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Intermolecular Interactions in Organic Crystals: Gaining Insight from Electronic Structure Analysis by Density Functional Theory

Mingtao Zhang and Tonglei Li [*]

Industrial & Physical Pharmacy, Purdue University, West Lafayette, Indiana 47907

Corresponding Author:

Tonglei Li, Ph.D.

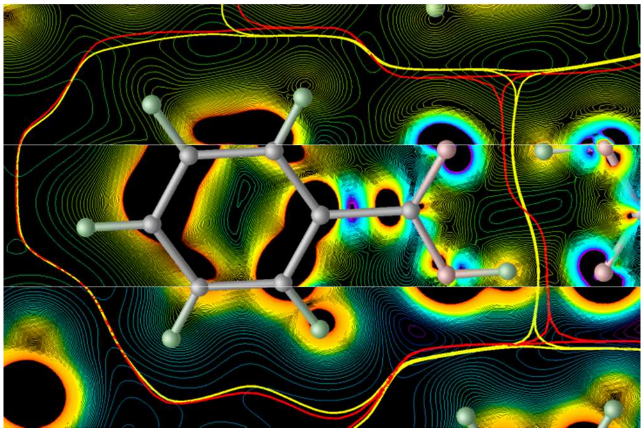
575 Stadium Mall Drive

West Lafayette, IN 47906

Phone: 765-494-1451

E-mail: tonglei@purdue.edu

Abstract: Conceptual density functional theory is exploited to extend the HSAB (hard and soft acids and bases) principle for investigating the locality and regioselectivity of intermolecular interactions in organic crystals. Local hardness and softness, facilitated by Hirshfeld analysis, appear to quantitatively characterize the strength of intermolecular interactions.



Introduction

Looking at a crystal structure on the computer screen, we are often amazed by how molecules arrange themselves in such a symmetric, intriguing tessellation! The strength and directionality of intermolecular interactions, governed by structural diversity and conformational flexibility of molecule, dictate crystal structure formation. Subtle variations in molecular interactions occasionally result in polymorphs of the same compound, driven by changes in crystallization conditions during the self-assembly process. Understanding and thereby predicting molecular packing in the crystal not only satisfies our curiosity, but also enables us to create new structures and materials with novel properties.

Predicting how molecules pack themselves into crystal structures has long been sought, but far from being realized. The doubt over the predictability of crystal structure remains lingering,[1-8] in part because of the poor performance of the energy models suitable for calculating molecular crystals, and in part resulting from the complexity of the energy space and a humongous number of hypothetical crystal structures to evaluate for the molecule of interest. From the mathematical viewpoint, the molecular shape considered when generating test crystal structures resembles the static electron density of a molecule without the account of interacting preferences by the molecule's functional groups. As one knows, the electron density itself has no direct indication of intermolecular interactions (at the van der Waals surface, for example, $–CH_3$ probably has the same electron density as –OH but they obviously have different interacting potentials). It is the polarizability and mobility of electron that define the strengths of two interacting molecules (for charged species, nonetheless, electron densities do matter).

In reality, it is not a random act at all for molecules to assemble and form a crystal. Throwing a molecule to Mother Nature, most likely, one will get exactly the same crystal structure faithfully back, over and over. Sometimes, a few more structures of the same molecule may come out under different conditions. Whether there is just one or a few polymorphs, the crystal structure(s) remains consistently defined and molecules always form the same packing motifs in the solid state, regardless of who/where/when/how to produce it. Clearly, a molecule "knows" which parts of its structure will interact with one another, resulting in unique intermolecular interacting patterns, or synthons,[9] such as hydrogen bonding and π-π stacking. Such locality or the electronic structure – its spatial distribution and response to external stimuli – of the molecule of interest.

Theoretical Background

To explore the electronic origin of intermolecular interactions in organic crystals, we have turned to density functional theory (DFT), in particular, conceptual density functional theory (CDFT). Over the last two decades, DFT has evolved into two branches, one for energy calculations [10-12] and other, generally referred to CDFT, for theoretically studying fundamental linkages between electron density and molecular properties, such as reactivity and electrophilicity.[13-17] Among various concepts derived by CDFT, Fukui function is particularly appealing.[18-25] It is a local, spatial function; it exhibits the intrinsic characteristics of local polarizability and electronic softness, and demonstrates the capability of illustrating how a molecule interacts with others.[26-31] In our laboratory, we have explored the concept of Fukui function for characterizing the locality of intermolecular interactions.[32-34] Along with other local electronic properties (such as electrostatic potential or ESP), the CDFT concept has become a cornerstone of our research to study intermolecular interactions of organic molecules.

The essence of our study stems from Pearson's HSAB (hard and soft acids and bases) principle, which states that hard acids prefer hard bases and soft acids prefer soft bases, both thermodynamically and kinetically.[35-39] The principle may be extended to characterizing the locality and regioselectivity of intermolecular interactions, especially in organic molecules where hardness is less dominant.[40-42] Namely, when two molecules interact in space, their spatial orientation and packing motif are determined by local softness and hardness. A soft region or functional group of a molecule prefers interacting with a soft region of another molecule; vice versa for the matching in local hardness.

While the HSAB principle was proposed in 1960's, it is CDFT that elegantly interprets the principle with precisely defined quantities. In essence, DFT assumes electron density as the underlying element for describing atomic and molecular ground states.[13, 15, 43] Accordingly, the total energy of a system is dependent upon the energy of the electronic structure and nuclear-nuclear Coulomb repulsion energy:

$$W[\rho,\nu]=E[\rho,\nu]+V_{nn}[\nu] \qquad \text{Eq. 1}$$

where E is the electronic energy, V_{nn} is the nuclear-nuclear repulsion energy, $\rho(\mathbf{r})$ is the electron density at point **r** in space, and $v(\mathbf{r})$ is the external potential defined by nuclear positions and charges. The electronic energy of a system is further defined as:

$$E[\rho, v] = F[\rho] + \int \rho(\mathbf{r}) v(\mathbf{r}) d\mathbf{r} \qquad \text{Eq. 2}$$

