

Evaluating Computational Predictions of the Relative Stabilities of Polymorphic Pharmaceuticals

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ABSTRACT: The ability of computational methods to describe the relative energies of polymorphic pharmaceuticals is investigated for a diverse array of compounds. The initial molecular geometries were taken from crystal structures, and energy differences between polymorphic pairs were calculated with various geometry optimization methods. Results using molecular mechanics were compared to experimental calorimetric data and periodic density functional theory (DFT) calculations. The best agreement with experimental heats of transition was shown with energies calculated from geometry optimizations using the Compass force field. Calculations that optimized atomic positions with the Compass force field gave correct energy rankings for all 11 polymorphic pairs studied, with an average deviation of 0.61 kcal/mol from experimental results. These findings suggest that computational methods are poised to predict enthalpy differences between polymorphic forms with levels of accuracy that are quite acceptable when proper approaches are employed. © 2007 Wiley-Liss, Inc. and the American Pharmacists Association *J Pharm Sci* 97:2121–2129, 2008

Keywords: computer modeling; molecular modeling; DFT; force field; thermodynamics; polymorphism; crystal; stability

INTRODUCTION

An important prerequisite for crystal structure prediction is the ability of a computational method to correctly rank the relative energies of different polymorphic packing structures. The correct energy ranking of polymorphs is also important to describe hypothetical or newly discovered polymorphic systems, which are sometimes energetically characterized by computational methods in lieu of calorimetric data. While many computa-

tional methods have been validated through comparisons with structural data,¹ fewer have been evaluated for their ability to reproduce experimental energies.² Most work comparing experimental and computational energy differences of polymorphic compounds has been done for isolated systems,³ and there is a dearth of energetic characterizations across classes of materials.⁴ We have undertaken a systematic study to evaluate the ability of computational methods to predict the relative energies⁵ for a prominent class of materials: polymorphic pharmaceuticals. Crystal polymorphism⁶ is a critical issue in pharmaceutical manufacture and dosage, because diverse properties, including solubility and stability, depend on crystal form.⁷

In this study, a number of computational methods were used to calculate energy differences between pairs of crystal polymorphs, and the values were compared with experimentally determined heats of transition (ΔH_{trs}). By using a

Tables with calculated energies, calculated transition energies, and experimental heats of transition. This material is available free of charge via the Internet (<http://www.interscience.wiley.com/>).

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variety of organic pharmaceutical compounds with diverse functional groups, this systematic investigation sought to determine if molecular mechanics methods are able to accurately rank the relative energies of arbitrary polymorphs, and if so, how well they reproduce experimental energy differences. These methods are a particularly attractive approach because of their low computational cost and ability to rapidly carry out calculations on large molecules and periodic systems. In addition, because they rely on empirical potentials for intermolecular interactions, they do not suffer from the problems in describing dispersive interactions that *ab initio* methods without explicit treatment of correlation encounter. Such problems can be partially addressed by density functional theory (DFT), with the substantial advantage over mechanics methods that extensive parameterization for new functionality is not needed. The molecular mechanics calculations were compared to these much more computationally intensive DFT calculations for several of the systems examined.

METHODS

The data set was chosen to contain pharmaceuticals with high quality structural and calorimetric characterization, such that direct comparison

could be made between experimental and computational results. If multiple crystal structures were available for a given pharmaceutical, structures acquired at low temperature or with lower *R*-values were selected. Specific compounds were chosen to create a set of pharmaceuticals with a variety of functional groups and hydrogen bonding motifs. Although the choice of systems is necessarily somewhat arbitrary, all molecules examined are included in the results presented without regard to agreement between experimental and computational results. Figure 1 shows the chemical structures of the molecules studied, along with their Cambridge structural database (CSD) reference codes.

Crystal structures were obtained from the CSD, and correct bond orders were assigned in the model using the crystal builder module in Cerius². The force field was loaded, and force field typing was applied to all of the atoms in the structure. Two force fields were used for this study: Dreiding 2.21⁸ and Compass.⁹ Dreiding is a generic force field designed for use with organic, biological, and main group inorganic compounds *in vacuo* or in periodic systems. Compass is a condensed-phase optimized, *ab initio* force field designed for use with organic and inorganic molecules and materials.

