

Inaccurate conformational energies still hinder crystal structure prediction in flexible organic molecules

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Abstract

Crystal structure prediction driven by density functional theory has become an increasingly useful tool for the pharmaceutical industry and others interested in understanding and controlling organic molecular crystal packing. However, delocalization error in widely-used density functionals leads to problematic conformational energies that can cause incorrect predictions of polymorph stabilities. In five examples ranging from small molecules to the polymorphically challenging pharmaceuticals axitinib and galunisertib, the present work demonstrates how inexpensively correcting the intramolecular conformational energies with higher-level electronic structure methods leads to polymorph stability predictions that agree far better with experiment. This approach also provides a valuable diagnostic for when skepticism about predicted polymorph stabilities is warranted.

Molecular crystal packing plays a key role in determining properties of the solid state, and the ability to predict crystal structures *a priori* would have major benefits for the pharmaceutical industry and other areas of chemistry. Crystal structure prediction (CSP) is increasingly used to help solve challenging crystal structures¹ and to aid solid form screening.² CSP driven by dispersion-corrected density functional theory (DFT) models has a long

record of successes in blind test species,^{3–10} pharmaceuticals,^{11–16} and other species.^{17–23}

However, polymorph stability depends on both intra- and intermolecular contributions to the crystal energy, and delocalization error in widely-used generalized gradient approximation (GGA) and hybrid density functionals can significantly impact the accuracy with which these interactions are predicted. Delocalization error spuriously stabilizes the salt forms of some neutral co-crystals, for example.²⁴ In conformational polymorphs,²⁵ where different intramolecular conformations enable alternate intermolecular packings, the artificially strong preference for extended π conjugation leads to highly incorrect polymorph rankings in systems such as ROY and *o*-acetamidobenzamide (Figure 1).²⁶ We recently showed how computing polymorph stabilities with higher-level correlated wave function methods via the fragment-based hybrid many-body interaction (HMBI) model²⁷ dramatically improves polymorph rankings in these systems.²⁶ Unfortunately, such calculations are computationally infeasible for many pharmaceuticals.

The present study demonstrates how conformational polymorph energy rankings can often be corrected by a simple and computationally affordable “monomer-corrected” DFT strategy that refines the conformational energy contribution to the lattice energy using a higher level of theory. The need for accurate conformational

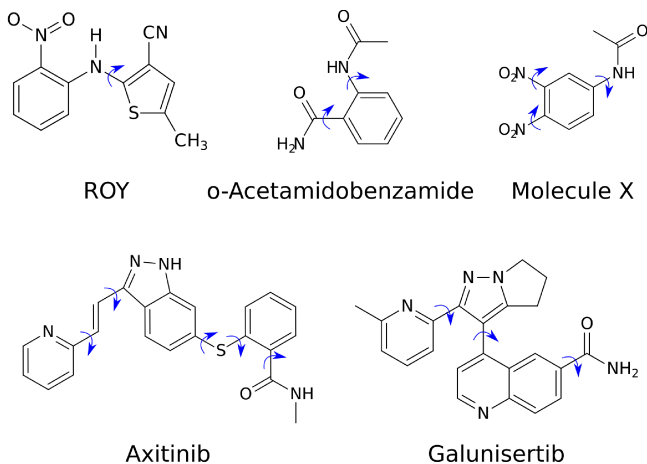


Figure 1: The five species whose crystal polymorphs are considered here. Arrows highlight the most important flexible torsion angles.

energies in flexible molecules has been recognized since the early years of CSP. Polymorph stability rankings computed from classical force fields improved considerably when they were augmented with quantum chemical conformational energies,^{28–30} but this idea has largely been abandoned with the shift toward computing lattice energies entirely with DFT. The three small molecules and two pharmaceuticals considered here (Figure 1) emphasize how important intramolecular conformational energy corrections to DFT lattice energies can be for obtaining polymorph stabilities that agree with experiment and/or higher-level calculations.

