elastic constants and related properties obtained by Brillouin scattering for the monoclinic polymorph of a drug, carbamazepine (5*H*-dibenz[*b,f*]azepine-5-carboxamide) (CBZ III), in the space group *P*2<sub>1</sub>/*c* with lattice parameters *a* = 7.529, *b* = 11.148, *c* = 15.470 and *β* = 116.17° at room temperature.<sup>41</sup> CBZ III crystallizes in the monoclinic system. Thus, a set of 13 elastic constants is required to fully describe the molecular displacements associated with an arbitrary stress. CBZ, an anticonvulsant and mood stabilizing drug, has four anhydrous polymorphs, commonly referred to as forms I–IV.<sup>42</sup> In all four, the CBZ molecules exist as hydrogen-bonded pairs connected by an amide group. Form I crystallizes in the space group *P*1̄, form II (*R*3̄) and form IV (*C*2/*c*). The elastic constants of CBZ III can provide a measure of the interaction energy that packs these dimers into a stable crystal-packing arrangement. In earlier reports, terahertz spectroscopy has been used to study the optical phonons of CBZ polymorphs.<sup>43</sup> The elasticity is, however, probed by acoustic phonons using Brillouin spectroscopy which directly measures their velocity. In the case of low symmetry molecular crystals, the number of elastic constants is large. Therefore, to determine them accurately requires many sets of acoustic velocities from different phonon directions. This is constrained by the demand of optical-quality crystals with a large number of faces that provide the various orientations that are needed.

In the following, the principle of Brillouin scattering is described, followed by the experimental description and results. All 13 elastic constants are calculated from the experimental results. The ensuing discussion of specific elastic constants involves comparison to other organic crystals to gain insight into the nature of the intermolecular interaction governing the elasticity of the material. Finally, linear compressibilities and many-body interactions are discussed.

## Principles of Brillouin Scattering

Thermally excited molecular motions in a condensed phase generate periodic fluctuations in the density that propagate

through the lattice as sound waves that are called acoustic phonons. Their velocity is directly related to the strength of the force constants holding the molecules in the unit cell in place. Brillouin spectroscopy probes acoustic phonons near the Brillouin-zone center where the wavelengths of phonons are on the order of hundreds of unit cells.<sup>44,45</sup> This long-wavelength approximation allows the material to be modeled as an elastic continuum. Brillouin scattering can be regarded as the Doppler shift of the incident visible light caused by Bragg reflection from the moving “grating” of the sound wave. The acoustic velocities are then calculated from these frequency shifts using the Brillouin-shift equation for an optically anisotropic medium

$$\delta\omega_e = \pm \frac{v_e \omega_i}{c} \sqrt{n_i^2 + n_s^2 - 2n_i n_s \cos \theta} \quad (1)$$

where *n<sub>i</sub>* and *n<sub>s</sub>* represent, respectively, the refractive indices of the crystal along the incident and scattered light directions, *θ* is the angle between these directions, *δω<sub>e</sub>* is the angular frequency shift relative to the incident angular frequency *ω<sub>i</sub>* and *v<sub>e</sub>* is the acoustic velocity.

In the absence of external forces, the general equation of motion of an elastic medium obtained by combining Newton's and Hooke's equations is

$$\rho \ddot{u}_i = c_{ijkl} \frac{\partial^2 u_l}{\partial r_j \partial r_k} \quad (2)$$

This relates the density *ρ* and the *i*th Cartesian component of the molecular displacement about the equilibrium position *u<sub>i</sub>* to its spatial derivatives through the elastic coefficient tensor *c<sub>ijkl</sub>*. Substituting a plane-wave solution to the above equation, and using the long-wavelength approximation yields

$$(c_{ijkl} q_k q_l - \rho v^2 \delta_{im}) u_m^0 = 0 \quad (3)$$

in which the *q<sub>k,l</sub>* are the appropriate direction cosines representing the phonon **q** referenced to the Cartesian system. Nontrivial solutions arise from the Christoffel determinant

$$|c_{ijkl} q_k q_l - \rho v^2 \delta_{im}| = 0 \quad (4)$$

whose eigenvalues are related to the three acoustic velocities for an arbitrary **q**. The polarization of the three acoustic modes is often not exactly parallel or perpendicular to **q**. Therefore, for each **q**, there are two quasitransverse modes, often differentiated as slow and fast quasitransverse modes, and one quasilongitudinal mode. When the elastic constants are not known, an overdetermined set of experimental sound velocities obtained from a variety of phonon directions can be used to calculate unknown elastic constants from eq 4.