For calculations conducted with the Dreiding 2.21 force field, the charges were calculated with

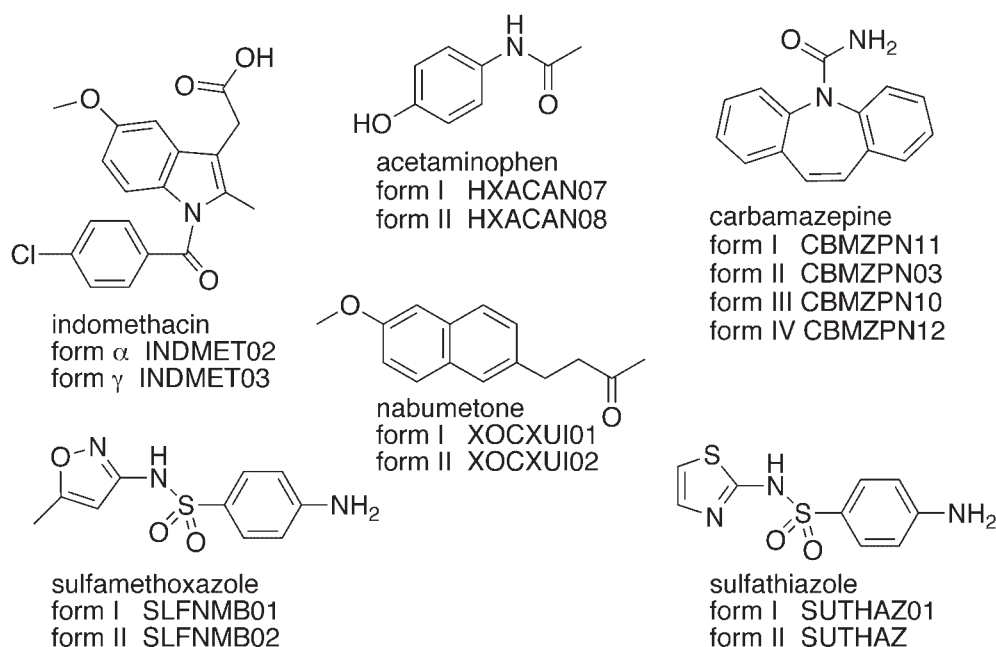


Figure 1. Pharmaceutical compounds studied: polymorphic forms and CSD codes.

the charge equilibration method,¹⁰ which was shown to give reasonable results for geometry optimizations in a wide survey of organic crystals.¹¹ In the case of the Compass force field, the atomic partial charges are calculated automatically with the atom typing function. For several of the compounds studied, the Compass force field as implemented in Cerius² version 4.6 was not parameterized for the functional groups present. Hence, calculations for carbamazepine, sulfathiazole, and sulfamethoxazole used the Compass 98-01 force field, which was suitably parameterized.

The default parameters in Cerius² for long-range and nonbonding interactions, which vary by force field, were used for all of the results herein. It was found that changing the methods for calculating van der Waals and Coulombic interactions usually did not change the relative energy ordering, but did lead to greater overestimates of the energy differences between polymorphs.

The calculated energies were divided by the number of molecules per unit cell such that energies are given in kcal per mole of molecules rather than kcal per mole of unit cells. In this way, direct comparison could be made between calculated energies and experimental results. The energies of transition (ΔE_{trs}) were calculated by finding the difference in calculated energies between two polymorphs (Eq. 1).

$$\Delta E_{\text{trs}}(\text{form II} \rightarrow \text{I}) = E_{\text{form I}} - E_{\text{form II}} \quad (1)$$

It is a convention in many sets of calorimetric data to give enthalpically favored heats of transition (ΔH_{trs}) as a positive number. In this article, all heats of transition follow the convention of Eq. (1); thus, all exothermic transitions have a negative sign.

RESULTS AND DISCUSSION

A number of computational approaches were explored for the set of polymorphs. The simplest calculation that can be employed is a single point energy, in which the energy for a crystal structure is directly calculated. Other strategies include constrained geometry optimizations, in which some atomic positions are allowed to vary, and full geometry optimizations with all atomic positions and cell parameters unconstrained. Figure 2 presents the geometry optimizations used in this study. For each type of calculation, the energy differences between pairs of polymorphs