where $F[\rho]$ is the sum of kinetic and electron-electron repulsion energy. From the perturbation-response perspective, the energy fluctuation of a molecular system defines its chemical and/or structural stability. Such variation may be described by the mutual coupling between the electronic structure (i.e., electron density) and the molecular skeleton (defined by nuclear charges and their positions).[44, 45] As a molecular system changes from a ground state to another because of the perturbation in electron population or the number of electrons, dN, as well as the external potential, $\delta v(\mathbf{r})$, the system energy change to the second order may be expanded as:[14, 46]

$$dE = \underbrace{\left(\frac{\partial E}{\partial N}\right)_v}_{\mu} dN + \int \underbrace{\left[\frac{\delta E}{\delta v(\mathbf{r})}\right]_N}_{\rho(\mathbf{r})} dv(\mathbf{r})d\mathbf{r} + \frac{1}{2}\underbrace{\left(\frac{\partial^2 E}{\partial N^2}\right)_v}_{\eta} (dN)^2 + \int \underbrace{\left[\frac{\delta^2 E}{\delta v(\mathbf{r})\partial N}\right]}_{f(\mathbf{r})} dv(\mathbf{r})d\mathbf{r}\, dN + \frac{1}{2}\int \underbrace{\left[\frac{\delta^2 E}{\delta v(\mathbf{r})\delta v(\mathbf{r}')}\right]_N}_{\beta(\mathbf{r})} dv(\mathbf{r})d\mathbf{r}\, dv(\mathbf{r}')d\mathbf{r}' \qquad \text{Eq. 3}$$

where μ is electronic chemical potential – the opposite of electronegativity [47] – characterizing electron's escaping tendency from the equilibrium, η is hardness, $f(\mathbf{r})$ is Fukui function, and $\beta(\mathbf{r})$ is linear response function. The hardness has been proved to be related to Klopman's frontier molecular orbital theory,[48] defined as the energy difference between ionization potential and electron affinity.[37] The inversion of hardness is softness, S.[49] The hardness and softness, both DFT concepts, corroborate with the HSAB principle,[35-39] and have been utilized for characterizing intermolecular interactions.[50, 51] Specifically, for an acid-base interaction, **A + :B → A:B**, where **A**, acceptor of electrons, is the acid, **B**, donor of electrons, is the base.[35, 36] Acids and bases can be classified as hard or soft:[49]

	Hard	**Soft**
Acids:	*high positive charge, low polarizability*	*low positive charge, high polarizability*
Bases:	*high electronegativity, low polarizability*	*low electronegativity, high polarizability*

CDFT supports the HSAB principle through the electronic softness and hardness. Parr and Yang prove that the energy change expanded to the second order, due to perturbation in electrons and external potentials when two molecular systems, **A** and **B**, interact, is given by:[14]

$$\Delta E = \left\{ \int \rho_A(\mathbf{r})\Delta v_A(\mathbf{r})d\mathbf{r} + \int \rho_B(\mathbf{r})\Delta v_B(\mathbf{r})d\mathbf{r} \right\} + \left\{ - \frac{\left[\mu_B^0 - \mu_A^0 + \int f_B(\mathbf{r})\Delta v_B(\mathbf{r})d\mathbf{r} - \int f_A(\mathbf{r})\Delta v_A(\mathbf{r})d\mathbf{r} \right]^2}{4(\eta_A + \eta_B)} \right\}$$

$$+ \left\{ \iint \left[\frac{\delta \rho_A(\mathbf{r})}{\delta v_A(\mathbf{r}')} \right]_{N_A} \Delta v_A(\mathbf{r})\Delta v_A(\mathbf{r}')d\mathbf{r}d\mathbf{r}' + \iint \left[\frac{\delta \rho_B(\mathbf{r})}{\delta v_B(\mathbf{r}')} \right]_{N_B} \Delta v_B(\mathbf{r})\Delta v_B(\mathbf{r}')d\mathbf{r}d\mathbf{r}' \right\} \quad \text{Eq. 4}$$

In the equation, there are three components enclosed in brackets. The first is the energy contribution from electrostatic interactions, which become dominant when **A** and **B** are hard, typically with high charges. The second is from covalence-type interactions due to the flow of electrons, and the third is from polarization. The last two contributions become significant when **A** and **B** are soft.[14]

Thus, CDFT allows the examination of intermolecular interactions based on the electronic structures of molecules.[16, 18, 52, 53] For organic crystals, the soft-soft type of intermolecular interactions dominates. Hydrogen bonding and close contacts can be regarded as partial sharing or flow of electrons and van der Waals interactions are caused by polarization of electron clouds. Pertinent to our investigation of intermolecular interactions, CDFT is extremely appealing as the theory offers a quantity to characterize the local softness (and hardness). This concept is Fukui function:[18-21]

$$f(\mathbf{r}) = \left[\frac{\delta^2 E}{\delta v(\mathbf{r})\, \partial N} \right] = \left[\frac{\delta \mu}{\delta v(\mathbf{r})} \right]_N = \left(\frac{\partial \rho(\mathbf{r})}{\partial N} \right)_v \quad \text{Eq. 5}$$

Being an electronic perturbation-response quantity, it is directly associated with local polarizability or softness of a molecular system.[23-25] Particularly, local softness, $s(\mathbf{r})$, is proportional to Fukui function:[49]

$$s(\mathbf{r}) = S f(\mathbf{r}) \quad \text{Eq. 6}$$

Intuitively, an outstanding region of Fukui function should contribute considerably to the local and overall intermolecular interactions (via the second and third contributions in Eq. 4). Several of our studies demonstrate the potential of Fukui function for characterizing the locality of intermolecular interactions.[32-34, 54-59]

