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Research Paper

Empirically Augmented Density Functional Theory for Predicting Lattice Energies of Aspirin, Acetaminophen Polymorphs, and Ibuprofen Homochiral and Racemic Crystals

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Purpose. Lattice energies of drug crystals are closely associated with many important physicochemical properties including polymorphism of the crystals. Current quantum mechanical methods that can be applied to calculate the lattice energy of most drug crystals are not capable of fully considering the van der Waals interaction energy, a dominant component in the lattice energy. Herein, we report the results of using empirically augmented quantum mechanical methods for predicting the lattice energies of selected drug crystals.
Methods. Long-range van der Waals energies were evaluated by atom–atom pairwise C_6R^{-6} functions that were damped at short interatomic distance where interatomic interactions could be better evaluated by density functional theory (DFT). The atomic C_6 coefficients were taken from literature, and three damping functions were tested. For the quantum mechanical calculations, different basis sets were tested with aspirin as the model system. Basis set superposition error (BSSE) was considered. In addition to aspirin, acetaminophen Form I and Form II, and s(+)- and (±)-ibuprofen were calculated and the results were compared to experimental values. Experimentally determined single crystal structures were optimized prior to both empirical and DFT energy calculations.
Results. Lattice energies calculated by the empirically augmented quantum mechanical methods are in very good agreement with experimental values, suggesting the approach is acceptable. The results also indicate that the long-range van der Waals or dispersion energy is a significant part of the lattice energy, which cannot be accurately estimated by the DFT methods alone.
Conclusions. Due to the empirical nature for estimating the dispersion energy, choosing the right empirical parameters is crucial. The methods and parameters tested seem to be able to produce reliable values of lattice energies of the drug crystals.

KEY WORDS: acetaminophen; aspirin; density function theory; dispersion energy; ibuprofen; lattice energy; organic crystal; polymorphism; van der Waals interaction.

INTRODUCTION

Molecular or organic crystals make up the majority of pharmaceutical materials. Their physicochemical and particulate properties play a critical role in the handling and manufacturing of drug products as well as the performance of final products. In particular, polymorphism and growth morphology are mostly studied due to their significant impact on both manufacturability and bioavailability. Nevertheless, prediction and consequent control of polymorphs and growth morphology have posed significant challenges, leading to few methods that can be used in practice. There are several approaches for morphology prediction, including Bravais-Friedel-Donnay-Harker (BFDH) (1,2), Attachment Energy (3–5), Surface Energy (6) and Hartman–Perdok methods (7–9), but none of these methods seem capable of accounting for growth conditions (e.g., type of solvents, amount of impurities and degree of the super-saturation) that have considerable effects on the growth morphology. It is even more difficult for predicting polymorphs of molecular crystals. One often used approach is to search all possible packing motifs of molecules in the energy space in order to identify lower-energy crystal forms (10,11). Partially due to the limitation of molecular mechanics or force fields that are typically used for calculating and ranking the intermolecular interactions of various packing motifs, however, little success has been achieved (12). The energy differences among different polymorphs of a molecular crystal can be 2 kJ/mol or even smaller, beyond the accuracy of typical force field methods.

The great need for polymorph and morphology predictions requires the accurate evaluation of intermolecular interaction energies, or lattice energies, of organic crystals.

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Lattice energy, E_{latt}, of a crystal can be defined by the difference between energies of a crystal, E_{cryst}, and its single molecule in vacuum, E_{mol}:

$$E_{latt} = E_{cryst} - E_{mol} \quad (1)$$

Current limitations of using force field methods for calculating lattice energies lead to applications of quantum mechanics, which may provide much better reliabilities, especially for small molecular systems. Nonetheless, the typical quantum mechanical methods that can be applied to organic crystals, including Hartree–Fock (HF) and density functional theory (DFT), have difficulties considering the van der Waals (vdW) energies at large interatomic distances. Due to the correlated motions of elections by the Coulomb interactions, vdW energies are associated with mutual polarization of electron clouds of interacting atoms (13,14). Because the London dispersion force is a major contributor to the vdW force (15), dispersion energy is often quoted exchangeably as the long-range vdW energy (16). In addition to short-range, electrostatic, and induction (polarization) energies, dispersion energy is believed to be a dominant component in the lattice energy of organic crystals (17). The HF theory has no correlation energy term built in; the DFT, in principal, describes the ground-state energy exactly, including the vdW energy. However, typical approximation methods for the exchange-correlation functionals, including local density approximation (LDA) (18) and generalized gradient approximation (GGA) (19–21), cannot satisfyingly describe the vdW energies (14), particularly at large interatomic distances where there is little overlap of atomic electron clouds. Although higher-level quantum mechanical theories (e.g., MP2 or second-order Møller–Plesset perturbation theory (22)) are capable of better considering the vdW energies, the application of these methods for organic crystals is challenging because of the formidable requirement of the computational resources.