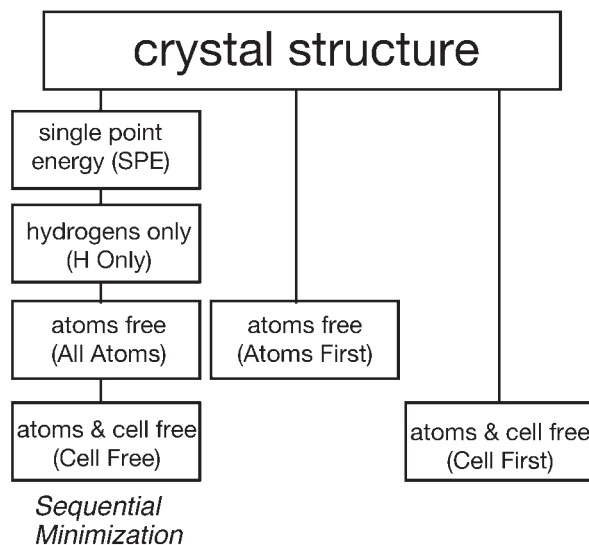


Figure 2. Calculations and geometry optimization sequences.

were calculated. The various calculation methods are discussed below. The results are summarized in Figures 3 and 4, which give the average deviation of calculated results from experimental data and the frequency of correct energy ordering predicted by each method.

SPE

The most straightforward route to calculate energy differences between polymorphs is to employ geometries directly from the crystal structure: a single-point energy calculation (“SPE”). However, X-ray diffraction systematically underestimates bond lengths involving hydrogen atoms due to the displacement of the electron density from the nuclear position; therefore, it cannot provide reasonable geometries for computation. Moreover, these bonds are subject to large uncertainties, such that the hydrogen positions are not systematically shortened, and these contracted bonds containing hydrogen lead to a dramatic overestimation of the calculated energies. Due to the magnitude of the covalent bond energies, slight differences in bond lengths in the set of polymorphs overshadow differences in noncovalent interactions. Thus, single point energy calculations are not a valid means of characterizing the energetics of polymorphs. The shortcomings of the calculation were reflected in the results: for both force fields, calculated ΔE_{trs} were in poor agreement with experimental values, and the correct

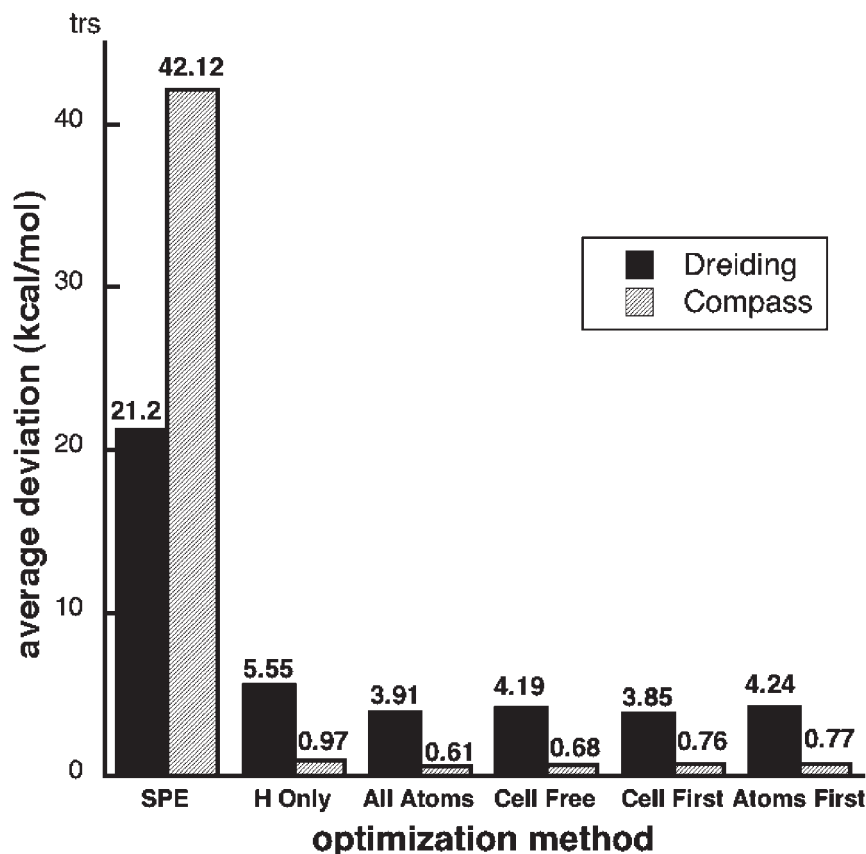


Figure 3. Average deviation from experimental ΔH_{trs} for each optimization method and force field.

