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Importance of Vibrational Zero-Point Energy Contribution to the Relative Polymorph Energies of Hydrogen-Bonded Species

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ABSTRACT: The relative stability of polymorphic crystal forms is a challenging conceptual problem of considerable technical interest. Current estimates of relative polymorph energies concentrate on lattice energy. In this work the contribution of differences in zero-point energy and vibrational enthalpy to the enthalpy difference for polymorphs is investigated. The specific case investigated is that of α- and γ-glycine, for which the experimental enthalpy difference is known. Periodic lattice density functional theory (DFT) computations are used to provide the vibrational spectrum at the Γ-point. It is confirmed that these methods provide reasonable descriptions of the inelastic neutron scattering spectra of these two crystals. It is found that the difference in the zero-point energy is about 1.9 kJ/mol and that the vibrational thermal population difference is 0.9 kJ/mol in the opposite sense. The overall vibrational contributions to the enthalpy difference are much larger than the observed value of ca. 0.3 kJ/mol. The vibrational contribution must be largely compensated by the lattice energy difference. The polymorphs of glycine differ in the pattern of their hydrogen bonds, a feature common to many polymorphs of interest. The consequent difference in the N−H stretching frequencies is a contributor to the zero-point correction, but the major effect stems from changes in the bending vibrations.

The principal difference between polymorphic forms in organic crystals is often the pattern of hydrogen bonding. It is well-known that hydrogen bonding interactions result in considerable changes to the stretching vibration energies of associated hydrogen atoms. Here we show that the changes in vibrational frequencies result in significant changes to the calculated zero-point energy (ZPE) for two polymorphic forms of glycine, with this resulting change in ZPE being larger than the reported enthalpy difference. This glycine example shows that, as a matter of standard practice for computational analyses, the ZPE must be taken into account in evaluations of the ability of computational methods to provide accurate relative enthalpies for polymorphic forms.

Recent studies in our laboratory of the vibrational spectroscopy of the polymorphic forms of glycine have led us to general conclusions regarding the enthalpy difference between polymorphic crystals. In these studies, we use inelastic neutron scattering (INS) to obtain vibrational spectra and periodic density functional theory (DFT) calculations to compute the harmonic vibrational frequencies and normal mode eigenvectors. INS spectra have the property that their intensity as a function of frequency can be simulated from an assumed knowledge of the atomic dynamics (i.e., determined from the combination of atomic displacements along their normal modes of vibration and their neutron scattering cross-sections), providing a check of the reliability of the computational method for reproducing the vibrational energies. INS is a particularly useful spectroscopic method in this respect since it has no selection rules. INS cannot be used as a direct method for determination of thermodynamic properties for complex structures, however, because of its hydrogen atom-weighted and overlapping transitions. A scaled computed spectrum provides a complete and accurate set of energy levels.

The crystal structure of α-glycine is best described as an antiparallel bilayer[1] (Figure 1), while that of γ-glycine is helical[2] (Figure 2). Each is entirely composed of zwitterions with essentially identical molecular geometry. The $P2_1/n$ unit cell of α-glycine contains 4 units with a density of 1.607 Mg m^{-3}, while γ-glycine has $Z = 3$ in $P3_2$ with density 1.584 Mg m^{-3} at 298 K. The average

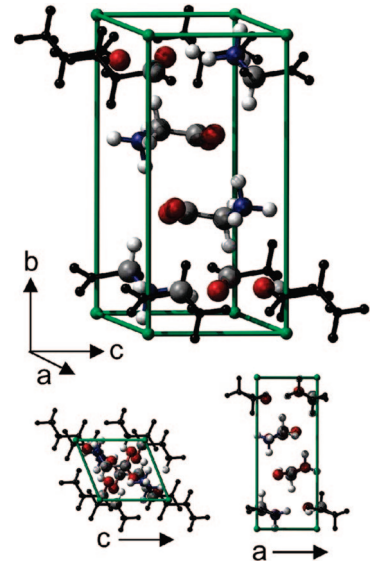

Figure 1. The $Z = 4$ α-polymorph of glycine (CCDC[16] code GLYCIN05, from ref 1) showing in-cell atoms (color) and completing molecular fragments (black).

of the four unique hydrogen bonded N−O distances in α-glycine is 2.91 Å, while in γ-glycine the average of the three unique N−O distances is 2.87 Å.