An iterative, linear, least-squares minimization routine is used to determine the elastic constants from the set of experimental sound velocities.<sup>46</sup> For each of the sampled acoustic phonons and for an arbitrary set of elastic constants, the program solves the eigenvalues of the determinant and compares them with the experimentally determined values. The minimization routine incrementally steps the value of the elastic constants until a minimum in the square of the vector difference *e*, between *ρv<sub>calcd</sub><sup>2</sup>* and *ρv<sub>obsd</sub><sup>2</sup>* is obtained.

$$e^T e = \sum_j |\rho v_{e,j,\text{obsd}}^2 - \rho v_{e,j,\text{calcd}}^2|^2 \quad (5)$$

This minimum represents the set of elastic constants that most accurately reproduces the experimental data.

## Experiment

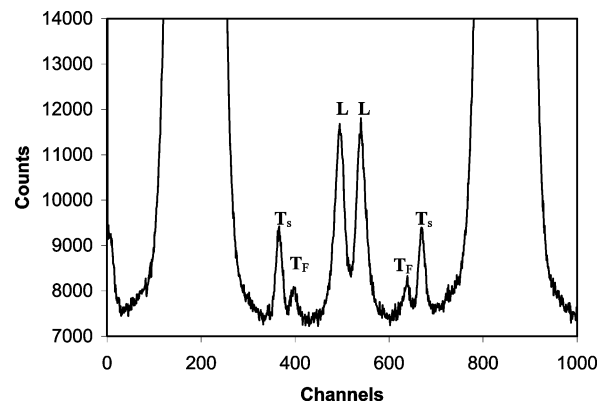
Optical-quality, untwinned, single crystals of CBZ III were grown from ethanol solution by slow evaporation at 25 °C. Lattice parameters were verified by X-ray diffraction and were consistent with the reported values.<sup>41</sup> The crystals formed prominent faces, with two sets of faces zonal to  $[20\bar{1}]$  and  $[301]$ . Faces were assigned by both optical goniometry and single-crystal X-ray diffraction to allow proper crystal alignment.

In addition to a well-defined scattering geometry, the refractive indices must be determined in order to solve eq 1. For CBZ III, only one axis of the optical indicatrix is constrained by symmetry to be coincident with the  $C_2$  crystallographic axis. Measuring the near-normal-incidence specular reflection at 514.5 nm, the wavelength used in these measurements along the principal directions of selected faces permitted calculation of the optical indicatrix using Fresnel's law.<sup>47</sup>

Brillouin scattering experiments were performed on two single crystals of CBZ III at 295 K and ambient pressure. A four-circle, Brillouin-scattering instrument was used that allows rotation of the incident light beam and crystal independently so that a large number of phonons could be sampled.<sup>48</sup> This facilitates a complete determination of the stiffness tensor. Frequency shifts were measured using a triple-pass Fabry–Perot interferometer. To ensure that the Brillouin peaks of CBZ were assigned to the correct spectral order, free spectral ranges (FSRs) of 1.279 and 1.028  $\text{cm}^{-1}$  were employed during this study. The FSRs were calibrated using the known shift of pure liquid benzene. For each scattering geometry, Brillouin spectra were recorded using all polarization combinations: VV, VH, etc.  $V$  and  $H$  are the directions of polarization corresponding to vertical and horizontal orientations of the light's electric vector, respectively, to the scattering plane. This standard designation for polarization is used for clarity, but the actual polarizations were aligned along the major and minor principal directions. If the light polarization is oriented close to vertical, then it is designated as  $V$  and similarly for  $H$  polarization. The need to align the polarization along the principal directions is to prevent depolarization of the incident and scattered light which can yield double peaks or cause peak broadening in the Brillouin spectra. The measured Brillouin spectra are each a result of 100–300 summed interferometer scans depending on the scattering intensity of the modes observed.