Intramolecular corrections to DFT crystal energies and properties have occasionally been used previously.^{9,31,32} Monomer-correction can also be viewed as the simplest version of incremental,³³ fragment,¹ and multi-layer methods.³⁴ Despite these precedents, the systematic failures of commonly-used density functionals for conformational polymorphs and the route for overcoming them have not been widely appreciated.

The monomer correction is performed here with our recently developed second-order Møller-Plesset perturbation (MP2D) theory model,³⁵ which describes conformational energies well and is affordable for molecules with up to ~ 100 atoms. The corrected crystal ener-

gies are computed as:

$$E_{crystal} = E_{crystal}^{DFT} + \sum_i (E_{mon,i}^{MP2D} - E_{mon,i}^{DFT}) \quad (1)$$

where $E_{crystal}^{DFT}$ is the energy of the crystal computed with periodic DFT, while the terms in parentheses correct the crystal energy based on the difference between MP2D and DFT for each isolated monomer in the unit cell. The gas-phase monomer correction only needs to be computed for the symmetrically unique monomers, and for systems of the size considered here, it can be evaluated with considerably less computational effort than the preceding DFT crystal geometry optimization. This intramolecular correction approach assumes that the chosen DFT functional performs well for the intermolecular interactions. While this assumption will often be true,^{1,36,37} there are notable exceptions for cases such as ions³⁸ and halogen bonds^{24,38,39} for which hybrid (or better) functionals may be needed for the intermolecular interactions.

All MP2D conformational energies are extrapolated to the complete basis set limit using standard Gaussian basis sets. The planewave DFT calculations here are performed using the dispersion-corrected B86bPBE-XDM GGA functional that has performed well in many previous studies.^{8,9,20,40} Importantly, the conformational energy problems demonstrated here are not unique to B86bPBE-XDM—they frequently occur for other common dispersion-corrected GGA and hybrid functionals like PBE-D3(BJ), PBE0-D3(BJ), and B3LYP-D3(BJ) as well. Further details of the computational methods, crystal structures, and detailed analysis of conformational and polymorph energies for each system are found in the Supporting Information (SI).

First, we consider two systems which were previously studied²⁶ using the more accurate and computationally demanding HMBI fragment model, which treats both intramolecular and intermolecular interactions with wave function-based methods. ROY has nine well-characterized polymorphs^{41–43} whose red, orange, and yellow colors are closely correlated

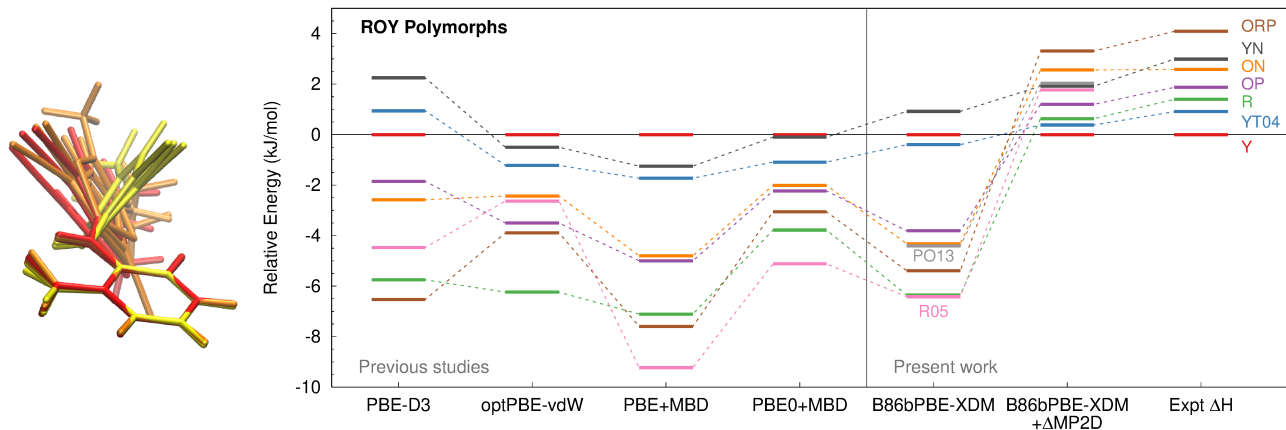


Figure 2: Overlay of the intramolecular conformations from the ROY polymorphs highlighting how the angle between the two rings generally decreases from yellow to orange to red polymorphs. Relative 0 K lattice energies of the nine known polymorphs of ROY calculated using dispersion corrected DFT and the monomer-corrected energies, compared to experimentally measured enthalpy differences. Many DFT functionals predict the ROY polymorph energies incorrectly, but correcting the B86bPBE-XDM lattice energies with MP2D conformational energies (“+ Δ MP2D”) performs far better.