Perlovich et al.[3] emphasize the importance of the pattern of hydrogen bonding in the energetic difference of the two glycine polymorphs. They note that the highest N−H stretching vibration for α-glycine is at 3154 cm^{-1} and for γ-glycine is at 3093 cm^{-1}, which they attribute to stronger hydrogen bonding in the γ-polymorph. This is consistent with their finding that γ-glycine is enthalpically more stable than α-glycine; that is, the γ-polymorph has a higher lattice energy than the α-polymorph. The magnitude of this enthalpy difference is 272 J/mol.[3−5] At 298.15 K the γ-polymorph is slightly more stable than the α-polymorph by $\Delta G = 157 \pm 145$ J/mol.[6]

The enthalpy difference of two polymorphic forms is the lattice energy difference plus the difference in the vibrational contributions

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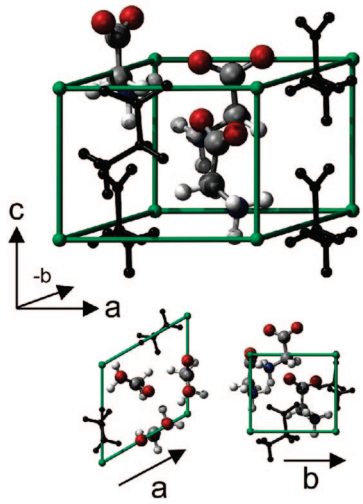

Figure 2. The $Z = 3$ γ-polymorph of glycine (CCDC[16] code GLYCIN15, from ref 2) showing complete molecules (color) and other in-cell constituents (black).

to the enthalpy. For condensed phase equilibria the PV term is negligible. The vibrational difference contribution has two parts: the vibrational ZPE difference, ΔE_{ZPE}, and the thermal energy term, $\Delta E_{vib}(T)$, due to excitation of the molecular and lattice vibrations. If $\Delta E_{ZPE} + \Delta E_{vib}(T)$ is significant, then it should be included in comparisons of calculations with experiment.

In order to provide an estimate of the vibrational "correction", we performed periodic DFT calculations with DMol^3 (ref 7) to obtain unit cell normal modes of vibration using the lattice parameters of the reported crystal structures. In the calculation the lattice parameters are kept fixed at the X-ray values. The contents of the unit cell are optimized to minimize the energy and the second derivatives of the energy with respect to all displacements computed. The normal-mode frequencies are given in the Supporting Information. The resulting INS vibrational spectra are compared to experimental INS spectra to test their validity. The computed set of harmonic frequencies is complete, including factor group splitting but not dispersion. The experimental INS spectrum includes dispersion for all modes for which H atoms move, showing that only low frequency modes have significant dispersion. Using the theoretically determined sets of vibrational states we can compute the difference in the ZPE and $\Delta E_{vib}(T)$ per molecule for the α- and γ-polymorphs of glycine. (Details in Supporting Information.)

The ZPE in the harmonic approximation is simply one-half of the sum of the frequencies. The difference in the ZPE for two polymorphic forms is found to be relatively insensitive to the particular computational method used, in contrast to the calculated lattice energy, which shows a noticeable density functional dependence. The lower frequency modes make a smaller contribution to the ZPE and are generally less anharmonic than the hydrogen stretches except in the very low frequency region where, for example, $-NH_3^+$ rotation occurs.

The α- and γ-polymorphs of glycine used here to illustrate the importance of ZPE contributions to the total energy have the feature that the structures of the zwitterionic molecules in the two polymorphs are nearly identical. The difference between the two structures is primarily in the pattern, and presumably the energy, of the hydrogen bonds. As the highest frequency modes, hydrogen stretches make the largest contribution to the ZPE. Hydrogen bonding interactions are well-established to result in large decreases in the vibrational mode stretching energies of [donor atom]−H stretches. This factor, in combination with the difference in hydrogen packing in many polymorphs, makes it likely that the ZPE difference will be of importance in other cases. It should be noted that considering only the N−H stretching modes would lead to the conclusion that a species with stronger hydrogen bonding would have a lower ZPE. This is the opposite of the conclusions reached on the basis of the full lattice calculations for reasons discussed below. This is resolved by examination of the effects of changes in the hydrogen bonding on the other degrees of freedom of the atoms involved.