In this report, we illustrate the application of empirically augmented quantum mechanical methods for estimating the lattice energies of selected drug crystals. Given the difficulties for the HF and DFT to consider the vdW energy, many efforts for the improvement have been made. One active research area is to include van der Waals functionals into DFT (13,23), resulting in a few models for energy evaluation that have limited applicability. What is interesting for our purpose is the approach that augments the HF and DFT methods with analytical vdW energy models based on interatomic distances and empirical parameters (24–27). Separated from the quantum mechanical calculation, the empirical augmentation is solely decided by positions and types of atoms. With the hybrid method, vdW energies are estimated with analytical models at large interatomic distance, but damped or tuned down at short distance where HF or DFT takes over and produces reliable energy values. It is shown that the method is capable of generating satisfactory results for pairs of organic molecules as tested by Wu and Yang (27). In this report, we present the results using the same approach for calculating the dispersion and lattice energies of selected molecular crystals.

MATERIALS AND METHODS

The lattice energy of a drug crystal is taken as the summation of the long-range (attractive) vdW energy, or dispersion energy, and DFT energy components (including short-range repulsion, electrostatic, polarization, and some of short-range correlation energies), evaluated, respectively, by empirical and DFT methods. The empirical calculation of dispersion energy, E_{disp}, is carried out by an analytical, atom–atom pairwise vdW energy model, which is gradually reduced to zero by a damping function at short interatomic distance (17,24,26–30):

$$E_{disp}(R) = -f_d(R)C_6R^{-6} \quad (2)$$

where R is the interatomic distance, C_6 is the dispersion coefficient, and $f_d(R)$ is the damping function. It is noted that the dispersion energy between a pair of atoms at long distance may include higher-order terms (e.g., C_8R^{-8}, $C_{10}R^{-10}$) in addition to the C_6R^{-6} term used in Eq. 2 (17). Being the dominant contribution, the C_6R^{-6} component describes the instantaneous dipole–instantaneous dipole interaction (14); the higher-order terms are associated with interatomic interactions between higher-order fluctuating multipole moments, and may be negligible.

Several types of damping functions have been reported (24,26,27,29,30). These functions typically reduce from one at long range to zero when $R = 0$. Three different forms of damping functions were tested in this study, including:

$$f_d(R) = \frac{1}{1 + \exp\left[-D_1\left(\frac{R}{R_m} - 1\right)\right]} \quad (3)$$

$$f_d(R) = \left(1 - \exp\left[-D_2\left(\frac{R}{R_m}\right)^3\right]\right)^2 \quad (4)$$

where R_m is the damping radius, often assigned as the sum of atomic van der Waals radii (31) of the pair of atoms. The coefficients, D_1 and D_2, determine the quality of the damping functions, and were given values of 23.0 and 3.54, respectively, from the literature (27). A value of 7.19 was also reported for D_2 (32). Another damping function tested is given by (30):

$$f_d(R) = \left(1 - \exp\left[-D_3\left(\frac{R}{R_m}\right)^7\right]\right)^4 \quad (5)$$

where the damping coefficient D_3 was given the value of 3.0. The damping effects by Eqs. (3), (4) and (5) on dispersion energy, Eq. (2), are illustrated in Fig. 1. With respect to the