with the torsion angle coupling the two aromatic rings.^{44,45} Accurate experimental enthalpies have been measured for seven of the forms.⁴¹ Both GGA and hybrid density functionals with high-quality dispersion corrections predict ROY polymorph stabilities incorrectly (Figure 2).^{26,42,45} They over-stabilize the intramolecular conformations found in the red and orange polymorphs that exhibit stronger coupling between the aromatic rings.^{26,44,45} In contrast, MP2D predicts ROY conformational energies in good agreement with CCSD(T) benchmarks (SI Figures S2–S3).²⁶ Simply monomer-correcting the B86bPBE-XDM crystal energies with MP2D dramatically improves the agreement between the predicted polymorph lattice energies and the experimental enthalpies. Only the YN and ON polymorph orderings are reversed compared to experiment, with YN over-stabilized by ~ 2 kJ/mol.

The two polymorphs of *o*-acetamidobenzamide represent another difficult case for common DFT functionals.^{26,46} In the α form, the side chains form an intramolecular hydrogen bond and are planar to the benzene ring, extending the π conjugation. The β form disrupts this planarity/conjugation in pursuit of better intermolecular hydrogen bonding. Experimen-

tally, the β form is more stable by 1.9–2.9 kJ/mol,^{46,47} but a variety of GGA and hybrid functionals incorrectly predict the α form to be 5–10 kJ/mol more stable.^{26,46} As we identified previously,²⁶ the primary error in the DFT calculations arises from over-stabilization of the highly-conjugated planar α form conformation (Table S3).

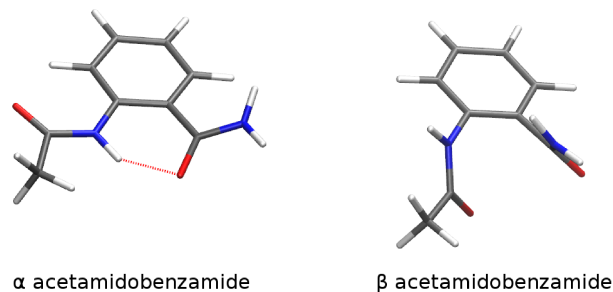


Figure 3: Comparison of the intramolecular conformations adopted by the α and β polymorphs of *o*-acetamidobenzamide. The α form is more planar and exhibits an intramolecular hydrogen bond.

Applying the simple MP2D monomer correction to the B86bPBE-XDM lattice energies dramatically stabilizes the β form relative to α and corrects the stability ordering. Estimating