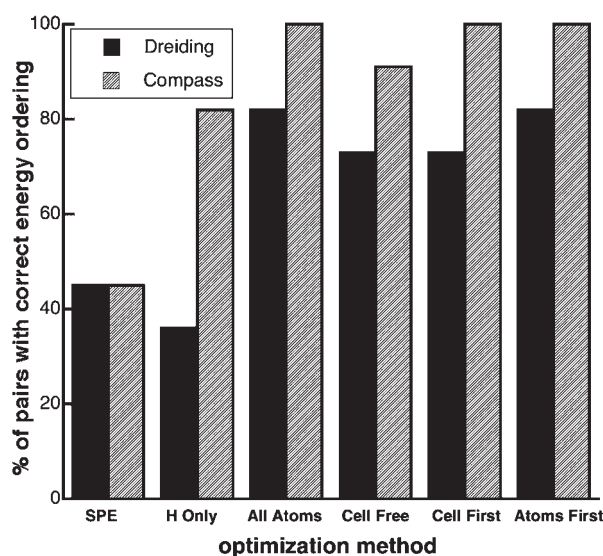


Figure 4. Percentage of polymorphic pairs with correctly predicted relative stabilities.

energy ordering was predicted for only 5 of the 11 polymorphic pairs.

H Only

To ameliorate the shortcomings of single point energy calculations, while retaining the more reliably determined experimental results, a constrained geometry minimization ("*H Only*") was carried out in which the positions of the hydrogen atoms were optimized. All other atomic positions and cell parameters were constrained. By adjusting the positions of the hydrogen atoms, the energies of the systems were lowered dramatically: with the Compass force field, the average energy difference between *SPE* calculations and *H Only* minimizations was 122 kcal/mol; for the Dreiding force field, the average energy difference was 49.9 kcal/mol. The dramatic lowering of energy, due to correcting the unphysical short

crystallographic C–H, N–H, and O–H distances, should provide more reliable energy values for the systems, while still maintaining fidelity to the original crystal structures. Indeed, this was true for the Compass force field: this method showed considerable improvement over the *SPE* calculations in the ability of the method to predict the correct energy ordering of polymorphic pairs, with 9 of 11 matching experimental ordering, and an average deviation from the experimental ΔH_{trs} value of 0.97 kcal/mol. However, for the Dreiding force field, the method gave poor agreement with the experimental energy ordering (4 of 11 correctly predicted) and an average deviation of 5.55 kcal/mol from experimental differences in heats of fusion.

All Atoms

Calculations were carried out in which all atomic positions were allowed to vary, while the unit cell lengths and angles were held constant. The high sensitivity of fixed geometry calculations to perturbations in bond length due to experimental errors was demonstrated in a study of lattice energy minimizations of multiple paracetamol (acetaminophen) crystal structures by Beyer and Price.¹² Uncertainties in the crystallographically determined molecular structure can lead to errors in covalent bond energies that overwhelm differences in lattice energy terms, leading to inaccurate energy differences in a set of polymorphs. For this reason, calculations in which the atomic positions are allowed to relax to their lowest energy position within the lattice may offer an improvement in accuracy over *H Only* optimizations. Indeed, this was seen for both force fields.¹³ For Compass force field, the average difference between *H Only* and *All Atoms* energies was 9.5 kcal/mol; the differences between *H Only* and *All Atoms* calculations were larger for Dreiding force field (34.4 kcal/mol average). The energy differences between the *H Only* and *All Atoms* minimizations are fairly large, and these energy changes and the discrepancies between the two force fields most likely correspond to the adjustment of the heavy atom bond lengths from the crystallographically determined positions to the equilibrium bond lengths for the given force fields.

For each force field, the *All Atoms* calculations gave the best agreement with experimental results within this survey: for the Compass force field, correct energy ordering was predicted for all

11 pairs, with an average deviation of 0.61 kcal/mol from experimental ΔH_{trs} ; the Dreiding force field gave correct energy ordering for 9 of 11 pairs, with an average deviation of 3.91 kcal/mol.