In practice, Fukui function may be evaluated by finite difference due to the discontinuity of N:

$$f^+(\mathbf{r}) \approx \rho(\mathbf{r})^+ - \rho(\mathbf{r})$$

$$f^-(\mathbf{r}) \approx \rho(\mathbf{r}) - \rho(\mathbf{r})^- \quad \text{Eq. 7}$$

where the superscript + or – denotes addition (i.e., under nucleophilic attack) or depletion (electrophilic attack) of an electron to or from the system. $f^+(\mathbf{r})$ and $f^-(\mathbf{r})$ are called nucleophilic and electrophilic Fukui functions, respectively. Since the frontier orbitals participate mostly in the electron addition (reduction) and depletion (oxidization), $f^+(\mathbf{r})$ and $f^-(\mathbf{r})$ correspondingly resemble the electron distributions on LUMO (lowest unoccupied molecular orbital) and HOMO (highest occupied molecular orbital). The difference between $f^+(\mathbf{r})$ and $f^-(\mathbf{r})$ is named dual descriptor and calculated by:[60-62]

$$f^2(\mathbf{r}) = \left(\frac{\partial^2 \rho(\mathbf{r})}{\partial^2 N}\right)_v = \left(\frac{\partial f(\mathbf{r})}{\partial N}\right)_v \approx f^+(\mathbf{r}) - f^-(\mathbf{r}) \qquad \text{Eq. 8}$$

As such, $f^2(\mathbf{r})$ can be regarded as $\rho(\mathbf{r})_{\mathrm{LUMO}} - \rho(\mathbf{r})_{\mathrm{HOMO}}$ so that a positive region is where an electron is attracted to (LUMO is more dominant) and a negative region is where an electron is donated from (HOMO is more dominant). As an example, Figure 1 illustrate these concepts of an organic compound whose crystal and electronic structures have been extensively studied in our laboratory, 2-(phenylamino)nicotinic acid (2-PNA).[58, 63-65] The resemblance between HOMO (or LUMO) and $f^-(\mathbf{r})$ (or $f^+(\mathbf{r})$) clearly shows. What can also be seen is, while the electron density provides little information of electron philicity – it merely suggests the traditionally defined molecular shape, as shown in Figure 1a – the Fukui functions, being local elements, do seem to suggest the locality of interacting potentials of the molecule, as explored in our studies.[58]

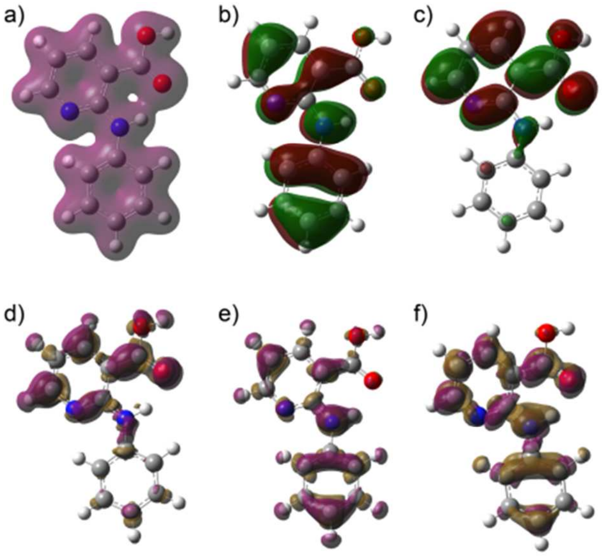


Figure 1. Isosurfaces of 2-PNA single molecule: $\rho(\mathbf{r})$ (a), HOMO (b), LUMO (c), $f^+(\mathbf{r})$ (d), $f^-(\mathbf{r})$ (e), and $f^2(\mathbf{r})$ (f). The isovalue of (a – c) is 0.02 a.u. and that of (d – f) is 0.002. Positive $f^2(\mathbf{r})$ shown in pink while negative ones in brown. (Adopted from Reference 57, with permission.)

While local softness is clearly defined (Eq. 6), an unambiguous definition is lacking for local hardness.[40, 41, 66, 67] Several approximations have been developed.[68, 69] For our studies of organic molecules, the hard-hard type of intermolecular interactions is less dominant (other than charged species). We thus choose to use a simple, conventional function, electrostatic potential (ESP), for examining hard-hard interactions. ESP is a local function and, in fact, has been shown to characterize the local hardness.[70]

Our theoretical framework for examining intermolecular interactions is thereby built on the HSAB principle. By examining local softness (and hardness), we aim to decipher and subsequently understand the spatial arrangement of molecular assembly in the crystal. For this purpose, CDFT provides a simple and yet effective way to quantify the local electronic properties pertinent to the locality of intermolecular interactions. From the mathematical viewpoint, by exploiting responses of electron density under electronic perturbation, we actually consider the first- and higher-order derivatives of electron density to characterize the polarizability and electron-sharing tendencies of the molecule. In addition, the perturbation-response quantities are local functions and have been demonstrated in our studies to identify the locality of intermolecular interactions regarding both interaction strength and directionality.[32, 33, 55, 59] These electronic properties can be directly derived from the electronic structure of a molecule, thereby representing the inherited propensity for the molecule to interact with its peers.

Case Study with Hirshfeld Surface Analysis

To illustrate how the CDFT concepts help understand intermolecular interactions in a crystal, herein, we report a study of electronic calculation and analysis of benzoic acid, a small but yet chemically rich system embodying almost all major types of interaction interactions encountered in the organic crystals. In brief, the computational steps started with the crystal structure of benzoic acid (Refcode: BENZAC12) being optimized by Crystal 09 [71] at the level of B3LYP/6-21G** with the lattice parameters kept constant. The optimized crystal structure was further evaluated by B3LYP/6-31G** for calculating electron densities of the neutral, cationic, and anionic states, respectively. When calculating an ionized state, an extra electron was introduced or extracted from the basis set definition for the crystal structure. The addition or depletion of the electron was then averagely shared among all the atoms by the program prior to the self-consistent field calculation. ESP was evaluated as well for the neutral state. Similar electronic properties were calculated from the single molecule of the same conformation as in the crystal. The properties were analyzed and processed by a program developed in our laboratory, which also generated input files used by OpenDX [72] for visualization.

