

New Tricks of the Trade for Crystal Structure Refinement

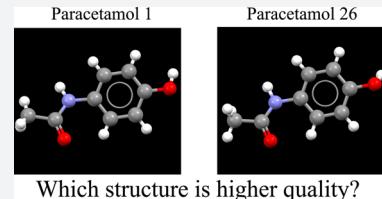
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ABSTRACT: Accurate crystal structures and their experimental uncertainties, determined by X-ray diffraction/neutron diffraction techniques, are vital for crystal engineering studies, such as polymorph stability and crystal morphology calculations. Because of differences in crystal growth and data measurement conditions, crystallographic databases often contain multiple entries of varying quality of the same compound. The choice of the most reliable and best quality crystal structure from many very similar structures remains an unresolved problem, especially for nonexperts. In addition, while crystallographers can make use of some professional software (i.e., *Materials Studio*) for structure refinement, noncrystallographers may not have access to it. In the present paper, we propose a simple method to study the sensitivity of the crystal lattice energy to changes in the structural parameters, which creates a diagnostic tool to test the quality of crystal structure files and to improve the low-quality structures based on lattice energy distribution. Thus, noncrystallographers could take the proposed idea and program/optimize crystal structure by themselves. They can have their in-house program to determine the reliability of the selected crystal data and then use the best quality data or carry out structural optimization for low-quality data. The proposed method will benefit a broad cross-section of scientific researchers, especially those in solid-state and physical chemistry.



1. INTRODUCTION

To improve industrial crystal engineering and crystal morphology studies of next-generation chemical products, the selection of high-quality crystal structures must be quick and easy,¹ which is the central goal of our study. The determination of a crystal structure by X-ray diffraction (XRD)/neutron diffraction experiments involves several important steps: crystal growth, unit cell determination, data collection, data reduction, space group determination, and structure solution. Ultimately, the crystallographer obtains atomic coordinates for some or all non-hydrogen atoms.^{2–4} However, during this process, the atom types assigned to some of the initial coordinates may be incorrect, and some details of the structure, such as groups of lighter atoms, disorder, and hydrogen positions, may be missing, and further techniques will be required to obtain all-atomic coordinates.^{5,6} In this context, crystal structure determination is a very complex process, and formal training and experience are necessary to obtain high-quality crystal structures. Unfortunately, not all released crystal structures are correct or sufficiently accurate.

The thermal motions of atoms and functional groups are key characteristics of molecular crystals, and the motion derived from XRD/neutron diffraction can be conveniently visualized by means of the uncertainties in the atomic coordinates.^{7–10} The measurement of the uncertainties in the atomic positions is an essential preliminary step in the determination of crystal structures, and these values are fundamental to many other branches of crystallography. Often, many scattering experiments are carried out for the same compound, generating many similar crystal structures, possibly because of the use of different

equipment, crystallographic ability, or experimental conditions (for example, temperature and density).¹¹ These similar crystal structures may have slight differences in the atomic positions or space groups, making the selection of the most accurate structure challenging. In addition, large uncertainties in the atomic coordinates for a crystal structure may result in problems in analysis. Therefore, handling of scattering data and the selection of a reliable high-quality crystal structure is a top priority for crystallographers and other interdisciplinary researchers in computational physics, chemical simulation, and biopharmaceutics.

A large quantity of crystal structure data has been collected in the Cambridge Structural Database (CSD)¹² and the Inorganic Crystal Structure Database (ICSD),¹³ which are global repositories for small-molecule organic/inorganic and metal crystal structures. The CSD and ICSD contain over 1,000,000 entries from many scattering analyses, and these databases have become essential resources for scientists around the world. For a given compound, the CSD or ICSD often contains several slightly different crystal structures in space group, atomic coordinates, data collection temperature, etc.¹⁴ For example, paracetamol (also known as acetaminophen), a commonly used organic molecule, has 31 crystal structures stored in the CSD. Some of these data sets were collected at the same temperature and have the same space group and volume, i.e., HXACAN01, HXACAN19, and HXACAN26, where “HXACAN” is the entry name for paracetamol in the CSD. In such a case, from the

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standpoint of morphological investigations, how reliable are these structures for crystal engineering and what is the sensitivity of the lattice energy to small variations in the atomic positions and interactions with neighboring atoms? To deal with these questions, crystallographers can use software (i.e., *Materials Studio*) for structure refinement, but many researchers are not professional crystallographers and do not have permission to use software for crystal refinement. Consequently, for noncrystallographers, the choice of the most reliable and the highest quality structure from a set of similar structures has long been challenging.