Table 1. DMol^3 DFT Lattice Energy Differences, $E_\gamma - E_\alpha$, in kJ/mol with the DNP Basis Set and the Indicated GGA Functional[a]

DMol^3 functional	$E_\gamma - E_\alpha$ (kJ/mol)	ΔE_{ZPE} (kJ/mol)	ΔE_{vib} (298.15) (kJ/mol)	$[\Delta E_{ZPE} + \Delta E_{vib}(T)]$ (kJ/mol)
BP	0.074	1.278	−0.794	0.484
BLYP	−0.265	1.943	−0.934	1.009
BOP	−0.624	1.524	−0.819	0.705
PBE	0.169	1.946	−0.932	1.014
PW91	0.366	1.285	−0.732	0.553
RPBE	−0.486	1.359	−0.781	0.578
VWNBP	0.081	1.254	−0.765	0.489

[a] The unit cell contents are optimized with each functional with the lattice parameters fixed at their experimental values. The zero-point energy and thermal vibrational energy differences and their sum are also shown for $T = 298.15$ K.

There have been several recent reports of computed lattice energies for the polymorphs of glycine including DMol^3 (atom centered basis set DFT), CASTEP (plane wave basis set DFT) and empirical methods.[8−10] The previously published values are +8.4 kJ/mol[8] for DMol^3 with BLYP, and +0.67, +0.88 and −1.25 kJ/mol[9] for CASTEP with the PBE and PW91 functionals and with LDA, respectively. Use of the Dreiding and Universal MM force fields yields −16.86 and +20.85 kJ/mol. DMol^3 lattice energies for the room temperature crystal forms using most of the generalized gradient approximation (GGA) functionals available with DMol^3 are given as $E_\gamma - E_\alpha$ in Table 1. The local density approximation values are 1.473 and 1.491 kJ/mol for PWC and VWN functionals, respectively. We concur with ref 9 that the variation with functional results in a very large uncertainty in the lattice energy. Because of this uncertainty it is impossible to provide a reliable value for the lattice energy difference for two polymorphic forms and thus it is impossible to provide a value for the enthalpy difference.

This strong variation in the lattice energy difference with functional is in contrast to the results for the ZPE difference, which only varies by about 20% of its mean value. These functionals are more or less related to each other, preventing standard statistical analysis. Theory that is scaled to match INS and Raman spectra permit even more reliable estimation of the thermal contributions. Here we have chosen to emphasize the results for the BLYP functional because it best fits the experimental INS spectra without scaling. All energy values reported are $E_\gamma - E_\alpha$.

The difference in the thermal vibrational energy for the two polymorphic forms using the BLYP functional of DMol^3 is found to be 0.93 kJ/mol in the opposite sense to that of the ZPE difference; that is, the α-polymorph has a higher thermal contribution to its enthalpy than the γ-polymorph. The most important vibrations so far as their contribution to the thermal vibrational energy is concerned are the ones that are near or slightly above kT in energy at the temperature of interest. High frequency modes are not significantly populated and so make no contribution to the energy while low frequency modes are fully populated and so contribute the same value, kT, to the thermal energy for each polymorph. This is illustrated in the Supporting Information for this specific case.

The experimental enthalpy difference for two polymorphic forms is the sum of the difference in the lattice energy and the vibrational difference term, that is, $\Delta H = \Delta E_{lattice} + [\Delta E_{ZPE} + \Delta E_{vib}(T)]$ where the negligible PV difference term has been omitted. We do not know $\Delta E_{lattice}$. We do know ΔH from the experimental value. Since we have computed the vibrational difference term we can determine what the lattice energy difference ($\Delta E_{lattice}$) must be in order that, when it is inserted into the expression above, one will obtain the experimental value as the sum. This is the value that should appear as an entry in Table 1 in the $E_\gamma - E_\alpha$ column. Since ΔH_{exp} is −0.27