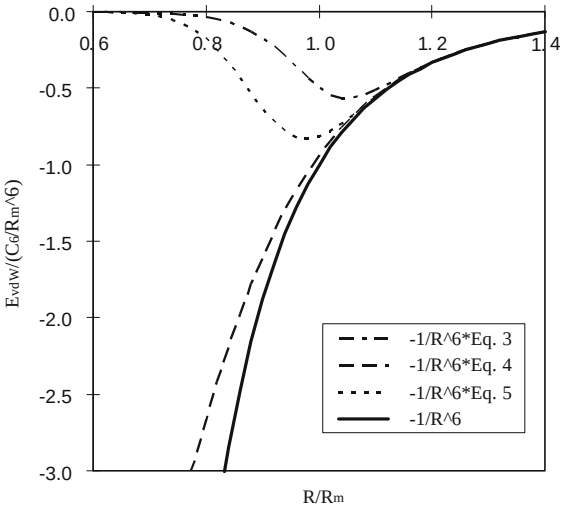

Fig. 1. Relative variation of dispersion energy, E_{disp}, with the three damping functions Eqs. (3), (4) and (5).

damping strength, Eq. (3) is the strongest, followed by Eq. (5), and Eq. (4) is the weakest.

The atomic dispersion coefficients, C_6, in Eq. (2) are taken without modification from Wu and Yang's report (27). In their development, atomic C_6 coefficients were derived by least-squares fitting to molecular C_6 coefficients. Their tests of evaluating the energies of molecular pairs demonstrated that both the augmented method to DFT and the C_6 coefficients were able to produce satisfactory results comparable to those calculated by MP2. In general, intermolecular C_6 coefficients can be accurately determined experimentally from the dipole oscillator strength distribution (33,34), or computationally from the frequency-dependent polarizabilities (35,36). However, the empirically derived interatomic C_6 coefficients may be limited by types of molecular systems whose intermolecular C_6 coefficients are used for the fitting. A recent report discusses possible ways for calculating interatomic dispersion coefficients without the data fitting to the intermolecular values (37).

Calculation of dispersion energies with the above equations was carried out on a crystal structure that was optimized by DFT. DFT energies were also calculated based on the optimized structure. For the selected drug crystals, their structures were retrieved from Cambridge Structural Database (38). Fractional coordinates of the crystals were optimized with respect to the total energy with lattice parameters being kept the same as experimental values. DFT with the B3LYP exchange-correlation functional (19,39) was used for the structural optimization and single-point energy calculations. It is noted that dispersion energies were not considered during the optimization of crystal structures. The basis set superposition error (BSSE) (40) was corrected by the counterpoise method (41) when calculating the DFT energies. To choose a proper number of ghost atoms, different numbers of ghost atoms were placed around the model molecule (aspirin) for testing the convergence of BSSE. In general, positions of a molecule and its ghost atoms were extracted from the corresponding crystal structure. A single molecule of each compound was further-more optimized with the DFT-B3LYP method when calculating lattice energies due to the possible energy reduction from the molecular conformational change from the solid state to the gas phase. The initial structure of the molecule was extracted from its crystal structure prior to the optimization. The effect of basis sets on the lattice energy was investigated by examining 6–21G, 6–21G**, 6–31G, 6–31G**, 6–311G, and 6–311G** on the model system (aspirin) as well. The same basis sets were used for a single molecule and its crystal structure when evaluating the lattice energy. Thus, calculation of the lattice energy of a crystal is given by:

$$E_{latt} = E_{DFT} + BSSE + E_{disp} \tag{6}$$

where E_{DFT} is the difference between energies of the crystal and its molecule calculated by the same DFT method and basis set, $BSSE$ is the energy due to the BSSE, and E_{disp} is the dispersion energy by Eq. (2). Following Eq. (1), E_{DFT} may be regarded as the lattice energy if BSSE and dispersion energies are ignored.

In this study, a periodic ab initio program, Crystal 03 (42), was used for the optimization and energy calculations of crystals and single molecules, including the BSSE, by the DFT-B3LYP method. The energy convergence of the optimizations and energy calculations was set to 10^{-7} Hartree. Root-mean-squares (RMS) were set to 0.0003 and 0.0012 atomic units for energy gradient and atomic displacement, respectively. Based on optimized crystal structures, dispersion energies were determined atom–atom pairwisely by Eq. (2) with a program developed in-house. The cut-off distance for considering an atom pair was set to 25 Å, leading to an uncertainty of 0.01 kJ/mol or smaller compared to no cut-off being used to evaluate the van der Waals energy. All calculations were conducted on a 16-CPU Linux cluster.