## Results

A representative Brillouin spectrum of CBZ III is shown in Figure 1. The spectrum clearly reveals the transverse slow, transverse fast and longitudinal modes. The Brillouin spectra recorded for different combinations of incident and scattered polarizations have shown clear differences in the relative intensity among the acoustic mode which helps to identify and estimate the frequency shifts of the Brillouin modes. The general calculation of scattering cross sections of Brillouin modes for different polarization combinations is rather complicated for phonons that do not propagate along symmetry directions. Most of the phonon directions used in the present study necessarily deviate from the symmetry directions; thus, the general mode-selection procedure has not been carried out to identify the Brillouin modes in the polarization-dependent spectrum.<sup>44</sup> The elastic constants were determined from a set of 19 velocities obtained from a variety of scattering geometries. All of the elastic constants of CBZ III, in standard Voigt notation,<sup>49</sup> are



**Figure 1.** VV-polarized Brillouin spectrum of CBZ III. Scattering is from the  $[-0.830, 0.260, 0.493]$  phonon.  $T_s$ ,  $T_F$  and  $L$  denote, respectively, the slow and fast quasitransverse modes and the quasi-longitudinal mode.

presented in matrix form. The elastic constant matrix is positive definite, thus satisfying the stability condition.

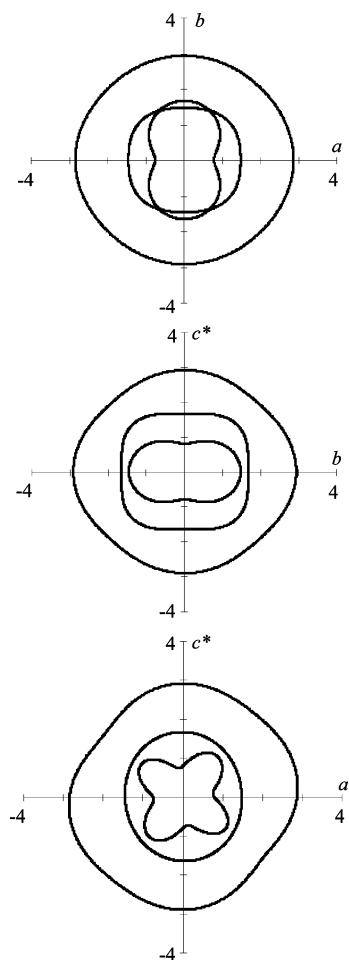
$$c_{ij} = \begin{bmatrix} 10.89 & 4.57 & 6.45 & 0 & 0.78 & 0 \\ & 11.47 & 1.51 & 0 & 0.23 & 0 \\ & & 11.32 & 0 & 0.04 & 0 \\ & & & 3.68 & 0 & -0.08 \\ & & & & 0.85 & 0 \\ & & & & & 2.89 \end{bmatrix} \text{ (GPa)}$$

The average deviation of the experimental velocities compared to those calculated from the minimized elastic constants were 0.783% for the transverse slow modes, 0.940% for the transverse fast modes and 0.160% for the longitudinal modes.

The elastic constants are referenced to a Cartesian system with the crystallographic  $x$ - and  $y$ -axes parallel to the  $a$ - and  $b$ -crystallographic axes, respectively, while the  $z$ -axis is parallel to the reciprocal lattice vector  $c^*$ .

## Discussion

The  $c_{11}$ ,  $c_{22}$  and  $c_{33}$  elastic constants associated with elongation along the  $x$ ,  $y$  and  $z$  directions, respectively, are nearly the same in magnitude.  $c_{44}$ ,  $c_{55}$  and  $c_{66}$  are the elastic constants associated with angle strain between respective axes. Among them,  $c_{55}$ , representing the angle strain between the  $z$ - and  $x$ -axes, is the smallest. The relatively low value of  $c_{55}$  (0.85 GPa) largely contributes to the mechanical softness of CBZ III. The sound velocities in CBZ III, which are calculated from the elastic constants, are presented for three orthogonal planes in Figure 2. The polar plots clearly reflect the effect of diagonal elastic constants on the sound velocity along three axes. For example, in Figure 2, the difference in sound velocity between the transverse slow and transverse fast phonons is greater along the  $a$ - compared to the  $b$ -crystallographic axis. Inspection of the polarizations (the displacement vector  $\mathbf{u}$ ) of the transverse elastic waves shows that the polarization vectors of the shear wave propagating along the  $a$ -axis are nearly along the  $b$ - and  $c^*$ -axes and that the shear wave propagating along the  $b$ -axis has polarizations close to the  $c^*$ - and  $a$ -directions. Hence, the difference in sound velocities between the transverse slow and transverse fast phonons is greater for the  $a$ - compared to the  $b$ -crystallographic axis which merely reflects the effect of  $c_{55}$  being smaller compared to  $c_{66}$ , and the small difference between  $c_{44}$  and  $c_{66}$ . Similarly, in Figure 2, the difference in sound



**Figure 2.** Sound velocity plots calculated from the elastic constants of CBZ III. From the center out, each contour represents the quasitransverse slow mode, the quasitransverse fast mode and the quasilongitudinal mode, respectively. Units are in km/s.

velocity between transverse fast and slow phonons along the  $c^*$ -direction is mostly caused by the difference between  $c_{44}$  and  $c_{55}$ .