Cell Free

If the intermolecular energy terms in a particular model are, on balance, too repulsive, there will be a stability bias toward the least dense crystal. Moreover, the temperature at which crystal structures are obtained may vary among polymorphs, and lower temperatures cause an anisotropic contraction in cell volume. In order to eliminate any bias based on density, a minimization was carried out in which the cell parameters (lengths and angles) were allowed to vary along with all atomic coordinates ("*Cell Free*").

When the *Cell Free* calculations were carried out, they were monitored for changes in the cell angles. A nearly isotropic expansion of cell volume was often observed during these calculations, along with slight (<5%) changes in cell angles. Notable exceptions are sulfamethoxazole and sulfathiazole, for which drastic changes in the β angle were observed when cell parameters were allowed to vary. The largest changes were seen in the sulfathiazole *Cell Free* calculations with Compass force field, with a change of 18° in the β angle of form II; indeed, this led to incorrect energy ordering. More importantly, this illustrates a caveat of the full geometry optimizations: when atomic positions and cell parameters are allowed to vary, polymorphic transitions can be predicted. In such cases, the "optimized structure" and calculated energy no longer represents the starting crystallographic structure.¹⁴ *Cell Free* optimizations must be monitored closely for such geometric changes lest the comparisons between forms become invalid. In spite of these drawbacks, calculated results had reasonable agreement with experimental data, but less so than the *All Atoms* minimizations. The Compass force field gave correct energy ordering for 10 of 11 pairs, with 0.68 kcal/mol average deviation from ΔH_{trs} ; the Dreiding force field gave correct energy ordering for 8 of 11 pairs with an average deviation of 4.19 kcal/mol.

Order of Optimization

The order in which the above calculations were carried out was varied, in order to determine the

effect that the starting point on the potential energy surface has on the resulting minimized geometry and energy in the *All Atoms* and *Cell Free* minimizations. In the calculations in which a full atomic geometry optimization was carried out without a prior adjustment of the bonds containing hydrogen ("*Atoms First*," see Fig. 1), the energy ordering matched the accuracy of the *All Atoms* minimization. The average deviations for both force fields were also comparable, although for both force fields, the *All Atoms* minimization gave slightly better agreement with experimental ΔH_{trs} values. Within the Compass force field, the calculated energies for the *Atoms First* minimization matched the calculated energies with the *All Atoms* minimization for 13 out of 14 structures investigated. For the same two minimizations with Dreiding force field, the calculated energies were identical for only half of the polymorphic pairs studied. The optimized structures obtained with Dreiding force field are more dependent on the minimization sequence used.

Cell First

In the "*Cell First*" geometry optimization, the atomic coordinates and cell parameters were unconstrained, and the energy was minimized starting directly from the crystal structure. For the Compass force field, the average energy difference between the single point energy (the energy of the starting crystal structure) and the *Cell First* minimization was 132 kcal/mol. In contrast, the average energy difference between the *All Atoms* and *Cell Free* minimizations is 0.97 kcal/mol. In spite of the vastly different starting points on the potential energy surface, the *Cell Free* and *Cell First* minimizations only led to different optimized structures and energies being calculated for 2 of the 14 polymorphs.

For the Dreiding force field, the average energy difference between the starting structure and the *Cell First* optimized structure was 88.8 kcal/mol. The average energy difference between the *All Atoms* and *Cell Free* minimizations was 4.7 kcal/mol. Compared to the Compass force field, energy differences vary more among each type of optimization with the Dreiding force field. The *Cell First* energies matched the *Cell Free* energies for only 2 of the 14 structures studied (both forms of nabumetone), which is reflective of the large structural and energetic differences in the starting points for each calculation. This again

demonstrates that, especially for the Dreiding force field, the sequence in which geometry optimizations are carried out can influence the results obtained.

Density Functional Theory Calculations

In crystal structure prediction methodology, structures that lie within 2.4 kcal/mol (10 kJ/mol) of the global minimum are often considered to be viable structures.¹⁵ Although all polymorphic pairs had experimental energy differences of less than 1.63 kcal/mol, some of the methods used in this study routinely calculated energy differences higher than 2.4 kcal/mol. This was the case for the single point energies with both force fields, and many calculations using different geometry optimization strategies with the Dreiding force field. Because energy rankings are crucial in crystal structure prediction, highly accurate force fields as well as robust geometry minimization procedures are critical to the development of this field.¹⁶