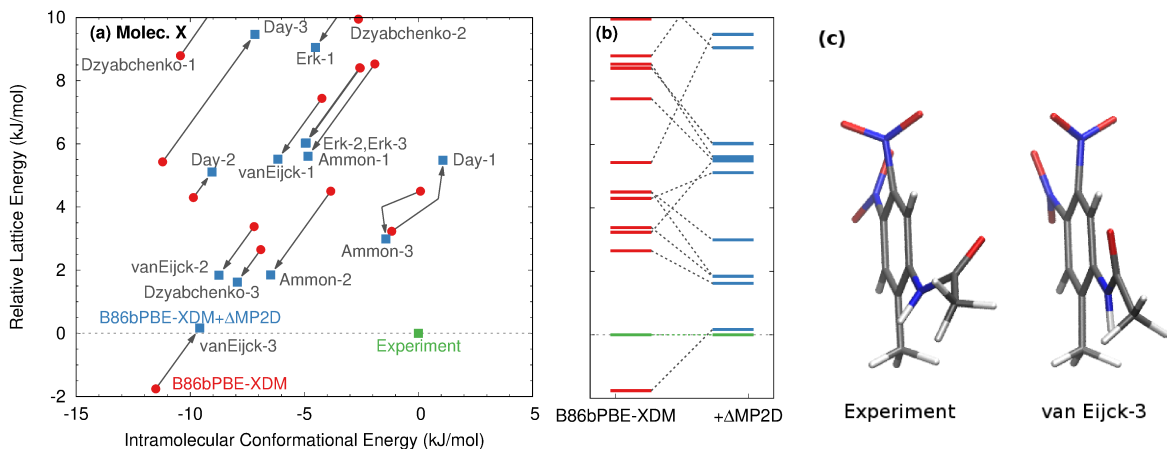


Figure 4: (a) Relative 0 K lattice energies versus conformational energies for the low-lying candidate structures of Molecule X before and after monomer correction (see Table S5 for data on higher-energy structures). (b) Another representation of the relative lattice energies that highlights the impact of the monomer corrections on the stability ordering. MP2D revises the intramolecular conformational energies and stability ordering of the crystal energy landscape considerably. (c) Comparison of the intramolecular conformation of the experimental and vanEijck-3 crystal structures. In contrast to the experimental structure, the amide group in vanEijck-3 is essentially planar relative to the aromatic ring.

the enthalpy difference between the two forms at the experimental 423 K transition temperature via the procedures used in Ref 26 (see SI Section 3.3 for details), the monomer-corrected model predicts $\Delta H_{\alpha \rightarrow \beta}(423\text{K}) = -0.8$ kJ/mol, versus -1.9 or -2.9 kJ/mol experimentally. This represents a major improvement over the qualitatively incorrect B86bPBE-XDM value of +5.9 kJ/mol and is close to the far more expensive HMBI MP2D value of -2.0 kJ/mol (Table S4).

Next, we examine Molecule X from the Third Blind Test of CSP,⁴⁸ in which the amide and two nitro groups can potentially conjugate with the benzene ring. Whittleton et al⁹ re-ranked twenty-four candidate structure submissions with B86bPBE-XDM. Unlike earlier PW91 calculations with empirical dispersion,⁷ they found the vanEijck-3 structure to be 1.8 kJ/mol more stable than the experimentally known structure (Figure 4), raising the question of whether the experimental structure is actually the most stable polymorph. The vanEijck-3 structure exhibits a nearly planar amide conformation that is artificially stabilized by the GGA functional. Whittleton et al showed how correcting the intramolecular conformational energy with MP2/aug-cc-pVTZ raises the energy

of the vanEijck-3 structure to 1 kJ/mol higher than the experimental one, restoring the experimental structure as the most stable one.

However, this story proves incomplete due to the finite basis set used in that work and the limitations of MP2. Performing the monomer correction with complete-basis-set MP2D instead leads to the vanEijck-3 structure being a mere 0.2 kJ/mol above the experimental one (Figure 4). Higher-level benchmarks confirm these MP2D-corrected stabilities: performing the monomer correction with CCSD(T) instead of MP2D places vanEijck-3 0.4 kJ/mol above the experimental structure, while full, fragment-based HMBI MP2D calculations that also refine the intermolecular description place vanEijck-3 at 0.1 kJ/mol above the experimental structure. In other words, vanEijck-3 is energetically competitive with the experimental structure. If these electronic energies are combined with earlier phonon calculations that suggest the vibrational free energy contribution preferentially stabilizes vanEijck-3 by ~ 1 kJ/mol relative to the experimental one,⁹ vanEijck-3 may indeed be more stable than the experimental crystal structure.