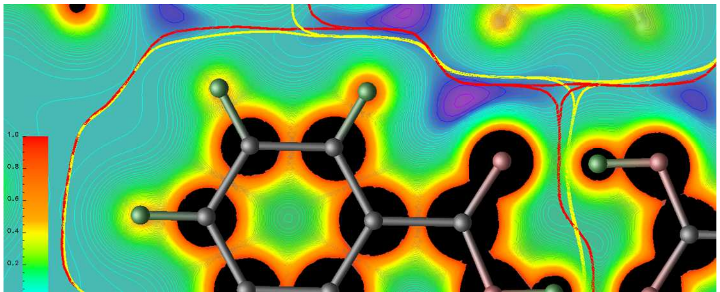
While Fukui function quantifies the local softness of a molecular system (Eq. 6), there is no straightforward way to utilize the concept to characterize intermolecular interactions. Being a local function of every point in space makes it difficult to probe a particular region or functional group with regard to its interacting potential. One scheme is the so-called condensed Fukui functions based on the imaginary atomic charges for the calculation.[73-75] Various population analysis schemes, including Mulliken,[76] Hirshfeld,[77] natural bond orbital (NBO),[78, 79] and Bader methods,[80] have been implemented to partition electron density into atom-centered regions and "condense" into every atom. Similar to Eq. 6, condensed nucleophilic and electronic Fukui functions can be calculated from the atomic charges of anionic, natural, and cationic species of a molecule. Condensed dual descriptor can also be derived. Note that the condensed properties including atomic charges have no direct physical linkage; their usage is merely of convenience for comprehending chemical insight from molecular structures.

In this report, we explore the utilization of Hirshfeld surface for visualizing and quantifying Fukui functions. Hirshfeld surface defines a seamless boundary between two molecules in the crystal. The concept originates from the electron density partition scheme proposed by F. L. Hirshfeld.[77] Thanks to the seminal work by M. A. Spackman, it is expanded into the solid-state field in a similar fashion, and a Hirshfeld surface is defined by portioning the electron density in the crystal according to a weight function:[81-83]

$$w_A(\mathbf{r}) = \rho_{pro-molecule}(\mathbf{r}) / \rho_{pro-crystal}(\mathbf{r}) \qquad \text{Eq. 11}$$

where $\rho_{pro\text{-}molecule}(\mathbf{r})$ is the electron density assembled from the density contributions by all the atoms in the molecule of interest (denoted as A) and $\rho_{pro\text{-}crystal}(\mathbf{r})$ is from all the atoms in the crystal. The electron density of an atom may be quickly evaluated by various methods or retrieved from a database. By plotting an isosurface of $w_A(\mathbf{r})$, typically at 0.5, one can obtain the Hirshfeld surface.

A major advantage of Hirshfeld surface as compared with the most commonly used van der Waals surface is that Hirshfeld surfaces in a crystal are in full contact with each other,



that a molecule occupies without extruding into its neighbors. There is thus little gap between Hirshfeld surfaces of adjacent molecules, defining a smooth molecular boundary. The concept thus becomes extremely appealing to us for examining the local intermolecular interactions and it provides a direct way to assess Fukui functions and other local functions. Concerning the rough calculation by the summation approach of atomic densities, we generate our Hirshfeld surfaces by calculating $\rho_{pro\text{-}molecule}(\mathbf{r})$ and $\rho_{pro\text{-}crystal}(\mathbf{r})$ directly from the respective molecular and crystal structures. The density values are much more reliable for defining a more accurate Hirshfeld surface. Figure 2 exemplifies the difference between the atomic summation and direction calculation methods, which is subtle mostly but significant in the acid-acid hydrogen-bonding region of benzoic acid; the surface by the improved approach contracts more toward the hydrogen of –OH, better representing the ESP in the region that is mapped to the slice.

From the electronic structures calculated of the crystal and Hirshfeld surface analysis, eight pairs of intermolecular contacts emerged from the benzoic acid crystal. Intermolecular interactions of each pair were further calculated by Gaussian 09 (Gaussian, Inc., Wallingford CT) at several levels, including MP2 (second-order Møller-Plesset)[84] and DFT-D (B2PLYP-D),[85, 86] with the 6-311g** basis set and having the BSSE (basis-set superposition error) corrected.[87] Fukui functions and ESP were mapped to the Hirshfeld surfaces for visual analysis. Moreover, the local functions were mathematically integrated over the contacted area on the Hirshfeld surface of each molecular pair for quantitative assessment. To compare with the crystal-based results and gain further understanding of the intermolecular interactions, Fukui functions and ESP calculated from the single molecule were also mapped to the Hirshfeld surface. The results are discussed as follows.