To validate the computational results, experimental values of sublimation energies of the crystals were used. The sublimation energy of a crystal is a direct measure of the lattice energy. By assuming that the gas phase is ideal and energy contributions from intramolecular vibrating motions are equal in the solid and gas phases, the lattice energy can be approximated by (43):

$$H_{sub}(T) = -E_{latt} - 2RT \tag{7}$$

where $\Delta H_{sub}(T)$ is the sublimation enthalpy, T is the temperature at which the sublimation enthalpy is measured, and R is the gas constant. In the study, a negative value of lattice energy indicates attractive interactions between molecules in a crystal.

RESULTS AND DISCUSSION

Aspirin, acetaminophen and ibuprofen were calculated with the empirically augmented DFT for predicting their lattice energies. Aspirin was used specifically for testing the effects of basis sets and BSSE on the energy calculations. By using the DFT-B3LYP with different basis sets, the crystal structure of aspirin that was determined at 20 K by neutron diffraction ($P2_1/c$, a = 11.186, b = 6.540, c = 11.217 Å, β = 95.07°) (44) was used for the structural optimization of

Table I. Calculated Energies of Aspirin, Including Non-Dispersive (E_{DFT}), BSSE, Dispersion (E_{disp}), and Lattice Energies (E_{latt}). E_{DFT} and BSSE were Calculated with Different DFT-B3LYP Methods

					E_{disp}			E_{latt}		
	E_{DFT}	BSSE	Number of ghost atoms	E_{DFT}+BSSE	Eq. (3)	Eq. (4)	Eq. (5)	Eq. (3)	Eq. (4)	Eq. (5)
6–21G	−140.78	116.83	225	−23.95	−94.48	−122.44	−104.55	−118.43	−146.39	−128.50
6–21G**	−130.83	121.75	238	−9.08	−93.75	−119.81	−103.54	−102.83	−128.89	−112.62
6–31G	−74.40	51.23	229	−23.17	−95.15	−119.79	−105.40	−118.32	−142.96	−128.57
6–31G**	−65.37	52.07	230	−13.30	−95.02	−117.97	−104.88	−108.32	−131.27	−118.18
6–311G	−59.11	39.09	229	−20.02	−95.46	−119.17	−105.68	−115.48	−139.19	−125.70
6–311G**	−49.06	36.57	234	−12.49	−95.02	−117.08	−104.75	−107.51	−129.57	−117.24

The same method was used for both the structural optimization and energy calculations. Numbers of ghost atoms are listed. Energy unit: kJ/mol.

molecules in the crystal. The lattice constants were kept fixed during the optimization. Different basis sets produced slightly different optimized structures. The same basis set for the structural optimization was used for calculating the non-dispersive energy, E_{DFT}. The results are listed in Table I. Based on each optimized crystal structure, the BSSE was evaluated with the same basis set. The BSSE values and corresponding numbers of ghost atoms that were used by the counterpoise method are also listed in Table I.

It is apparent from Table I that the non-dispersive intermolecular interaction energies and the BSSE calculated by the DFT-B3LYP are absolutely decreased as the basis set becomes bigger. This suggests that the effect of basis set on the total energy of the isolated molecule is more significant than on the energy of the crystal. This may be due to the fact that real basis sets used in calculating a periodic system are Bloch functions, which use the Gaussian-type orbitals to build their local functions. The decrease in the BSSE is likely to be caused by the delocalization of a larger basis set. After taking the BSSE into account, the non-dispersive energies (E_{DFT} + BSSE) show the impact by the polarized basis sets (6–21G**, 6–31G** and 6–311G**) as compared to their non-polarized counterparts (6–21G, 6–31G and 6–311G). The energy difference within those calculated by polarized or non-polarized basis sets is relatively small, about 4 kJ/mol. Using a polarized basis set gives electrons larger degrees of freedom and leads to lower-energy electronic structures, but requires much more computing power. For calculating acetaminophen and ibuprofen, the 6–31G** was used.

More than 200 ghost atoms were employed for estimating the BSSE of aspirin (Table I). As it is shown in Fig. 2, the selection of the numbers of ghost atoms appears sufficient. For both 6–31G** and 6–311G**, the trend of how the BSSE is affected by the number of ghost atoms is similar, approaching the convergence when 90 or more ghost atoms are used. Assuming that the BSSE may have similar trends for calculating acetaminophen and ibuprofen crystals, 200 or more ghost atoms were used in their calculations.