More broadly, the low computational cost of

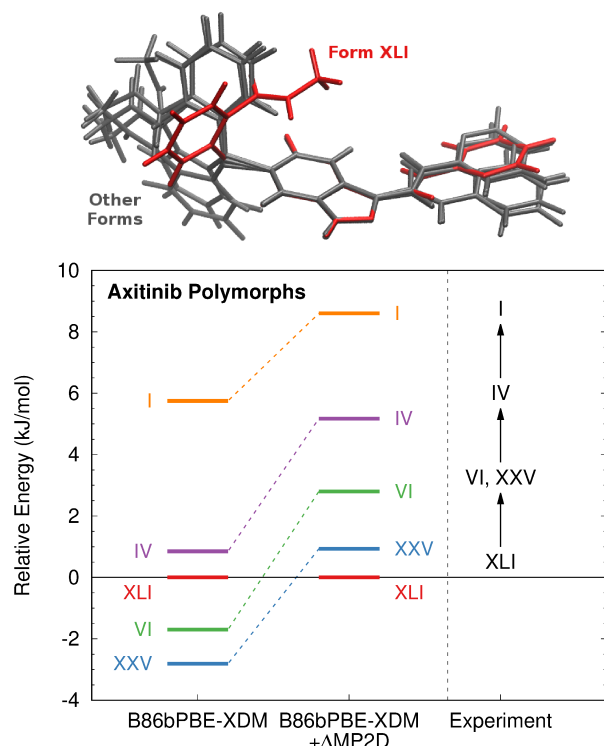


Figure 5: Overlay of the monomer conformations and relative 0 K lattice energies for the five axitinib polymorphs compared to the experimentally inferred stability ordering. The thermodynamically stable XLI polymorph of axitinib (red) adopts a folded conformation, in contrast to the extended conformers found in the other polymorphs. B86bPBE-XDM ranks the form XLI incorrectly relative to the other forms, but monomer-correction fixes the qualitative polymorph ordering.

the monomer correction enables re-ranking of the entire crystal energy landscape. As shown in Figure 4, doing so transforms the Molecule X landscape, with a mean absolute energy change of 1.9 ± 1.0 kJ/mol and substantial re-ordering of the candidate structures. Such changes are significant when half of all experimentally known polymorphs are separated by 2 kJ/mol or less in lattice energy.^{49,50} Even if the monomer-corrected rankings turn out to be imperfect due to the limitations of the GGA intermolecular interaction treatment, the high sensitivity of the crystal energy landscape to the conformational energy indicate that the DFT rankings may warrant skepticism.

Finally, DFT conformational energy problems

can have significant impacts when studying the solid forms of pharmaceuticals, as demonstrated by two challenging examples here. Pfizer’s anti-cancer drug axitinib has five known neat polymorphs and 66 solvates to date.^{51,52} Forms I, IV, VI, and many solvates were discovered via standard experimental solid form screening procedures. Form IV was believed to be the thermodynamically stable form and was initially targeted for development.⁵¹ However, more stable forms XXV and XLI were fortuitously discovered later on during the manufacturing campaign, and thermodynamically stable form XLI became the commercial form.^{51,52} The difficulty in crystallizing Form XLI has been attributed to its distinct intramolecular conformation and unique 1-D chains of hydrogen bonds instead of the hydrogen bonded dimers found in the other polymorphs. Differential scanning calorimetry and solubility experiments indicate the stability ranking:

$$\text{XLI (most stable)} > \text{XXV, VI} > \text{IV} > \text{I}$$

where the energy ordering of XXV and VI is uncertain.^{51,52}

The difficulties in discovering the Axitinib polymorphs experimentally make it an excellent example where CSP could help. Previous CSP studies based largely on force fields generated the experimental crystal structures but ranked them poorly.^{53,54} In Ref 54, for example, form XLI lies 10 kJ/mol above form VI. Here, B86bPBE-XDM predicts most of the polymorph stability orderings reasonably, but it incorrectly suggests that form XLI is 2–3 kJ/mol less stable than forms XXV and VI (Figure 5).