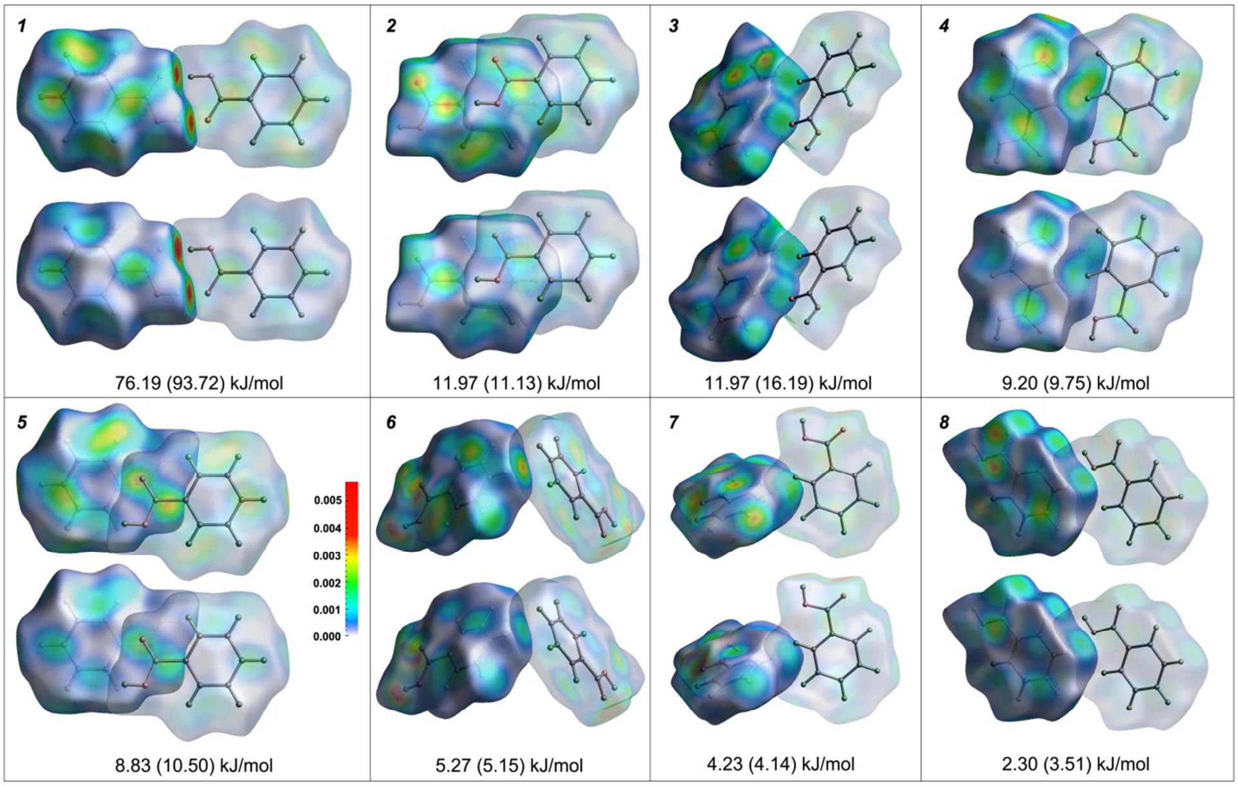


Figure 3. Hirshfeld surfaces of eight packing motifs mapped with the crystal- (top of each motif) and molecule-based f^+ (bottom) respectively. The color bar shown in #5 applies to all. The energy values are intermolecular interaction energies of respective pairs by MP2 and DFT-D (in the parentheses).

Figures 3-5 show Hirshfeld surfaces of eight identified packing motifs – arranged in the descending order of intermolecular interactions – with $f^+(\mathbf{r})$ (Figure 3), $f^-(\mathbf{r})$ (Figure 4), and $f^2(\mathbf{r})$ (Figure 5) mapped that were respectively calculated from the crystal and single-molecule structures. The first pair has the strongest interaction, 76.19 or 93.72 kJ/mol by MP2 or DFT-D, largely contributed by the hydrogen bonding. Note that we use positive numbers for the attractive intermolecular interactions. The Fukui functions obtained from both the crystal and molecule are also largest on the Hirshfeld surface between the carboxyl groups, while f^- displays noticeable difference between the crystal- and molecule-based calculations. Because $f^2(\mathbf{r}) = f^+(\mathbf{r}) - f^-(\mathbf{r})$, it can be further concluded from Figure 5 that the molecule-based f^- is dominant near the =O region but f^+ may be slightly bigger than f^- at -OH. Note that, because $Z' = 1$, all the Hirshfeld surfaces mapped with the same Fukui functions, either calculated from the crystal or single molecule, are identical in each figure. Also note that the Fukui functions at the molecular when the values come from the molecule, the two surfaces do not share the same values at any contacting points (the values of the transparent surface may be examined from the other surface at proper locations). In addition, for the case of #1 motif (as well as #3 and #5), the two surfaces are reciprocal at the contact.

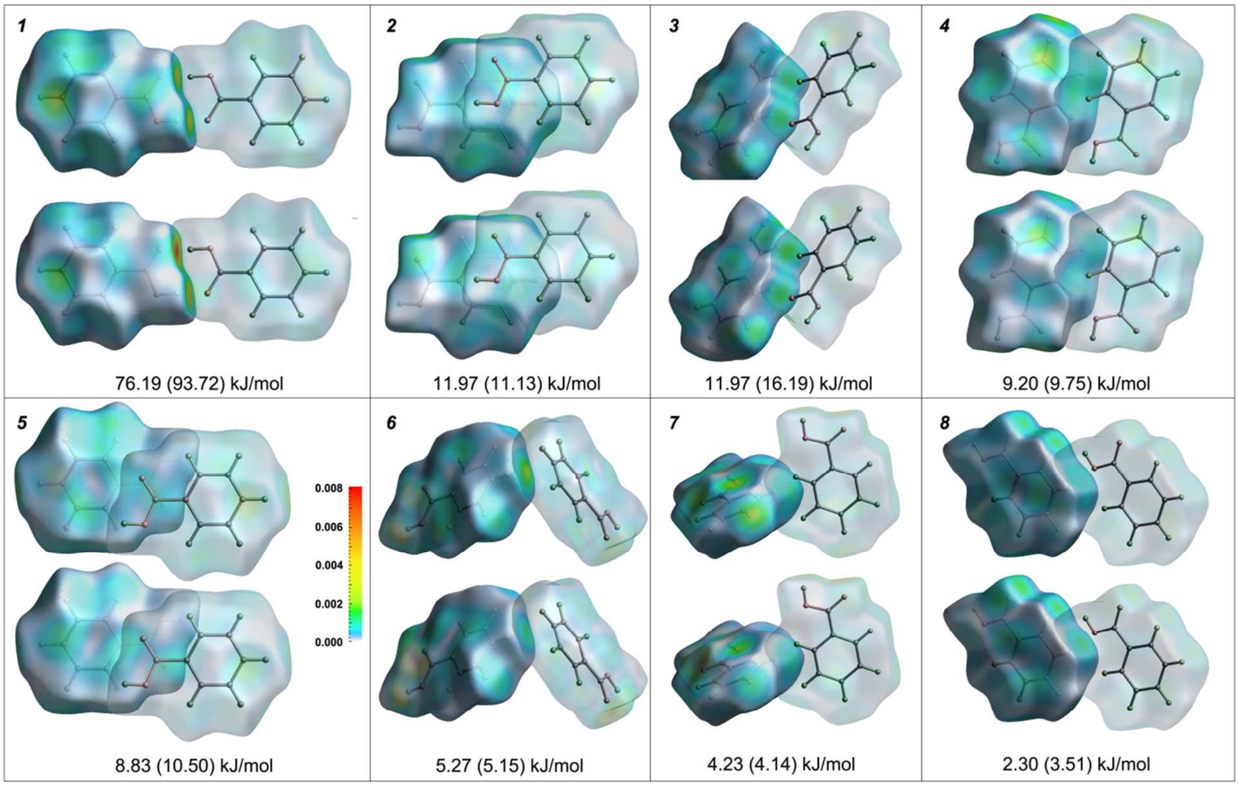


Figure 4. Hirshfeld surfaces of eight packing motifs mapped with the crystal- (top of each motif) and molecule-based f^{-} (bottom) respectively. The color bar shown in #5 applies to all. The energy values are intermolecular interaction energies of respective pairs by MP2 and DFT-D (in the parentheses).