Based on each DFT-optimized crystal structure, the dispersion energies of aspirin were calculated with Eq. (2), and the results are listed in Table I. The three damping functions, Eqs. (3), (4) and (5), were tested. Because of the slight difference in the optimized structures, dispersion energies calculated with the same damping functions are not identical, but the differences are small (<4 kJ/mol). As shown in Fig. 1 of the relative damping strengths by the three functions, using Eq. (3) produced the smallest absolute values of dispersion energy while using Eq. (4) gave the largest values. By adding the BSSE-corrected non-dispersive energies, the lattice energies of aspirin, listed in Table I, clearly indicate that the dispersion energies account for more than 80% of the total intermolecular interaction energies. Consequently, the lattice energies by using Eqs. (3), (4) and (5) have the smallest, the largest and intermediate absolute values. For comparison, the sublimation enthalpy of aspirin was experimentally determined as 109.7 kJ/mol at 298 K (45). Accordingly, the lattice energy can be approximated as −114.7 kJ/mol by Eq. (7). The experimental value appears in an excellent agreement with the calculated values, particularly those by the DFT-B3LYP/6–31G** and 6–311G** with Eqs. (3) and (5) as the damping functions. The comparison also suggests that the empirically augmented DFT method with the damped vdW energies is capable of predicting fairly accurate intermolecular interaction energies of a molecular crystal.

Energy calculations of two polymorphs of acetaminophen and two chiral crystals of ibuprofen are listed in Table II. The results of acetaminophen show that the monoclinic Form I ($P2_1/c$, a = 7.073, b = 9.166, c = 12.667 Å, β = 115.51°) (46) and the orthorhombic Form II (Pbca, a = 17.165, b = 11.7773, c = 7.212 Å) (47) have a difference of about 2 kJ/mol of the BSSE-corrected non-dispersive energies that were calculated by the DFT-B3LYP/6–31G**. The lattice energies,

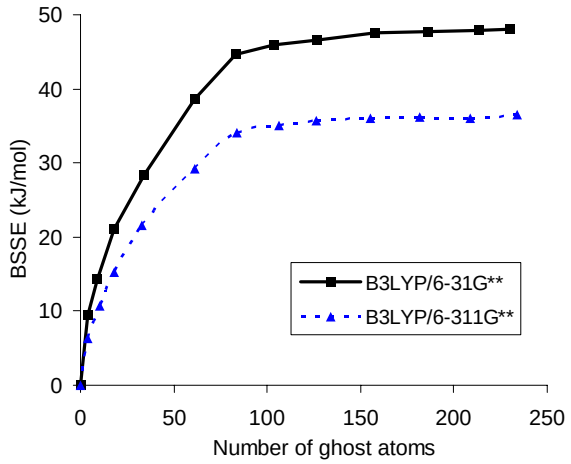

Fig. 2. Basis set superposition error (*BSSE*) versus the number of ghost atoms when calculating aspirin with DFT-B3LYP/6–31G** and 6–311G**.

Table II. Calculated Energies of Acetaminophen and Ibuprofen Crystals, Including Non-Dispersive (E_{DFT}), BSSE, Dispersion (E_{disp}), and Lattice Energies (E_{latt}). E_{DFT} and BSSE were Calculated With DFT-B3LYP/6–31G**

	E_{DFT}	BSSE	Number of ghost atoms	E_{DFT}+BSSE	E_{disp} Eq. (3)	E_{disp} Eq. (4)	E_{disp} Eq. (5)	E_{latt} Eq. (3)	E_{latt} Eq. (4)	E_{latt} Eq. (5)
Acetaminophen I	−76.78	46.43	230	−30.35	−94.36	−116.87	−103.31	−124.71	−147.22	−133.66
Acetaminophen II	−76.35	44.11	232	−32.24	−96.10	−118.34	−105.85	−128.34	−150.58	−138.09
S(+)-Ibuprofen	−54.71	48.00	226	−6.71	−102.67	−117.50	−107.98	−109.38	−124.21	−114.69
(±)-Ibuprofen	−48.02	53.60	242	5.58	−119.55	−139.21	−127.49	−113.97	−133.63	−121.91