Once again, the key problem with the GGA ranking of the axitinib polymorphs lies in the intramolecular conformation energies. Whereas axitinib adopts an extended conformation in most polymorphs, form XLI folds the molecule to interact the amide π system with the indazole ring, disrupting the π conjugation between the amide and the benzene ring (Figure 5). GGA functionals like B86bPBE-XDM and PBE-D3(BJ) predict the XLI conformation to be one of the least stable intramolecular conformations found in the polymorphs. In con-

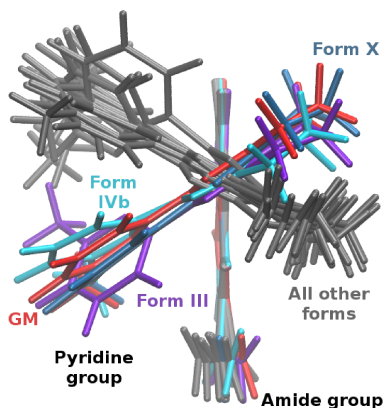


Figure 6: Overlay of the galunisertib monomer conformations. The viewer is looking down the central torsion angle in the middle of the image. The GM conformer is in red. Monomers III, IVb, and X have similar conformations around the central torsion angle, but they differ in the degree of planarity in the pyridine and amide groups relative to the adjacent parts of the molecule.

trast, higher-level models like MP2D, MP2, or B3LYP-D3(BJ) reveal that the XLI conformation is actually one of the most stable conformations (Figure S6). The favorable intramolecular conformation and strong intermolecular hydrogen bond network actually make form XLI the most stable polymorph. Indeed, applying the MP2D monomer correction stabilizes form XLI by several kJ/mol relative to the other forms and reproduces the experimental stability ordering (Figure 5). Advance prediction of the highly stable form XLI enabled by the monomer-correction approach might have accelerated the experimental discovery of this thermodynamically stable form.

Lilly’s anti-cancer drug candidate galunisertib provides another example where monomer correction could have been useful. The solid form landscape for this drug has been studied extensively, with ten well-characterized polymorphs and over 50 solvates.¹⁵ Two different CSP studies were commissioned during the solid form screening, and both predicted a global minimum (GM) structure that was more stable than any of the experimental forms. All attempts to crystallize the GM structure have failed, despite years of effort. It was argued

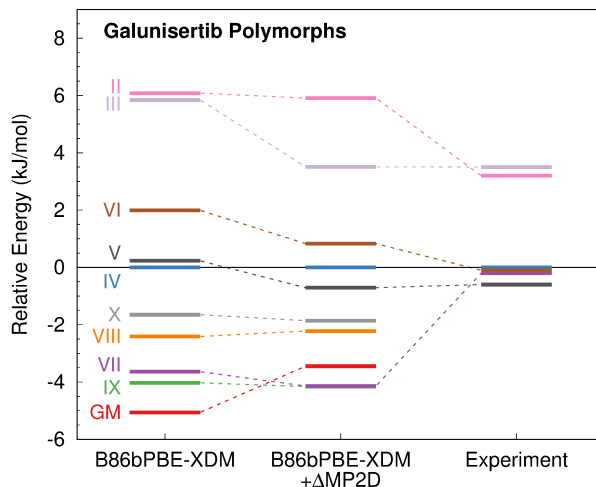


Figure 7: Relative 0 K lattice energies of nine experimentally known galunisertib polymorphs (higher-energy form I is omitted here) and the putative GM structure compared to the experimental enthalpies that have been measured for several polymorphs. Monomer-correcting galunisertib with MP2D destabilizes the GM structure by ~ 1.7 kJ/mol and generally shifts the lattice energies closer to the experimentally measured enthalpies.

that the intramolecular conformation of the GM structure is too strained to crystallize effectively.¹⁵

However, we propose an additional factor that inhibited its crystallization: the GM structure is actually somewhat less stable than the earlier DFT studies suggested. Galunisertib contains three key flexible torsion angles that impact the degree of π conjugation throughout the molecule. While none of the conformations considered exhibits appreciable conjugation between the pyrazole and quinoline rings (i.e. across the central torsion angle), the GM structure has the most planar conformations at the other two torsion angles, thereby extending conjugation from pyrazole to pyridine and from quinoline to amide (Figures 6 and S7). Accordingly, GGA and hybrid functionals tend to over-stabilize the GM relative to the other forms (Figures S8 and S9).

