

Visualizing the locality of intermolecular interactions in organic crystals

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Abstract

Density functional theory (DFT) provides a rigorous theoretical framework for analyzing and interpreting electronic structures of molecules and crystals. One electron density-based concept is the Fukui function, which describes the responding sensitivity of a molecular system to electronic perturbations. As a local property, the Fukui function is directly associated with local polarizability, so it may be capable of describing the intermolecular interaction in an organic crystal with regard to molecular packing. Herein, we demonstrate such an application to the aspirin single crystal and discuss potentials of the DFT-based concepts for studying electronic structures of organic crystals.

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1. Introduction

Molecular packing determines various properties of organic crystals, including polymorphism and growth morphology. The study of intermolecular interactions in an organic crystal permits the understanding of the self-assembling process and makes it possible to predict crystal structures. In particular, knowing or even visualizing the anisotropic interaction “distribution” in a crystal with regard to the molecular conformation and packing motif can provide great insights on crystal growth mechanisms.

The energy of a molecular system at a ground state is a functional of its electron density as stated in density functional theory (DFT) [1]. Developing and applying DFT-based concepts to fundamental molecular phenomena have produced many fruitful results within the last decade [2]. Despite many reported DFT studies of molecular systems, fewer applications have been seen for organic crystals.

Analyzing how a molecular system responds to electronic perturbation within the framework of conceptual DFT may reveal underlying mechanisms with respect to the structure-property relationship. As a molecular system changes from one ground state to another because of perturbations in the electron population, dN , as well as in the external electrostatic potential,

$\delta v(\mathbf{r})$, the change of system energy to the second order may be expressed as [1]:

$$\begin{aligned} dE = & \underbrace{\left(\frac{\partial E}{\partial N} \right)_v}_{\mu} dN + \underbrace{\int \left[\frac{\delta E}{\delta v(\mathbf{r})} \right]_N}_{\rho(\mathbf{r})} dv(\mathbf{r}) d\mathbf{r} \\ & + \frac{1}{2} \underbrace{\left(\frac{\partial^2 E}{\partial N^2} \right)_v}_{\eta} (dN)^2 + \underbrace{\int \left[\frac{\delta^2 E}{\delta v(\mathbf{r}) \delta v(\mathbf{r}')} \right]}_{f(\mathbf{r})} dv(\mathbf{r}) d\mathbf{r} dN \\ & + \frac{1}{2} \underbrace{\int \left[\frac{\delta^2 E}{\delta v(\mathbf{r}) \delta v(\mathbf{r}')} \right]_N}_{\beta(\mathbf{r})} dv(\mathbf{r}) d\mathbf{r} dv(\mathbf{r}') d\mathbf{r}' \end{aligned} \quad (1)$$

where $\rho(\mathbf{r})$ is electron density and \mathbf{r} denotes a position in space. Integrating $\rho(\mathbf{r})$ in space gives N , the total number of electrons; external potential $v(\mathbf{r})$ is determined by nuclear charges and positions. The partial derivatives in the equation are key DFT concepts: μ is electronic chemical potential of the system, η is hardness, $f(\mathbf{r})$ is the Fukui function, and $\beta(\mathbf{r})$ is the linear response function. Characterizing the escaping tendency of electrons from equilibrium, the electronic chemical potential is shown to be the opposite of electronegativity [3]. The hardness (η) indicates a resistance to charge transfer; being the inverse of hardness, softness (S) measures the ease of charge transfer and is associated with high polarizability. The concepts of hardness and softness have been proved to support the

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well-known Pearson's HSAB (hard and soft acids and bases) principle [4,5], which claims that hard acids prefer hard bases and soft acids prefer soft bases both thermodynamically and kinetically [6,7].