A comparison of the elastic constants of CBZ III with other organic crystals is useful for gaining insight into the nature of intermolecular interactions that govern the elastic properties of the crystal. The elastic constants of a variety of organic crystals involving varying degrees of hydrogen-bonding and dispersive interactions are listed in Table 1. Comparison shows that the magnitudes of the elastic constants of CBZ III are close to aromatic systems.<sup>13</sup> The packing arrangements of these flat aromatic molecules are a result of largely nondirectional dispersive interactions that tend to arrange these molecules in a close-packing arrangement.<sup>13</sup> Dispersive forces are such that the molecules interlock to achieve a good space-filling arrangement. Since the amide–amide hydrogen-bonding interactions are localized between the CBZ units, they may be expected to have only a minor effect on increasing elastic constant values.

The diagonal elastic constants of nitrobenzene and urea (see Table 1) that are associated with networks of intermolecular hydrogen bonding<sup>50</sup> are 2–3 times larger compared to the elastic constants of CBZ III and other aromatic systems with nondirectional interactions. Hydrogen-bonding interactions are directional which results in alignment of the hydrogen-bond network to one particular direction. Thus, it leads to more anisotropy among  $c_{11}$ ,  $c_{22}$  and  $c_{33}$  compared to systems with dispersive interactions only.

Similar to CBZ III, Dianin's compound [4-*p*-hydroxyphenyl-2,2,4-trimethylchroman] forms localized hydrogen-bonding hexamers. Two supramolecular units, bound by van der Waals interactions, stack on top of each other, creating an hourglass-shaped cavity where a guest molecule can reside. The relative orders of magnitude of elastic constants of Dianin's compound obtained from Brillouin spectroscopy<sup>51</sup> are similar to those of CBZ III. Thus, Dianin's compound shows a similar effect of the localized hydrogen-bonding interaction on the elasticity, as seen in CBZ III. Elastic constants of Dianin's compound show weakening of the  $c_{33}$  elastic constant when a guest is present. This has been attributed to competitive hydrogen bonding of the guest with the hydrogen-bonded structure.<sup>51</sup>

The Reuss ( $B_s$ ) bulk modulus or volume compressibility, which is a function of the entire compliance tensor, provides an overall picture of the elasticity of the crystal associated with compression. It is useful because pharmaceutical processing involves both isotropic (e.g., compaction)<sup>35</sup> and anisotropic (e.g., browning) stress.<sup>52,53</sup>

$$B_s = \left( \sum_{i,j} s_{ij} \right)^{-1} \quad (6)$$

The compliances of CBZ III, in standard Voigt notation,<sup>49</sup> used in this calculation are

$$s_{ij} = \begin{bmatrix} 0.184 & -0.057 & -0.096 & 0 & -0.148 & 0 \\ & 0.107 & 0.018 & 0 & 0.023 & 0 \\ & & 0.141 & 0 & 0.077 & 0 \\ & & & 0.272 & 0 & 0.008 \\ & & & & 1.295 & 0 \\ & & & & & 0.346 \end{bmatrix} \quad (\text{GPa}^{-1})$$

The bulk modulus of CBZ III, calculated using<sup>49</sup> eq 6, is 6.2 GPa.  $s_{ij}$  denotes the elements of the compliance tensor. This value is fairly close to those of naphthalene ( $B_s = 5.3$  GPa) and stilbene ( $B_s = 6.5$  GPa) but higher than those of tolan ( $B_s = 4.07$  GPa) and dibenzyl ( $B_s = 4.54$  GPa).<sup>13</sup> The trend in the variation of the bulk modulus among these organic systems has been observed to parallel the packing fraction.<sup>13</sup> The correlation between the bulk modulus and packing fraction mainly arises from the undirected forces that govern the packing of these aromatic molecules.<sup>13</sup> The packing fractions of these planar organic systems are in the range 0.69–0.72 GPa.<sup>13</sup> The packing fraction and bulk modulus of a variety of organic crystals are shown in Table 1. The packing fraction of CBZ III calculated<sup>13</sup> from the crystal structure available at normal temperature is 0.75. Thus, a higher packing fraction of CBZ III infers an efficient contribution of undirected forces to this crystal. A high packing fraction and related preponderance of nondirectional dispersion interactions has also been discussed for energetic materials.<sup>54</sup>