Contacts #2, #4, and #5 are π-π stacking of respectively much smaller intermolecular interactions, 11.97, 9.20, and 8.83 kJ/mol by MP2, or 11.13, 9.75, and 10.50 kJ/mol by DFT-D. The duos involve –COOH and phenyl (#2), phenyl and phenyl (#4), and -COOH and -COOH (#5), well confirmed by sizable f^{+} and f^{-} spots (both the crystal- and molecule-based). It can be further concluded from Figure 5 that these motifs engage larger f^{+} regions from the two interacting molecules. Contact #3 consists of a weak hydrogen bond between =O and –CH, calculated at 11.97 or 16.19 kJ/mol by MP2 or DFT-D. Fukui functions are mostly noticeable at the =O side and f^{+} is more dominant. From the –CH side, f^{+} and f^{-} appear to be trivial. #6 yields an

The akin f^{+} and f^{-} spots, whether calculated from the crystal or from the molecule, match each other from the two contacting surfaces. #7 and #8 are the weakest interactions of 4.23 and 2.30 kJ/mol by MP2, or 4.14 and 3.51 kJ/mol by DFT-D, respectively. The edge-edge contacts between phenyl rings mostly engage van der Waals interactions. Still, local f^{+} and f^{-} values noticeably stand out.

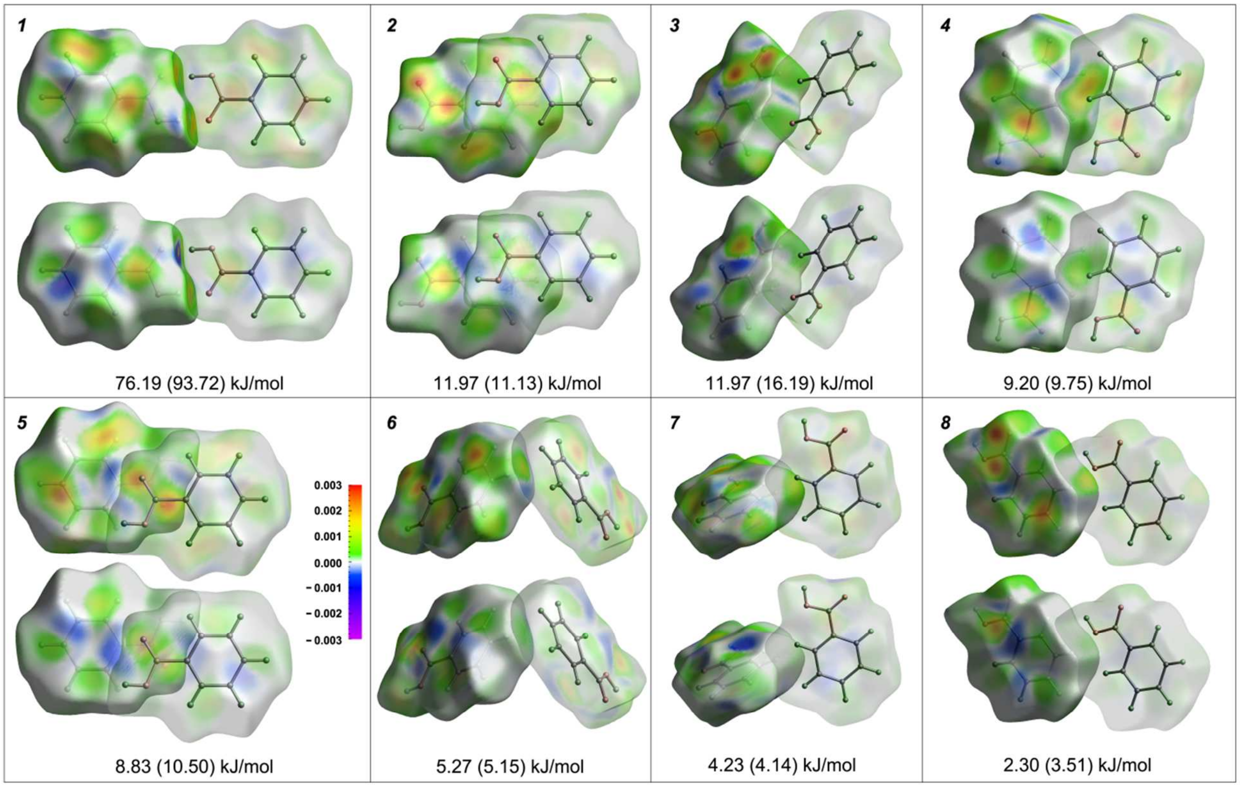


Figure 5. Hirshfeld surfaces of eight packing motifs mapped with the crystal- (top of each motif) and molecule-based f^{2} (bottom) respectively. The color bar shown in #5 applies to all. The energy values are intermolecular interaction energies of respective pairs by MP2 and DFT-D (in the parentheses).

The visual analyses demonstrate that the intermolecular packing motifs couple with regions or spots of relatively large f^{+} and f^{-}. The hydrogen bonding between –COOH groups is clearly the dominant force, much stronger than any of the rest of motifs. It engages the largest Fukui functions and points out two matching scenarios of respective Fukui functions, one being larger f^{-} on =O against larger f^{+} on –OH and other being larger f^{+} on both groups. The π-π stacking motifs, although much smaller, are the next significant forces mostly engaging the larger f^{+}-larger f^{+} matching. The weakest interactions still associate with smaller but noticeable f^{+} and/or f

Fukui functions, suggesting the opportunity of utilizing the chemical information embodied in the molecule to discover intermolecular interactions.