In this paper, we report an algorithm to determine the sensitivity of the crystal lattice energy (SCLE) to changes in the crystal structure, which can reduce the number of similar alternative structures or their uncertainties, and has specific applications in crystal engineering. In the SCLE algorithm, lattice energy calculations are performed using the generalized Amber force field (GAFF)^{15,16} on many similar structures, and the results are compared with the experimental sublimation enthalpy. Thus, the quality of a tested structure can be determined by the lattice energy distribution, which will help users to pick a high-quality structure and to improve low-quality structures. The SCLE algorithm provides a simple theoretical framework to account for the uncertainties of atomic positions of a molecule, which will guide relevant experiments and calculations in a more efficient search for the best crystal structures produced under different growth conditions. In this case, ideas from our paper can be used to develop a program to analyze and optimize crystal structures. The nonprofessional users could write their in-house program to determine the reliability of the selected crystal and, if necessary, optimize the structure. The SCLE algorithm has been tested for a variety of molecules, both centrosymmetric and non-centrosymmetric cases, resulting in the successful choice of the best structure and the improvement of lower-quality structures.

2. METHODS

The proposed SCLE algorithm is quite general and applies to crystal structures determined at any temperature, but it does not distinguish between crystals grown from different solvents and at different degrees of supersaturation. This section introduces the methods used in the SCLE algorithm; in particular, we describe the generation of families of molecular structures based on the uncertainties in the atomic positions.

For a crystal, all atoms vibrate within the crystalline lattice. These atomic vibrations, which increase with temperature, are one of many factors that are together termed “thermal motion”. Thermal ellipsoids (the famous “ORTEP” drawings, an abbreviation of Oak Ridge thermal ellipsoid plot^{1,17,18}), known as anisotropic displacement parameters (ADP), represent this thermal motion in a crystal structure, indicating the magnitudes and directions of the thermal vibration of atoms. The area inside this ellipsoid is the uncertainty in the atomic position, which is calculated, along with the atomic coordinates, during the scattering experiment. Our SCLE algorithm is as follows:

- (1) Step one: A thermal ellipsoid is built based on the thermal parameters of different atoms, as shown in Figure 1, where x , y , and z are the axes of the thermal ellipsoid and a , b , and c are the lengths of the x , y , and z axes, respectively. The values of a , b , and c can be obtained from the thermal parameters of each atom. Next, a cuboid is constructed that encloses the ellipsoid and whose faces are tangential to the surface of the thermal ellipsoid along three axes.

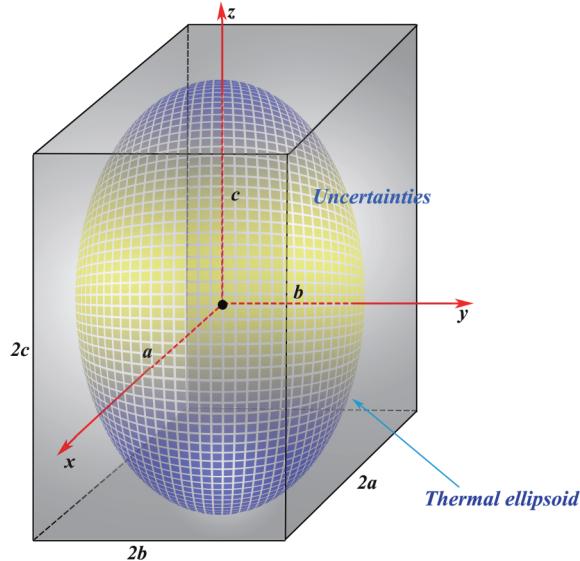


Figure 1. Thermal ellipsoid of the central black atom. The cuboid, with the length, width, and height of $2a$, $2b$, and $2c$, respectively, has faces that are tangential to the surfaces of the thermal ellipsoid along the x , y , and z axes. a , b , and c are the lengths of the polar axes. The cutting lines drawn on the ellipsoid are the bisectors that divide the polar axes equally. In the SCLE algorithm, samples are selected from 1000 uncertainties that have similar atomic positions to that of the central atom (black point).

The length, width, and height of this cuboid are $2a$, $2b$, and $2c$, respectively.

- (2) Step two: “ a ”, “ b ”, and “ c ” are divided into ten equal intervals. The x , y , and z are randomly selected from ten “ a ” intervals, ten “ b ” intervals, and ten “ c ” intervals. Consequently, there are a total of 1000 points, which correspond to 1000 similar structures for the central atom in Figure 1. The atomic positions of these 1000 similar structures can be treated as 1000 uncertainties in the position of the central atom. In this case, there are $1000N$ uncertainties for a molecule that contains N atoms, yielding $1000N$ similar structures using the proposed SCLE algorithm.
- (3) Step three: One-hundred or more molecules are selected randomly from the $1000N$ similar structures, and the lattice energy calculations are carried out for each structure using GAFF. In this case, 100 or more lattice energies can be generated at the same time, corresponding to 100 or more similar structures. Therefore, the sensitivity of the crystal lattice energy to the atomic positions can be visualized using the lattice energy distribution based on the range of uncertainties in the atomic positions discussed in the next section.

3. CASE STUDIES

In the following subsections, two examples of tested crystal systems are presented to introduce the SCLE algorithm and illustrate the method, including paracetamol (non-centrosymmetric molecule) and adipic acid (centrosymmetric molecule).