The variation in the compression as a function of direction, information that may be expected to be pertinent to processing, can be obtained from the linear compressibility which is calculated from<sup>49</sup> eq 7.

$$\beta = \sum_i \sum_j s_{ijk} q_i q_j \quad (7)$$

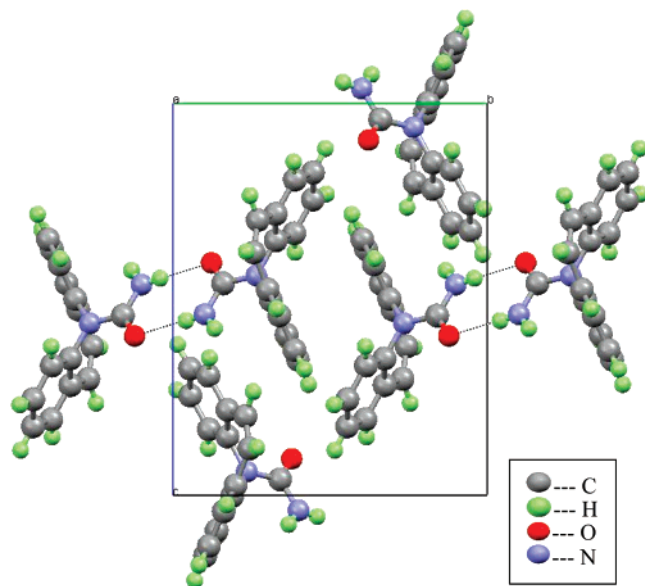
where  $s_{ijk}$  is a component of the compliance tensor. The polar plots of compressibility in three orthogonal planes are presented in Figure 4. These plots show nearly isotropic compression in the  $bc^*$  crystallographic plane, whereas the compressibilities



**TABLE 1: Comparison of Elastic Constants (GPa), Bulk Modulus ( $B_s$ ) ( $\text{GPa}^{-1}$ ) and Packing Fraction ( $k$ ) of Organic Crystals**

elastic constant	CBZ III <sup>a</sup> $B_s = 6.2$ $k = 0.75$	dispersive type interaction				hydrogen-bonding network <sup>c</sup>	
		stilbene <sup>b</sup> $B_s = 6.5$ $k = 0.72$	naphthalene <sup>b</sup> $B_s = 5.3$ $k = 0.70$	dibenzyl <sup>b</sup> $B_s = 4.5$ $k = 0.71$	tolan <sup>b</sup> $B_s = 4.1$ $k = 0.69$	urea <sup>c</sup> $B_s = 11.1$ $k = 0.68$	<i>m</i> -dinitrobenzene <sup>c</sup> $B_s = 6.8$ $k = 0.75$
$c_{11}$	10.89	9.30	7.80	9.45	7.85	23.50	10.70
$c_{22}$	11.47	9.20	9.90	6.80	8.55	23.50	11.30
$c_{33}$	11.32	7.90	11.90	7.20	6.45	51.00	20.27
$c_{44}$	3.68	3.25	3.30	3.10	2.90	6.20	4.37
$c_{55}$	0.85	6.40	2.10	2.55	5.45	6.20	2.04
$c_{66}$	2.89	2.45	4.15	2.60	1.85	0.50	5.31