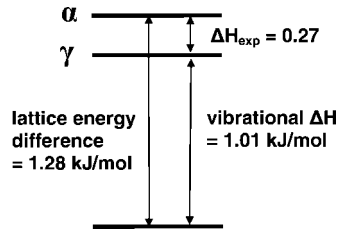

Figure 3. Diagram showing that a correct computation of the lattice energy difference for α- and γ-glycine must have γ more stable than α-glycine by ca. 1.28 kJ/mol.

kJ/mol and for the BLYP functional $[\Delta E_{ZPE} + \Delta E_{vib}(T)] = [1.94$ kJ/mol − 0.93 kJ/mol] = 1.01 kJ/mol, we have $\Delta E_{lattice} = \Delta H_{exp} - [\Delta E_{ZPE} + \Delta E_{vib}(T)] = -0.27 - 1.01 = -1.28$ kJ/mol. This result is shown schematically in Figure 3. None of the values of $E_\gamma - E_\alpha$ in Table 1 are in this range, but the value of −1.25 kJ/mol[9] from a CASTEP LDA treatment is very close. The lattice energy of γ-glycine relative to that of α-glycine must be more negative than the experimental ΔH in order to accommodate the positive difference in the thermal contribution and remain in agreement with experiment. The value of the vibrational contribution to the enthalpy difference, $[\Delta E_{ZPE} + \Delta E_{vib}(T)]$, used in this computation is believed to be reliable on the grounds that it is relatively independent of the computational method and, perhaps more importantly, because each of its components, as individual vibrational frequencies, is in agreement with the experimental INS spectra.

What we have shown is that the vibrational contributions to the enthalpy difference cannot be ignored for hydrogen bonded polymorphs in cases where the pattern and strength of the hydrogen bonds differ in the two crystals. It would appear that this result has no predictive consequences at present since reliable lattice energies do not appear to be available. One of the factors in making progress toward obtaining reliable lattice energies for polymorph prediction[11] will necessarily be inclusion of these vibrational corrections. We do not claim that we have obtained precise values for the zero-point and thermal contributions to the enthalpy difference between γ- and α-glycine. We claim that we have made a reasonable case that this contribution to the enthalpy difference should be considered.

It has not gone unnoticed that this analysis suggests that exchange deuteration is expected to have significant effects on the relative stability of polymorphic forms. The value of ΔE_{ZPE} computed with the BLYP functional of 1.94 kJ/mol for $(NH_3^+)CH_2(COO^-)$ is reduced to 1.61 kJ/mol for $(ND_3^+)CH_2(COO^-)$. This decrease of 0.33 kJ/mol means that γ-glycine-d_3 will be considerably more stable relative to α-glycine-d_3 than is the case for the two parent polymorphic species. What we have observed is that the α-d_3 species converts to the γ-d_3 material spontaneously. Specifically, the preparation of crystalline glycine-d_3 under conditions that would, under normal conditions, produce the α-form, resulted in what appeared to be a mixture by powder X-ray diffraction. This mixture converted spontaneously to the γ-form. This is not observed for the −d0 case. Our observations are very similar to the early report by Iitaka[12] that glycine in D_2O gives γ-glycine when seeded. Systematic investigations of this behavior have recently appeared[13,14] leading to the conclusion that unseeded glycine-d_3 in D_2O forms α-glycine nuclei that convert to the more stable γ-glycine form. It would appear that the crystal transformation kinetics is strongly influenced by deuteration and, we argue, this is due to the doubling of the driving force for the α to γ conversion.

The final point concerns an explanation as to why the lower enthalpy γ-glycine polymorph with stronger hydrogen bonds has the higher ZPE per molecule. Examination of the list of vibrational frequencies for both α- and γ-glycine and, especially, of a table of average values in bands of increasing energy shows (Supporting Information) that the polymorph differences in the $-NH_3$ stretch region are of both signs and that these nearly cancel but that a significant net positive contribution remains. The major contributions to the positive ZPE(γ) − ZPE(α) zero-point energy difference, however, comes from the bending region. Formation of a stronger hydrogen bond restricts the angular motion of the hydrogen bond away from the heavy atom axis. The major contribution to the difference in the thermal vibrational energy for the two polymorphic forms is seen to come in the low frequency regions.

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Supporting Information Available: This material is available free of charge via the Internet at http://pubs.acs.org.

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