3.1. Non-Centrosymmetric Case: Paracetamol. We first present a non-centrosymmetric example, paracetamol, to examine the reliability of crystal structure analysis using SCLE. There are three similar paracetamol structures in the CSD, HXACAN01, HXACAN19, and HXACAN26, which were all determined using room temperature data. Two of these

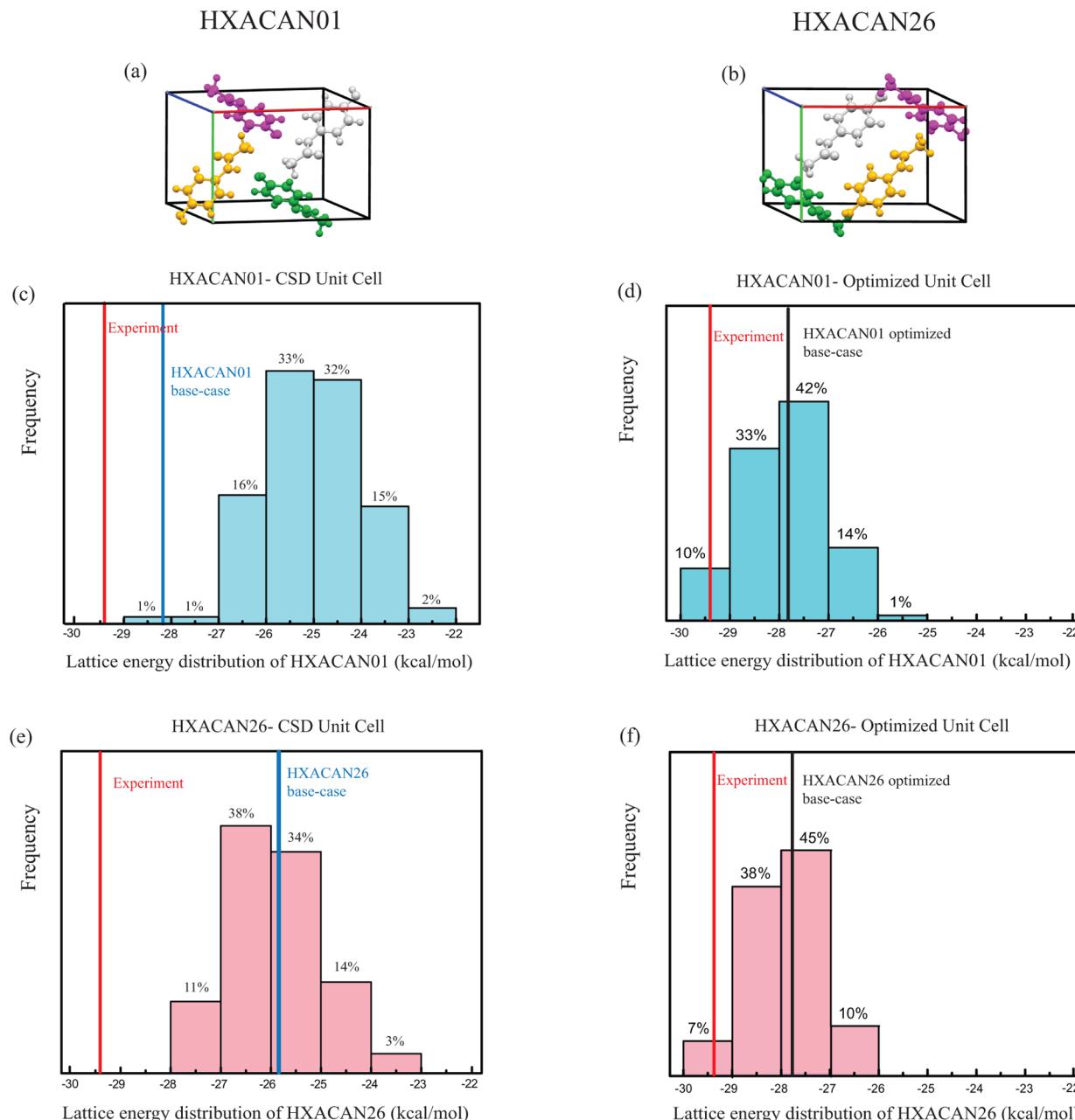


Figure 2. Unit cells of paracetamol for HXACAN01 (a) and HXACAN26 (b), where the molecules are colored by symmetry operation. The lattice energy distributions of HXACAN01 with the original unit cell (c) (from CSD) and the optimized unit cell (d). The blue line in panel c and the black line in panel d represent the base-case lattice energies of HXACAN01 and optimized HXACAN01. The lattice energy distributions of HXACAN26 with the original unit cell (e) (from CSD) and the optimized unit cell (f). The blue line in panel e and the black line in panel f represent the base-case lattice energies of HXACAN26 and the optimized HXACAN26. The red lines in panels c, d, e, and f correspond to the experimental lattice energy of paracetamol, which is -29.4 kcal/mol .²² The experimental lattice energy was calculated from the experimental sublimation enthalpy²² according to the relationship $E_{\text{latt}} = -\Delta H_{\text{sub}} - 2RT$,²³ where R is the gas constant and T is the experimental temperature.

structures were picked randomly and treated with the SCLE algorithm: HXACAN01 determined by Haisa et al. in 1976¹⁹ and HXACAN26 determined by Stone et al. in 2009.²⁰ These two structures are very similar, having been solved in the same space group and collected at the same experimental temperature. In addition, they have similar cell lengths, angles, and volumes. Thus, it is difficult to determine which structure to select as an input for crystal engineering calculations, such as lattice energy calculations, and morphology prediction.