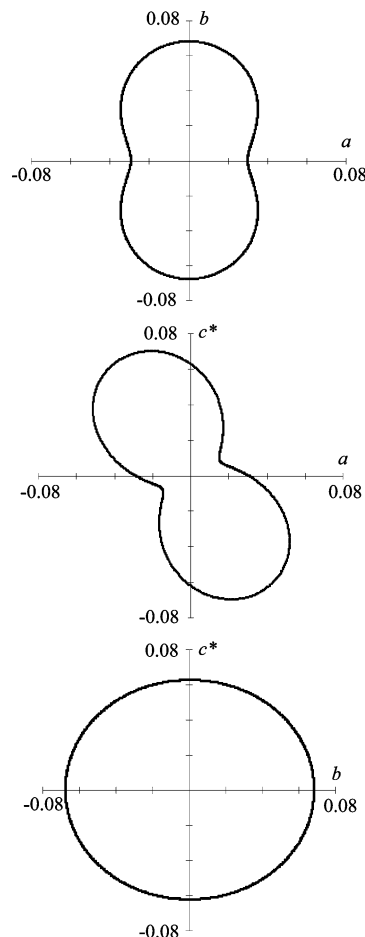
<sup>a</sup> This work. The packing fraction is calculated using Kitaigorodsky's formalism<sup>13</sup> from crystal structures available at normal temperature. <sup>b</sup> The elastic constant, bulk modulus and packing fraction are obtained from ref 13. <sup>c</sup> The elastic constant is obtained from ref 50, and the bulk modulus of hydrogen-bonded systems are calculated from the elements of the inverse of the elastic constant matrix (compliance matrix). The packing fraction is calculated using Kitaigorodsky's formalism<sup>13</sup> from crystal structures available at normal temperature.

**Figure 3.** Crystal structure of CBZ III viewed along the  $a$ -crystallographic axis.<sup>39</sup>

for  $ab$  and  $ac^*$  are more anisotropic. The compressibility along the  $a$ -axis is the lowest. A close examination of the effect of each element of the compliance matrix on the compressibility reveals that the anisotropy in compressibility is mainly affected by the off-diagonal elements of the compliance matrix.

The effect of many-body forces on the intermolecular potential of CBZ III can be investigated by examining the deviation of the elastic constants from Cauchy's relation. This assumes that the potential energy between two particles in the lattice is solely a quadratic function of their separation and that all constituent molecules are at sites of inversion. This approximation leads to the following relations between the elastic constants:<sup>55</sup>  $c_{12} = c_{66}$ ,  $c_{13} = c_{55}$ ,  $c_{23} = c_{44}$  and  $c_{25} = c_{46}$ . For CBZ III, the ratios of the elastic constants  $c_{66}/c_{12}$ ,  $c_{55}/c_{13}$ ,  $c_{44}/c_{23}$  and  $c_{46}/c_{25}$  were found to be 0.632, 0.132, 2.437 and 0.348, respectively. The significant deviations from unity suggest the presence of many-body forces such as angular and torsional interactions in CBZ III. Clearly, significant deviation from harmonic behavior is present in the polymorph.

Farina, Santos and Tort report<sup>56</sup> a simple model that demonstrates the nonadditivity of dispersion forces. These workers also<sup>56</sup> show that the magnitude of many-body forces increases with density which is consistent with the high packing fraction of CBZ III.<sup>54</sup> It may also be argued from perturbation theory<sup>57</sup> that long-range dispersive forces are additive only to second order. In CBZ III, the large discrepancy of Cauchy's

**Figure 4.** Linear compressibility diagrams for CBZ III. Units are in  $\text{GPa}^{-1}$ .

relation from unity indicates that the many-body effect of dispersive interactions predominates in the elastic properties of CBZ III.

## Conclusions

Brillouin scattering has been used to determine the set of 13 elastic constants for the monoclinic polymorph of the pharmaceutical carbamazepine. Comparison with previously reported elastic constants of organic crystals shows that the magnitude of the CBZ III elastic constants is similar to those of aromatic systems with delocalized  $\pi$  bonds such as naphthalene, stilbene and dibenzyl. The intermolecular forces that govern this major class of organics are mainly undirected dispersive interactions. Long-wavelength elastic forces in CBZ III are shown to be similarly governed by nondirected dispersive interactions.

The elements of the compliance matrix have been used to determine the bulk modulus and linear compressibility of CBZ III. The anisotropy in the linear compressibility has been observed to be mainly influenced by the off-diagonal elements of the compliance matrix. The linear compressibility is more anisotropic in the  $ab$  and  $ac^*$  planes than for the  $bc^*$  plane. The torsional and angular interactions that arise from many-body forces are consistent with the significantly anharmonic intermolecular potential indicated by significant lack of compliance with the Cauchy relations.