Applying the MP2D monomer correction destabilizes the GM structure by about 1.7 kJ/mol relative to form IV, such that it be-

comes less stable than two of the experimentally known polymorphs (Figure 7). The monomer correction shifts several other polymorphs closer to the experimental enthalpies, though considerable differences remain. Further work is needed to understand the role of intermolecular interactions (including dispersion treatments¹⁵) and phonon contributions to the polymorph stabilities. Errors from those sources could each be similar to or larger than the ~ 2 kJ/mol monomer corrections here. Regardless, the destabilizing impact of the monomer correction on the GM structure calls its exceptional stability into question. Such results might have reduced the effort spent trying to crystallize the GM form unsuccessfully.

In conclusion, commonly used GGA and hybrid density functionals struggle to rank crystal structures in which the degree of intramolecular π conjugation varies significantly. A simple, intramolecular monomer correction computed at a higher level of theory improves the conformational energies and therefore the polymorph rankings significantly. The specific electronic structure model used to correct the conformational energies is at the discretion of the user: dispersion-corrected MP2 was used here because it provides high-quality conformational energies at modest computational cost, but one could also use double-hybrid density functionals or any other model that predicts conformational energies reliably.

Monomer correction has limits. It cannot solve problems in the lattice energies that stem from the intermolecular DFT interactions. In cases like oxalyl dihydrazide,²⁶ the monomer correction would disrupt the fortuitous error cancellation observed between the inter- and intramolecular interactions that enables reasonable GGA polymorph stability orderings. Common hybrid functionals do not fix the conformational energies in several of the examples discussed here, but perhaps they would be sufficient to improve the intermolecular interactions when GGAs prove inadequate. Nevertheless, hybrid functionals still exhibit mean absolute lattice energy errors of ~ 4 kJ/mol in even relatively simple crystals.^{1,36,55,56} Even if

some of that intermolecular interaction error cancels when computing energy differences between polymorphs, the residual errors in the intermolecular description will often probably exceed the errors in the monomer-corrected conformational energies.

In addition, most of the work presented here examined 0 K lattice energies and omitted thermal vibrational contributions to the free energy. Vibrational contributions cause thermal expansion of the unit cell and can impact polymorph stability appreciably.⁴⁹ Enantiotropism, or temperature-dependent changes in polymorph stability orderings, is relatively common.⁵⁷ Several of the axitinib polymorphs are enantiotropically related, for example, and it would be interesting to examine to what extent the combination of monomer-correction and thermal contributions can correctly reproduce those temperature-dependent stability changes.

Even if the monomer-corrected polymorph rankings are imperfect, a large monomer correction serves as a warning that the DFT polymorph rankings may not be reliable. Use of such a diagnostic might have increased skepticism regarding the putative GM form of galunisertib, for example. Given the low computational cost, monomer conformational energy corrections can and should be applied routinely in CSP when the conformations vary widely across crystal forms, especially if they alter the degree of π conjugation or the nature of the intramolecular non-covalent interactions changes appreciably.

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Supporting Information Available: Computational methods, Optimized crystal structures, and detailed analysis of conformational energies and polymorph stabilities for each system. This material is avail-

able free of charge via the Internet at <http://pubs.acs.org/>.

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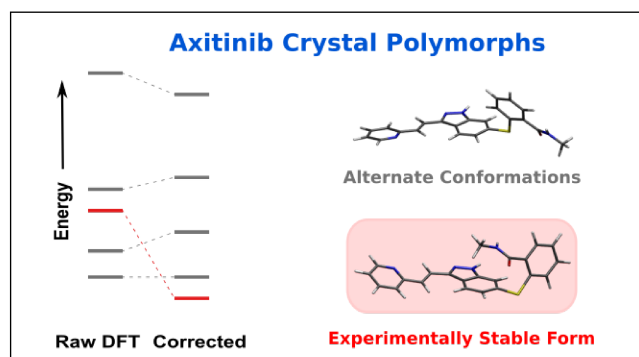
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Title: Inaccurate conformational energies still hinder crystal structure prediction in flexible organic molecules

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Synopsis: Commonly used density functionals have difficulty ranking certain types of conformational polymorph structures correctly. Correcting the intramolecular conformational energies with higher-level quantum chemistry methods can improve the accuracy of crystal structure prediction stability rankings considerably.