Figures 2a and 2b show the unit cells of HXACAN01 and HXACAN26, where the molecules within the unit cell

are colored by symmetry operation. Both HXACAN01 and HXACAN26 contain four molecules in one unit cell and 20 atoms in each molecule. However, the atomic positions within each unit cell are slightly different. Figures 2c, 2d, 2e, and 2f show the lattice energy distributions of HXACAN01 in the original and optimized unit cell and those of HXACAN26 in the original and optimized unit cell, respectively. The lattice energy calculations were made using the GAFF,^{15,16} and more details of these calculations can be found in our recent review paper.²¹ The blue lines in Figures 2c and 2e represent the calculated “base-case” lattice energies of HXACAN01 and HXACAN26 within the

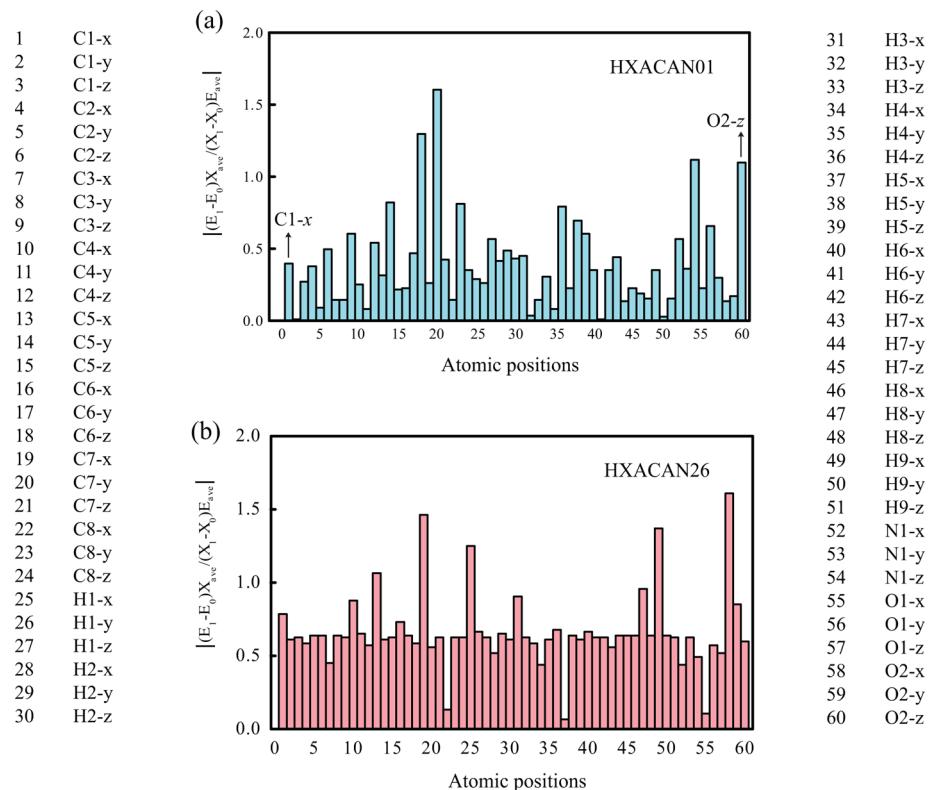


Figure 3. Sensitivity of the lattice energy to slight changes in the atomic positions of HXACAN01 (a) and HXACAN26 (b). The ordinate axes in panels a and b are scaled by the change in lattice energy with atomic position shifting. The 60 numbers on the abscissa axis represent the 60 directions of one paracetamol molecule, corresponding to the *x*, *y*, and *z* directions of the 20 atoms in the left and right columns.