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## References and Notes

- Bernstein, J. *Polymorphism in Molecular Crystals*; Clarendon Press: Oxford, U.K., 2002; Vol. 14.
- Bernstein, J.; Davey, R. J.; Henck, J. O. *Angew. Chem., Int. Ed.* **1999**, 38, 3441.
- Kariuki, B. M.; Bauer, C. L.; Harris, K. D. M.; Teat, S. J. *Angew. Chem., Int. Ed.* **2000**, 39, 4485.
- Gavezzotti, A.; Filippini, G. *J. Am. Chem. Soc.* **1995**, 117, 12299.
- Dunitz, J. D.; Bernstein, J. *Acc. Chem. Res.* **1995**, 28, 193.
- Brittain, H. G. In *Polymorphism in Pharmaceutical Solids, Drugs and the Pharmaceutical Sciences*; Brittain, H. G., Ed.; Marcel Dekker: New York, 1999; Vol. 95.
- Duncan-Hewitt, W. C.; Weatherly, G. C. (a) *J. Pharm. Sci.* **1990**, 79, 147; (b) *J. Pharm. Sci.* **1990**, 79, 273.
- Bernstein, J. *Prog. Clin. Biol. Res.* **1989**, 289, 203.
- Smith, R. Jay.; Xu, W.; Raftery, D. *J. Phys. Chem B* **2006**, 110, 7766.
- Bontchev, R. P.; Moore, R. C. *Carbohydr. Res.* **2005**, 340, 2195.
- Bergstroem, P.-O.; Fischer, A.; Kloos, L.; Sebatu, T. *J. Pharm. Sci.* **2006**, 95, 680.
- Elliott, J.; Hancock, B. *MRS Bull.* **2006**, 31, 869.
- Kitaigorodsky, A. I. In *Molecular Crystals and Molecules*; Loebl, E. M., Ed.; Academic Press: New York and London, 1973.
- (a) Bernstein, J.; Bar, I. *J. Phys. Chem.* **1984**, 88, 243 and references therein. (b) Bernstein, J. In *Organic Crystal Chemistry*; Garbarczyk, J. B., Jones, D. W., Eds.; International Union of Crystallography Book Series; Oxford University Press: Oxford, U.K., 1991; Chapter 2, p 6. (c) Bernstein, J. *J. Phys. D: Appl. Phys.* **1993**, B66, 26.
- Lommerse, J. P. M.; Motherwell, W. D. S.; Ammon, H. L.; Dunitz, J. D.; Gavezzotti, A.; Hofmann, D. W. M.; Leusen, F. J. J.; Mooij, W. T. M.; Price, S. L.; Schweizer, B.; Schmidt, M. U.; Van Eijck, P.; Verwer, P.; Williams, D. E. *Acta Crystallogr.* **2000**, B56, 69.
- Price, S. L.; Beyer, T. *Trans. ACA* **1998**, 33, 23.
- Van Eijck, B. P.; Spek, A. L.; Mooij, W. T. M.; Kroon, J. *Acta Crystallogr.* **1998**, B54, 291.
- Beyer, T.; Price, S. L. *J. Phys. Chem. B* **2000**, 104, 2647.
- Gavezzotti, A.; Filippini, G.; Kroon, J.; Van Eijck, B. P.; Klewinghaus, P. *Chem.—Eur. J.* **1997**, 893, 3.
- Verwer, P.; Leusen, F. J. J. In *Reviews in Computational Chemistry*; Lipowitz, K. B., Boyd, D. B., Eds.; Wiley-VCH: New York, 1998; Vol. 12, Chapter 7, p 327.
- Payne, R. S.; Roberts, R. J.; Rowe, R. C.; Docherty, R. *Int. J. Pharm.* **1999**, 177, 231.
- Karfunkel, H. R.; Wu, Z. J.; Burkhard, A.; Rihs, G.; Sinnreich, D.; Buerger, H. M.; Stanek, J. *Acta Crystallogr.* **1996**, B52, 555.
- Gavezzotti, A. *J. Am. Chem. Soc.* **1991**, 113, 4622.
- Karfunkel, H. R.; Gdanitz, R. J. *J. Comput. Chem.* **1992**, 13, 1171.
- Gibson, K. D.; Scheraga, H. A. *J. Phys. Chem.* **1995**, 99, 3765.
- Gavezzotti, A. *Acta Crystallogr.* **1996**, B52, 201.