An alternative method that has been used to describe the energies of periodic systems is DFT calculations using a plane wave basis set. These methods have great utility when dramatic structural changes occur, as in the case of extended solids,¹⁷ and do not suffer from the need to parameterize extensively. We sought to compare molecular mechanics results with DFT calculations. Due to the computational expense, the systems and methods employed in this DFT study were limited. With large periodic systems, full geometry optimizations with DFT are computationally intensive and not routine; therefore, constrained optimizations that allowed the hydrogen positions to vary were implemented. The crystal structures were preoptimized with an *H Only* minimization using molecular mechanics in Cerius².¹⁸ The DFT calculations were carried out with the CASTEP code,¹⁹ using GGA-PW91 theory²⁰ and a fine basis set. Polymorphs of acetaminophen, nabumetone, indomethacin, sulfathiazole, and sulfamethoxazole were studied. The results are given in Table 1.²¹ In all cases but nabumetone, the transition energies were overestimated by *H Only* DFT calculations with the PW91 functional. Within this limited investigation, DFT calculations were found to be neither an efficient nor reliable method, relative to molecular mechanics methods, for calculating the relative energies of polymorphs.

Table 1. Summary of ΔE_{trs} from *H only* DFT Calculations and Comparison with Experimental Values

Compound	Transition	Calculated ΔE_{trs} (kcal/mol)	Experimental $\Delta H_{\text{trs}}^{21}$ (kcal/mol)	Deviation (kcal/mol)
Acetaminophen	II \rightarrow I	-1.71	-0.78 ^{21a}	0.93
Indomethacin	$\alpha \rightarrow \gamma$	-2.44	-0.27 ^{21b}	2.17
Nabumetone	II \rightarrow I	-1.54	-1.63 ^{21c}	-0.09
Sulfamethoxazole	II \rightarrow I	4.31	-0.34 ^{21d}	4.65
Sulfathiazole	II \rightarrow I	-13.19	-1.62 ^{21d}	11.57

CONCLUSIONS

Because of the low computational expense of molecular mechanics methods and good agreement with experimental results using the Compass force field, such methods for geometry minimizations of known crystal structures have been shown to be the best computational approach to describe the energetics of polymorphic pharmaceutical compounds in this survey. Table 2 summarizes how well each method agrees with experimental data. Quantitative agreement was rarely seen with Dreiding force field calculations, at best giving agreement within 1 kcal/mol for 4 of the 11 pairs in the *All Atoms* and *Atoms First* minimizations. More promising, the *All Atoms* and *Cell Free* minimizations using the Compass force field agreed with experimental results within 1 kcal/mol for 9 of the 11 pairs. It is encouraging that some methods are able to consistently predict the correct energy

rankings, as observed with all minimization methods using the Compass force field.

DFT methods are less versatile: fewer types of calculations can be attempted on organic crystals because of computational expense. This brief survey of DFT calculations indicates that the *H Only* minimization with the PW91 functional does not, in general, give reliable values for heats of transition. Indeed, the calculations largely overestimated the ΔH_{trs} for three of the five pairs studied. However, because four of the five energy rankings were correct with DFT methods, this approach may be useful as a method to corroborate energy rankings found by molecular mechanics calculations. In conclusion, the best method for calculating relative energies in this survey of pharmaceutical polymorphs was a geometry optimization of all atomic coordinates with the unit cell parameters constrained using the Compass force field.

Table 2. Summary of all Computational Methods and Their Agreement with Experimental ΔH_{trs}

	Number Pairs With Correct Energy Ordering	Average Deviation From Experimental ΔH_{trs}	Standard Deviation From Experimental ΔH_{trs}	Number Pairs With <1.0 kcal/mol Deviation
Compass FF				
<i>SPE</i>	5	42.12	59.74	1
<i>H Only</i>	9	0.97	1.33	6
<i>All atoms</i>	11	0.61	0.55	9
<i>Cell Free</i>	10	0.68	0.92	9
<i>Cell First</i>	11	0.76	0.70	8
<i>Atoms First</i>	11	0.77	0.64	7
Dreiding FF				
<i>SPE</i>	5	21.2	32.15	0
<i>H Only</i>	4	5.55	8.38	3
<i>All Atoms</i>	9	3.91	6.88	2
<i>Cell Free</i>	8	4.19	5.40	2
<i>Cell First</i>	8	3.85	5.39	1
<i>Atoms First</i>	9	4.24	6.77	4
DFT (PW91)				
<i>H Only</i>	4 of 5	3.88	4.67	2

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