original unit cell, respectively. The red lines represent the experimental lattice energy of paracetamol crystal, which is -29.4 kcal/mol .²² The blue bars in Figure 2c and the red bars in Figure 2e correspond to the lattice energy distributions of 100 slightly different structures of HXACAN01 and HXACAN26, which were generated by the SCLE method. Figure 2c shows that, among the 100 similar HXACAN01 structures, 1% have lattice energies between -29 and -28 kcal/mol , 1% have lattice energies between -28 and -27 kcal/mol , and 2% have lattice energies between -23 and -22 kcal/mol . As shown in Figure 2c, 8% of tested structures are within 5% of the energy of the HXACAN01 base-case (blue line). In contrast, as shown in Figure 2e, 80% of the tested structures are within 5% of the HXACAN26 base-case. In Figure 2c, the blue line (HXACAN01 base-case) is located at the lowest bar on the chart, while the blue line in Figure 2e (HXACAN26 base-case) lies close to the highest bar on its chart. Such differences demonstrate that HXACAN26 is a high-quality, reliable crystal structure, while the structure of HXACAN01 is questionable. Furthermore, the highest bar in Figure 2e, located in the area between -27 and -26 kcal/mol , is closer to the experimental red line (-29.4 kcal/mol) than the highest bar in Figure 2c, which lies in the area between -26 and -25 kcal/mol . Such comparison further demonstrates the higher quality of the HXACAN26 structure compared to that of HXACAN01. However, we can improve the quality of the HXACAN01 structure by shifting its atomic positions to the highest bar area in Figure 2c. The lattice energy distributions provide a more useful representation of the crystal structure quality than the base-case lattice energy alone. For example, although the lattice energy of the HXACAN01 base-case in Figure 2c is closer to the experimental result than that of the HXACAN26 base-case in Figure 2e, the highest bar in the

lattice energy distribution of HXACAN01 is far from the experimental value compared to the highest bar in Figure 2e. In this case, the comparison between the highest bar in the lattice energy distribution and the experimental result is the most important characteristic for determining crystal structure quality. The closer the highest bar in lattice energy distribution is to the experimental value, the higher the quality of a crystal structure.

Figures 2d and 2f show the lattice energy distributions of HXACAN01 and HXACAN26 with optimized unit cells. Crystallographic structure optimization was performed using *Materials Studio 8.0* (BIOVIA Software Inc.). The COMPASS II force field²⁴ was used with the associated charges. During the geometry optimization, molecular and crystal packing relaxation was allowed, while the cell parameters were fixed. An atom-based summation method was utilized to calculate the van der Waals energies. Ewald-based summation was used for electrostatic energy calculations. Figures 2d and 2f show that, after optimization, the calculated structures of HXACAN01 and HXACAN26 have very similar lattice energy distributions and base-case lattice energies. In both cases, the base-case lattice energy occurs at the highest bar of the distribution, and these are both close to the experimental value. Sometimes, however, it is not possible to optimize the unit cell, e.g., software might not be available for the desired atomic force field. In this case, it is necessary to have an alternative algorithm to determine the quality of crystal structures from a crystal database without structure optimization, and the SCLE algorithm is an effective and simple method that meets this requirement. For example, after using the SCLE algorithm, users can select HXACAN26 from the paracetamol database as the initial crystal structure with which to perform their research. Users can also choose the