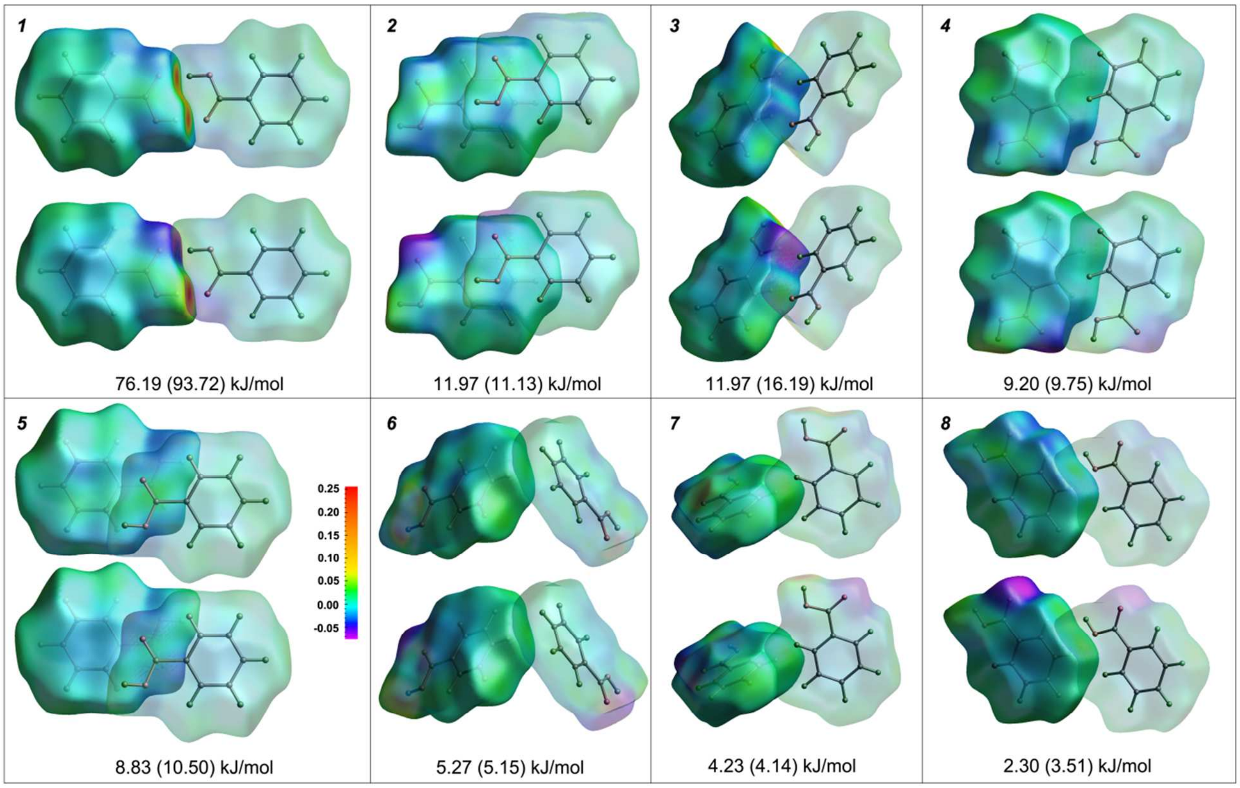


Figure 6. Hirshfeld surfaces of eight packing motifs mapped with the crystal- (top of each motif) and molecule-based ESP (bottom) respectively. The color bar in #5 applies to all. The energy values are intermolecular interaction energies of respective pairs by MP2 and DFT-D (in the parentheses).

Figure 6 shows the Hirshfeld surfaces mapped with ESP calculated from the crystal and single molecule structures, respectively. It seems that the only large spots of either positive or negative ESP values are converged around the –COOH dimer where the hydrogen bonds form. No other significant regions are associated with other intermolecular interactions. It is also interesting to see no similarity between the crystal- and molecule-based ESP values, particularly, of the –COOH. Both =O and –OH bear positive potentials in the crystal, but =O is negative and –OH positive on the Hirshfeld surface base on the molecular calculation.

To further explore the connection between the packing motifs and the local electronic properties, Fukui function and ESP are integrated over the contacting area of Hirshfeld surfaces and plotted against the intermolecular interactions (Figure 7). It is found that DFT-D (B2PLYP-D) generally yield better correlations than MP2, which is known less capable for fully evaluating weak intermolecular interactions.[88] Thus Figure 7 only presents the correlations with the energy values by DFT-D. Note that each ESP data point is a sum of absolute values of both positive and negative numbers integrated over the contact (Figure 7A), attempted to mirror the electrostatic interaction by positive and negative charges. The correlations are significant, better with the molecule-based Fukui functions. Nonetheless, because the hydrogen bonding is several times larger than the rest, the linear regressions are biased by the largest value. When the #1 is excluded, the integrated ESP correlates more poorly with the intermolecular interactions (inset in Figure 7A). The crystal-based ESP values show almost no correlation, but the molecule-based values have an R^2 of 0.80.

Shown in Figure 7B, the molecule-based Fukui functions, especially f^{-}, show strong correlations with the interactions (R^2 = 1.00