The same method was used for the structural optimizations. Numbers of ghost atoms are listed. Energy unit: kJ/mol.

by using Eq. (3) as the damping function for calculating the dispersion energies, indicate a nearly 4 kJ/mol difference with the Form II having the larger absolute value. The experimental values of sublimation enthalpy were measured as 117.9 and 115.9 kJ/mol for Form I and Form II, respectively, at 298 K (48). The lattice energies can then be estimated by Eq. (7) as −122.9 for Form I and −120.9 kJ/mol for Form II. The calculated lattice energies appear to agree with the experimental values very well, particularly when Eq. (3) was used for calculating the dispersion energies. More interestingly, despite the close agreement, the ranking orders of lattice energies are opposite between the prediction and measurement. The sublimation enthalpies, which were estimated experimentally at 298 K, indicate that the Form I is more stable than the Form II, a fact that is supported by many studies. The calculated values, on the other hand, suggest that the Form II has a larger absolute value of lattice energy than the Form I. Because both the DFT and dispersion energy calculations were conducted implicitly at 0 K, the difference in the ranking order may indicate that acetaminophen is an enantiotropic system, as echoed by several other investigators (49–51). It should be pointed out that the experimental value of sublimation enthalpy of the Form I was directly determined, but it was estimated for the Form II based on solution calorimetry data (48). Nonetheless, similar to aspirin, the dispersion energies of acetaminophen are dominant, accounting for about 75% of the lattice energies.

As a chiral compound, ibuprofen can be grown into homochiral or racemic crystals. The lattice energies of s(+)-ibuprofen ($P2_1$, a = 12.456, b = 8.0362, c = 13.533 Å, β = 112.86°) (52) and (±)-ibuprofen ($P2_1/c$, a = 14.397, b = 7.818, c = 10.506 Å, β = 99.70°) (53) were calculated and listed in Table II. The non-dispersive energies calculated by the DFT-B3LYP/6–31G** are very small; the value of the racemic crystal is even positive, indicating that the short-range interactions between ibuprofen molecules are repulsive. Conversely, the dispersion energies are significant for both ibuprofen crystals, almost making 100% contributions to the lattice energies. The nature of intermolecular interactions of these crystals is mainly of the vdW energies. By using Eq. (5) as the damping function for estimating the dispersion energies, the lattice energies for s(+)- and (±)-ibuprofen are −114.69 and −121.91 kJ/mol, respectively, agreeing well with the estimated values Eq. (7), −112.8 and −120.8 kJ/mol. The sublimation enthalpies of s(+)- and (±)-ibuprofen were measured as 107.8 and 115.8 kJ/mol at 298 K, respectively (54).

Despite the excellent agreement between calculated and experimental values of lattice energies, one possible contribution to the computational errors may stem from the structural optimization of crystals. No dispersion energies were considered during the optimization processes, which were conducted by the DFT only with lattice constants being fixed as experimental values. The thought behind this approach is that DFT energies are responsible for the conformation of individual molecules in a crystal, while the dispersion energies can affect the volume of the unit cell, or relative intermolecular distances, particularly when the dispersion energy is dominant in the lattice energy (e.g., ibuprofen). By keeping the lattice constants fixed, ignoring the dispersion energies during optimization likely has little influence on the fractional coordinates of atoms in a crystal. Compared to the total system energy of a crystal calculated by DFT during optimization, the dispersion energy is insignificant (less than 10^{-4} for aspirin). Shown in Table III, the root-mean-square (RMS) values of Cartesian coordinates are very small, suggesting that the optimization method was acceptable. In particular, the crystal structures of aspirin and the Form I for acetaminophen were measured by neutron

Table III. Root-Mean-Square (RMS) Values of Atomic Cartesian Coordinates of Aspirin, Acetaminophen and Ibuprofen Crystals Due to the Structural Optimization