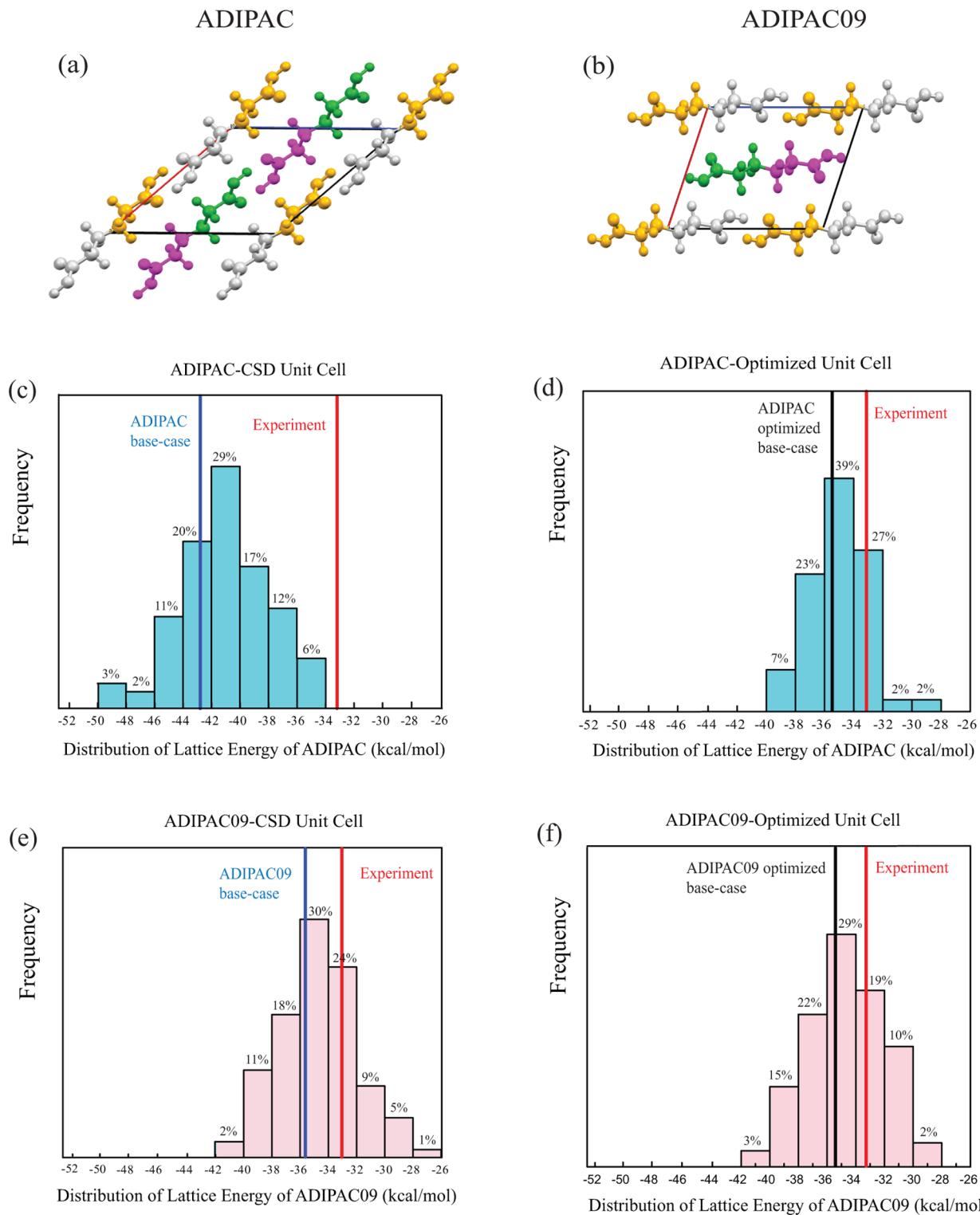


Figure 4. Unit cells of ADIPAC (a) and ADIPAC09 (b) generated from CSD data. The molecules are colored by symmetry operation. The lattice energy distributions of ADIPAC with the original unit cell (c) (from CSD), and the optimized unit cell (d), and ADIPAC09 with with original unit cell (e) (from CSD), and the optimized unit cell (f). The blue lines in panels c and e are the base-case lattice energies of ADIPAC and ADIPAC09. The black lines in panels d and f are the lattice energies of optimized ADIPAC and optimized ADIPAC09. The red lines correspond to the experimental lattice energy, which is -33.1 kcal/mol for adipic acid.²⁷ The experimental lattice energy of -33.1 kcal/mol²⁷ was calculated from the sublimation enthalpy according to the relationship $E_{\text{latt}} = -\Delta H_{\text{sub}} - 2RT$,²³ where R is the gas constant and T is the experimental temperature.

HXACAN01 structure after shifting its atomic positions to one of the structures within the highest bar in Figure 2c. Thus, shifting the atomic positions is a quick new way to improve the quality of crystal structure without the need for *ab initio* calculations.

Figure 3 plots the sensitivity of the lattice energy of HXACAN01(a) and HXACAN26 (b) as a function of atomic position. There are 20 atoms in a paracetamol molecule, and each atom has three degrees of freedom; thus, the 60 numbers on the