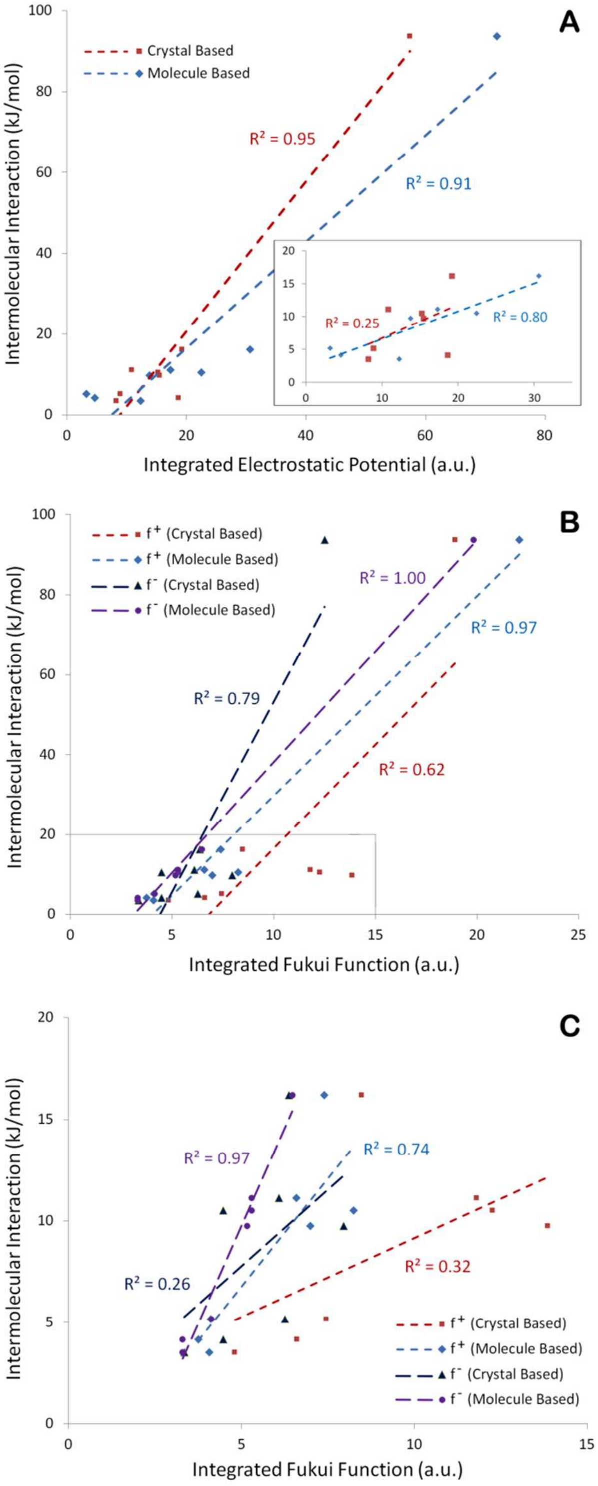


Figure 7. Intermolecular interaction energy as a function of integrated absolute ESP (A) and Fukui function (B), whose small value regions are shown in the inset of A and C, respectively. Dashed lines are linear regressions of

crystal-based Fukui functions bear some degrees of correlation and semi-quantitative trends still remain, especially given the visual similarity between the crystal- and molecule-based Fukui functions. Again, when #1 is excluded, the relationships become less significant, but f^- still shows an excellent correlation and f^+ is good as well ($R^2 = 0.97$ and 0.74, respectively; Figure 7C). This quantitative finding may be far-reaching, considering the scale of these weak interactions ranging from a few to less than 20 kJ/mol. The relationship with the crystal-based Fukui functions, however, is only semi-quantitative.

Two major points may be drawn from the visual and quantitative analyses of the benzoic acid study. Firstly and foremostly, the intermolecular interactions in the crystal are governed by the electronic properties calculated from the single molecule, including ESP and Fukui functions (f^+ and f^-). Based on the correlation coefficients between the interaction energy values and these electronic properties, the nature of the interactions is dominated by the electronic softness, especially for the interactions that are much weaker than hydrogen bonding. The hard-hard type of interaction, characterized by ESP, may play a role for these weak interactions but appears to be less significant. In addition, the crystal-based ESP and Fukui functions seem to retain some of hardness and softness instilled by the single molecule (calculated in gas phase while a molecule in the crystal is surrounded by eight other molecules), but they only correlate semi-quantitatively or worse with the interaction values. Specifically for the hydrogen bonding, the vicinity of ESP around carbonyl O becomes mainly positive in the crystal differing from the outstanding negativity in the single molecule.

Secondly, there appears to be matching of these electronic properties that decides the strength of the intermolecular interactions. The hydrogen bonding of the –COOH dimer is of both hard-hard and soft-soft types of interaction, indicated by the larger ESP and Fukui functions at the Hirshfeld surface. Matching of larger f^+ and f^- spots leads to partial sharing of electrons (e.g., hydrogen bonding); f^+- f^+ or f^--f^- matching likely induces delocalization of antibonding or bonding orbitals. And it is seen that π-π stacking engages significant f^+- f^+ matching (e.g., stacking between –COOH groups in the #5 contact). From the outstanding correlation between the interaction values and molecule-based f^- (Figure 7B and C), it is tempted to believe that overlapping of HOMO's plays a more decisive role between two interacting molecules. Delocalization of electrons at the frontier orbitals, especially HOMO, seems to increase the

Conclusions and Outlook

Our study of benzoic acid suggests the applicability of HSAB in quantitatively assessing the intermolecular interactions of organic molecules. Being local functions, the DFT-based concepts such as Fukui functions are enabling for unveiling the local softness in characterizing the locality or regioselectivity with regard to how a molecule interacts with another. Matching of the local functions suggests a possibility of developing new approaches for predicting crystal structures. Still, our analyses are based on Hirshfeld surface, which is a crystal property. Without a crystal structure, there is no Hirshfeld surface for mapping electronic properties of the single molecule. To overcome the conundrum, one possibility is to start with a surface scheme that is defined by the molecule itself, for example, van der Waals or solvent-accessible surface,[89] map the Fukui functions and ESP calculated from the molecule, respectively, and build test crystal structures based on the analysis of the local functions. Subsequently from the test crystal structures, we can generate Hirshfeld surfaces, map and analyze the local functions again to tweak and refine the crystal structures. The process could repeat until some convergence criteria are met. Additional studies to examine the distributions of Fukui functions and ESP and see how they intersect with Hirshfeld surfaces could provide further insights.

While analyzing benzoic acid and pondering its crystal packing motifs, it strikes us that, when molecules start to pack with themselves in solution or melt, they are unlikely to traverse an energy landscape of all possible crystal structures and then decide which structure is the best. In the case of benzoic acid, it becomes obvious that the hydrogen bonding, which is several times stronger than any other intermolecular interactions, should plays the decisive role in drawing molecules together and arrange them in a primary motif while the other minor forces simple fill up the space accordingly. Mathematically, it is indeed possible to have a structure where the hydrogen-bonding strength is compromised but other minor interactions get stronger. As a result, the lattice energy could remain slightly varied with a few kJ/mol or might be even lower – lattice energy being negative – as compared with that of the experimental structure. Nevertheless, such a mathematically possible structure may not ever emerge in the reality and using the lattice energy landscape approach to predict crystal structures might need to be reconsidered.

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