	RMS (Å) (excluding H)	RMS (Å) (H only)	RMS (Å)	Temp (K)
Aspirin				20
6–21G	0.185	0.129	0.250	
6–21G**	0.192	0.136	0.259	
6–31G	0.092	0.062	0.127	
6–31G**	0.041	0.040	0.042	
6–311G	0.049	0.048	0.050	
6–311G**	0.037	0.039	0.033	
Acetaminophen I				20
6–21G**	0.188	0.155	0.221	
6–31G**	0.071	0.053	0.088	
Acetaminophen II				123
6–21G**	0.209	0.184	0.235	
6–31G**	0.145	0.093	0.190	
S(+)-Ibuprofen				298
6–21G**	0.274	0.209	0.318	
6–31G**	0.210	0.137	0.255	
(±)-Ibuprofen				100
6–21G**	0.097	0.075	0.111	
6–31G**	0.094	0.068	0.111	

The temperature at which the crystal was determined is also listed.

diffraction at low temperature so the RMS values of these two crystals are relatively small. Neutron diffraction is capable of detecting H atoms directly. Thus, by maintaining the lattice constants "constant" and keeping the space group during the structural optimization of organic crystals, excluding the dispersion energy should have trivial influence on the conformation of individual molecules. The long-range, collective vdW interactions can only affect the relative distance between molecules because of irrelevant scales as compared to the DFT energies that decide bonding, close contacts, and short-range interactions. Still, full optimization by considering both DFT and dispersion energies is needed for correcting the temperature effect on the volume of unit cell, especially for those crystals that are determined under the ambient condition or at higher temperature.

All of the three crystal systems, aspirin, acetaminophen and ibuprofen, have intermolecular hydrogen bonds. Hydrogen bonds are formed between –COOH groups of adjacent molecules in aspirin and ibuprofen. In acetaminophen, both polymorphs have networks of hydrogen bonds extended through the whole crystals. The percentage of the DFT energies, which include the hydrogen bonding, in the lattice energy is significantly varied among the three crystals. For aspirin and acetaminophen where the DFT energies account for about 20 and 25%, respectively, using Eq. (3) for evaluating the vdW energies seems appropriate. For ibuprofen crystals where the intermolecular DFT energies are insignificant, Eq. (5) gives better estimations. As illustrated in Fig. 1, Eq. (3) has the strongest damping power to mask the vdW energy at short interatomic distance, followed next by Eq. (5). This suggests that a stronger damping function (such as Eq. (3)) be used when there are many close contacts or overlaps of electron clouds between molecules in a molecular crystal. A weaker function (such as Eq. (5)) should be used when there are no close contacts or even such contacts are not energy-favorable. This also implies that the damping function should be tailor-made for each crystal system, particularly the selection of the damping coefficient, D_i, in any of Eqs. (3), (4) and (5). In addition, it is expected that the interatomic dispersion coefficients can affect the calculation results due to the empirical nature to derive these parameters. A recent report by Johnson and Becke illustrates a theoretical framework for computing the damping function and interatomic C_6 without the data fitting to intermolecular C_6 (37), likely circumventing the limitation of current C_6 coefficients used in this study that may overlook the molecular environment of a specific system.

When comparing computational results to experimental data, it is necessary to realize that there are experimental variances and systematic uncertainties associated with the measurement of sublimation enthalpies of drug crystals as well as with the derivation of lattice energies by Eq. (7). The measured results can be greatly varied due to different analytical methods, different research groups and different batches of samples. The defects and impurities can have great influences on the results. Possible phase transition from one polymorph to another can happen without notice during a measurement, especially at low temperature. It is common to see large variances in sublimation enthalpy of the same compound in the literature (55). Moreover, using a *2RT* correction term in Eq. (7) for estimating the lattice energy from the sublimation measurement is an approximation of the exact connection between the two thermodynamic properties:

$$H_{sub}(T) = -E_{latt} - E_0 + \int_0^T C_p(T)dT \tag{8}$$

where E_0 is the zero-point energy, and ΔC_p is the difference in heat capacity between the gas and solid phases. Because ΔC_p is temperature-dependent and difficult to determine at low temperature, using Eq. (8) to estimate lattice energy is hardly practical. It is indicated that the zero-point energy is less than 1% of the lattice energy of an organic crystal and the contribution by heat capacity is no more than 10% (56). Thus, using Eq. (7) may have an uncertainty of 10% of estimating the lattice energy from sublimation measurements.

In summary, the lattice energies of aspirin, acetaminophen and ibuprofen crystals were calculated with an empirically augmented DFT method. The results appear in good agreement with experimental values, suggesting the method is reliable for the application to organic crystals.

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