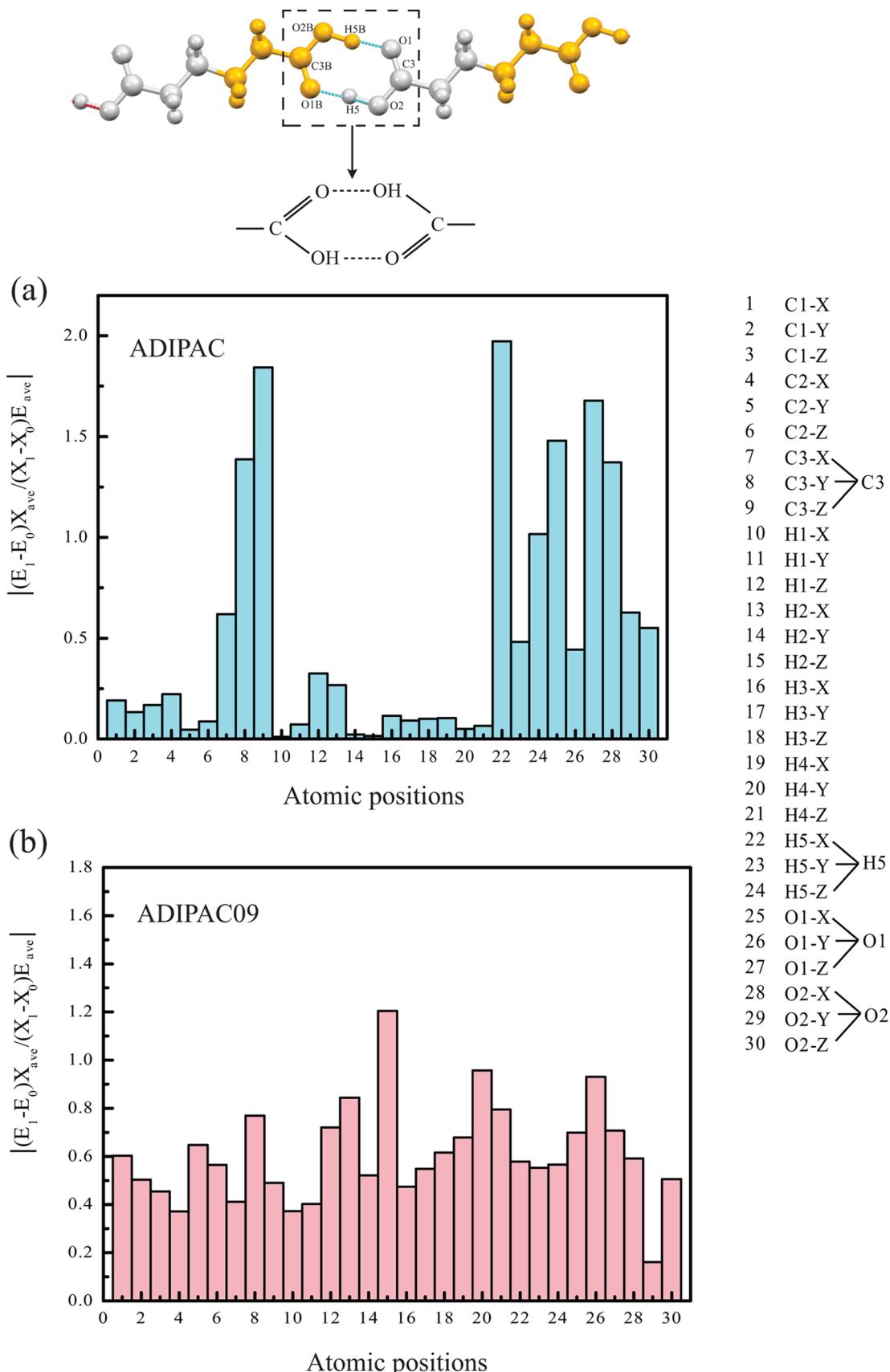


Figure 5. Lattice energy sensitivity of ADIPAC (a) and ADIPAC09 (b) on changing the atomic positions within their uncertainties. The top structure shows two adipic acid molecules connected by hydrogen bonds (blue lines). The molecules are colored by symmetry operation. The 30 numbers in the right column and the 30 numbers on the abscissa axis correspond to the *x*, *y*, and *z* directions of the 30 adipic acid atoms.

abscissa axis of Figure 3 represent the x , y , and z directions of the 20 atoms. Figure 3 was generated from 60 lattice energies after a ± 0.0001 Å shift in each of the 60 base-case atomic positions in HXACAN01 and HXACAN26. The choice of a 0.0001 Å shift is based on the experimental uncertainties in the atomic coordinates of paracetamol reported in the crystal structures. The ordinate axis, $|E_1 - E_0|/\hat{E}|/(X_1 - X_0)/\hat{X}|$, represents the fractional change in the lattice energy divided by the fractional change in position, where X_0 is the initial atomic position, X_1 is the atomic position after the shift by ± 0.0001 Å, \hat{X} is the average change in the atomic position, E_0 is the lattice energy of the base-case structure, E_1 is the lattice energy after each of the 60 atomic positions has been shifted by ± 0.0001 Å, and \hat{E} is the average lattice energy of all 60 E_1 . In Figure 3a, the leftmost blue bar (C1-x) is lower than the rightmost blue bar (O2-z), which means that the lattice energy changes more significantly when O2 is shifted in the z direction than when C1 shifted in the x direction. After making light changes to the atomic positions for paracetamol, Figure 3 shows that the changes in lattice energy are not even for shifts in different directions of the HXACAN01 atoms in panel a; in contrast, the lattice energy changed evenly for shifts in the x , y , and z directions of the atoms in HXACAN26 (panel b). The uneven distribution in Figure 3a and flat distribution in Figure 3b suggest that the atoms in the HXACAN26 structure are stable with respect to shifts in the x , y , and z directions, which is a characteristic of a reliable and high-quality crystal structure.

3.2. Centrosymmetric Case: Adipic Acid. We next study the lattice energy sensitivity of a centrosymmetric molecule, adipic acid, which has 19 similar entries in the CSD. Figures 4a and 4b show the unit cells of ADIPAC and ADIPAC09, which were determined by Housty et al. in 1965²⁵ and Mahmoudkhani et al. in 2001,²⁶ respectively. Both structures were determined by experienced scientists, and data collection was carried out at room temperature; however, the structures have different atomic positions.

To determine which structure is higher quality, we used the SCLE algorithm to calculate the lattice energy distributions of ADIPAC (Figures 4c and 4d) and ADIPAC09 (Figures 4e and 4f). When ADIPAC is used as the base-case to generate 100 similar crystal structures within the atomic uncertainties, most of the configurations have lattice energies between -42 kcal/mol and -40 kcal/mol, which accounts for 29% of the bars in Figure 4c. The ADIPAC base-case (blue line), which has a calculated lattice energy of -42.8 kcal/mol by GAFF, lies in the second-highest bar of the lattice energy distribution, and the highest bar is far from the experimental value of -33.1 kcal/mol (red line).²⁷ Such disagreement illustrates that ADIPAC is not a reliable structure for adipic acid and may contain disordered or displaced atoms. In this context, structural optimization is necessary to place the atoms into the correct and ordered positions. Figure 4d shows the lattice energy distribution of optimized ADIPAC, where the black line is the lattice energy of optimized ADIPAC, which is located at the highest bar (39%) and is much closer to the experimental lattice energy. Therefore, we conclude that optimization is vital to improving the quality of the ADIPAC structure.