- Day, G. M.; Motherwell, W. D. S.; Ammon, H. L.; Boerrigter, S. X. M.; Della Valle, R. G.; Venuti, E.; Dzyabchenko, A.; Dunitz, J. D.; Schweizer, B.; van Eijck, B. P.; Erk, P.; Facelli, J. C.; Bazterra, V. E.; Ferraro, M. B.; Hofmann, D. W. M.; Leusen, F. J. J.; Liang, C.; Pantelides, C. C.; Karamertzanis, P. G.; Price, S. L.; Lewis, T. C.; Nowell, H.; Torrisi, A.; Scheraga, H. A.; Arnautova, Y. A.; Schmidt, M. U.; Verwer, P. *Acta Crystallogr.* **2005**, B61, 511.
- Beyer, T.; Day, G. M.; Price, S. L. *J. Am. Chem. Soc.* **2001**, 123, 5086.
- Price, S. L. *Adv. Drug Delivery Rev.* **2004**, 56, 301.
- Dunitz, J. D.; Filippini, G.; Gavezzotti, A. *Helv. Chim. Acta* **2000**, 83, 2317.
- Verwer, P.; Leusen, F. J. J. *Rev. Comput. Chem.* **1998**, 12, 327.
- Arslantas, Ali.; Ermler, Walter. C.; Yazici, R.; Kalyon, D. M. *Int. J. Mol. Sci.* **2005**, 6, 291.
- Gavezzotti, A. *CrystEngComm* **2002**, 4, 343.
- Morris, K. R.; Griesser, U. J.; Eckhardt, C. J.; Stowell, J. G. *Adv. Drug Delivery Rev.* **2001**, 48, 91.
- Wu, C.-Y.; Ruddy, O. M.; Bentham, A. C.; Hancock, B. C.; Best, S. M.; Elliot, J. A. *Powder Technol.* **2005**, 152, 107.
- Roberts, R. J.; Rowe, R. C.; Kendall, K. *Chem. Eng. Sci.* **1989**, 44, 1647.
- Duncan-Hewitt, W. C.; Weatherly, G. C. *J. Pharm. Sci.* **1990**, 79, 147.
- Duncan-Hewitt, W. C.; Weatherly, G. C. *J. Pharm. Sci.* **1990**, 79, 273.
- Luty, T.; Eckhardt, C. J. *J. Chem. Phys.* **1984**, 82, 1515.
- Luty, T.; Ordon, P.; Eckhardt, C. J. *J. Chem. Phys.* **2002**, 117, 1775.
- Reboul, J. P.; Cristau, B.; Soyfer, J. C.; Astier, J. P. *Acta Crystallogr., Sect B* **1981**, 37, 1844.
- Grzesiak, A. L.; Lang, M.; Kim, K.; Matzger, A. J. *J. Pharm. Sci.* **2003**, 92, 2260.
- Day, G. M.; Zeitler, J. A.; Jones, W.; Rades, T.; Taday, P. F. *J. Phys. Chem. B* **2006**, 110, 447.
- Cummins, H. Z.; Schoen, P. E. *Laser Handbook*; Arecchi, F. T., Schulz-Dubois, E. O., Eds.; North-Holland: Amsterdam, The Netherlands, 1972; Chapter E1.
- Hayes, W.; Loudon, R. *Scattering of Light by Crystals*; John Wiley & Sons: New York, 1978.
- Brose, K. H.; Eckhardt, C. J. *Chem. Phys. Lett.* **1986**, 125, 235.
- Eckhardt, C. J.; Pennelly, R. R. *Chem. Phys. Lett.* **1971**, 9, 572.
- Dye, R. C.; Sartwell, J.; Eckhardt, C. J. *Rev. Sci. Instrum.* **1989**, 60, 2610.
- Nye, J. F. *Physical Properties of Crystals*; University Press: London, 1957.
- Day, G. M.; Price, S. L.; Leslie, M. *Cryst. Growth Des.* **2001**, 1, 13.
- Sandstedt, C. A.; Michalski, D.; Eckhardt, C. J. *J. Chem. Phys.* **2000**, 112, 7606.
- (a) Gilman, J. *AIP Conf. Proc.* **2000**, 505, 809. (b) Gilman, J. *AIP Conf. Proc.* **1998**, 429, 313. (c) Gilman, J. *Science* **1996**, 274, 65.
- Luty, T.; Eckhardt, C. J. *J. Am. Chem. Soc.* **1995**, 117, 2441.
- Eckhardt, C. J.; Gavezzotti, A. *J. Phys. Chem. B* **2007**, 111, 3430.
- Love, A. E. H. *The Mathematical Theory of Elasticity*, 4th ed.; Cambridge University Press: London, 1934.
- Farina, C.; Santos, F. C.; Tort, A. C. *Am. J. Phys.* **1999**, 67, 344.
- Margenau, H. *Theory of Intermolecular Forces*; Pergamon Press: Oxford, U.K., 1969.