Figures 4e and 4f show the results for ADIPAC09, where the lattice energy distributions for the two cases are similar, and the base-case lattice energies of both are located in the highest bars (-36.7 kcal/mol for ADIPAC09 and -35.5 kcal/mol for optimized ADIPAC09). Because the calculated lattice energies of ADIPAC09 and the optimized ADNPAC09 structure are very

similar and close to the experimental value, we conclude that optimization for ADIPAC09 is not necessary. By comparing the bar charts in Figures 4c and 4e, we notice that the highest bar in Figure 4c, which does not include the ADIPAC01 base-case, is far from the experimental value, while the highest bar in Figure 4e, which contains the ADIPAC09 base-case, is close to the experimental value. Such comparison confirms that ADIPAC09 is a more reliable and higher quality structure than ADIPAC. For both structures, optimization moves the entire distribution closer to the experimental lattice energy and also centers the base-case lattice energy at the maximum of the distribution.

To further demonstrate the sensitivity behavior, SCLE produces sensitivity histograms in Figure 5a for ADIPAC and Figure 5b for ADIPAC09. The sensitivity histograms show how lattice energy changes when x , y , and z directions of atoms shift within their uncertainties at 0.0001 Å. The top structure in Figure 5 shows two adipic acid molecules connected by hydrogen bonds (blue lines). Because each adipic acid molecule has 10 atoms, there is a total of 30 directions for one adipic acid molecule. The 30 numbers on the abscissa axis of Figures 5a and 5b and the right column are these 30 directions. As shown in Figure 5a, the movement of different atoms affects the lattice energy distinctly, showing that the lattice energy of ADIPAC is very sensitive to the atomic positions, indicating that ADIPAC is an unstable structure. However, the even height of the bars in Figure 5b indicates the collective stability of ADIPAC09, which confirms the high quality of the structure of ADIPAC09. From Figure 5a, the most unstable bars are at atomic positions 7, 8, 9, 22, 23, 24, 25, 26, 27, 28, 29, and 30, which correspond to the x , y , and z directions of "C3", "H5", "O1", and "O2". The top crystal structure shows that "C3", "H5", "O1", and "O2" are the atoms connected by hydrogen bonds, which typically provide a crucial contribution to the lattice energy, although the hydrogen atom positions are difficult to determine in X-ray scattering experiments.^{1,28}

In this case, the SCLE algorithm provides evidence that the most unstable atoms in ADIPAC are those connected by hydrogen bonds; consequently, ADIPAC is a lower-quality structure. Hydrogen bonds are a key factor affecting the crystal structure. The determination of a crystal structure by X-ray diffraction involves several important steps, but not all hydrogen atoms' positions can be obtained during this process. Sometimes, the positions of hydrogen atoms are difficult to determine, because the hydrogen atoms only scatter X-radiation weakly. Therefore, X-ray diffraction has some limitations when applied to the detection of light elements such as hydrogen atoms. Lighter elements (with lower electron densities) are thus not "visible" to X-rays, and the diffraction experiments becomes less accurate with regard to locating their positions.²⁹ Thus, our method provides an effective and easy method to detect the hydrogen atoms and hydrogen bonds accurately. As a case study, using adipic acid, we can either pick the high-quality structure ADIPAC09 or pick the low-quality structure ADIPAC after shifting its atomic positions to a configuration lying within the highest bar in Figure 4c. SCLE not only provides a simple algorithm for the assessment of crystal structure quality in a structural database but also offers a new way to distinguish and improve the positions of poorly determined atoms without requiring *ab initio* calculations.

4. CONCLUSIONS

Crystallographic databases usually contain several crystal structures for one molecule, obtained from different diffraction

experiments. The most reliable structure can often be selected by professional researchers, because they have access to refinement and analysis software, such as *Materials Studio*. However, for researchers those do not have access to these programs, the choice of a reliable and high-quality crystal structure from many similar structures is challenging, possibly slowing or even preventing research. Here, we have introduced a simple algorithm, the sensitivity of crystal lattice energy (SCLE) for crystal structure data, which can be used to help with the selection and improvement of crystallographic structures without the need for crystallographic software. By analyzing the changes in the lattice energy on slightly shifting the atomic positions within their uncertainties, the data generated by SCLE produces histograms that can help users determine the reliability of a crystal structure, pick high-quality structures, and improve low-quality structures. The sensitivity algorithm generated by SCLE identifies the most reliable or “optimal” structure from a crystal database without the need for *ab initio* calculations, thus providing useful parameters for solid-state calculations and experimental measurements.

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Notes

The authors declare no competing financial interest.

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