What is relevant and interesting for our purpose – to study the intermolecular interactions in an organic or molecular crystal – is the Fukui function. Representing the molecule's responding sensitivity to a simultaneous perturbation in N and $v(\mathbf{r})$, the Fukui function can be calculated by the fluctuation in electron density due to the change in the number of electrons [8]

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

In practice, the Fukui function is obtained by the finite-difference approximation because of the discontinuity of N . It can be calculated by the difference in electron density between the neutral and cationic forms, denoted as $f^-(\mathbf{r})$ or the electrophilic Fukui function. It can also be calculated by the difference between the anionic and neutral forms, denoted as $f^+(\mathbf{r})$ or the nucleophilic Fukui function [9].

The Fukui function is shown to be associated with local softness by [4]:

$$s(\mathbf{r}) = S f(\mathbf{r}) \quad (3)$$

According to Pearson's HSAB principle, the Fukui function is likely to describe the spatial distribution and relative degree of intermolecular interactions in an organic crystal since the soft–soft type of intermolecular interactions is believed to be dominant. In fact, the static dipole polarizability has been directly linked to the Fukui function, and for an atomic system, its polarizability, α , can be described by [10]

$$\alpha = S \int \mathbf{r} \mathbf{r} f(\mathbf{r}) d\mathbf{r} \quad (4)$$

As such, the Fukui function may be able to characterize the “local” polarizability, a concept discussed in other reports [11,12]. The larger the Fukui function is, the softer or the more polarizable the molecule is at a local region (i.e., at \mathbf{r}). It is known that the van der Waals (vdW) energy is determined by polarizability since the physical nature of vdW force stems from instantaneously fluctuating dipoles (i.e., induced dipole–induced dipole interactions). Consequently, Fukui functions are expected to describe the locality of vdW and other polarizability-associated intermolecular energies. Our recent calculations of organic crystals indicate the long-range van der Waals (vdW) or dispersion energies are the major component of intermolecular interactions or lattice energies [13,14]. We are thereby led to the belief that calculating and visualizing Fukui functions in an organic crystal can reveal the underlying connection between the packing motif and the chemical structure. To gain further support, we have examined Fukui functions of a common organic crystal, aspirin.

2. Methodology

Calculations of electronic structures of aspirin single crystal ($P2_1/c$, $a = 11.43$, $b = 6.591$ and $c = 11.395$ Å, $\beta = 95.68^\circ$) [15] were conducted by DFT computational methods. The B3LYP method was used with the Lee–Yang–Parr correlation energy and a mixing of Hartree–Fock exchange energy (20%) and Becke's 3-parameter exchange energy (80%) [16]. The periodic crystal system was calculated with Bloch functions, which used the linear combinations of Gaussian-type orbitals as the local functions; in our studies, the 6-21G basis set was used to build the local functions. Due to the periodicity of Bloch functions, a larger or even diffusive basis set may not necessarily improve calculations. The energy convergence was set to 10^{-7} Hartree. All calculations were performed on a Linux cluster with the Crystal 03 program [17]. Visualization was done with OpenDX [18].

The aspirin crystal structure was first optimized with the lattice constants fixed. Electron densities of both neutral and anionic forms were calculated, and Fukui functions, $f^+(\mathbf{r})$, were obtained at each point in the structure. The anionic form, not the cationic form, was used in the calculations of Fukui functions due to its lower system energy. Additionally, we have built slab models of two growth faces (1 0 0) and (0 0 1), of aspirin. These two faces were reported as the major growth faces [19]. The slab models were calculated, and Fukui functions, $f^+(\mathbf{r})$, were obtained. Our test results (not shown) indicated that although electron densities could be affected by different basis sets (STO-3G versus 6-21G), few effects were seen on the Fukui functions. For the slab calculation, the layer thickness (1, 2, or 4-unit cell) showed little influence on the results of Fukui functions as well.

3. Results and discussion

Fukui functions of aspirin bulk structure were calculated. Shown in Fig. 1 are Fukui functions color mapped on isosurfaces of electron density of 0.03, 0.1, and 0.17 e/Bohr³, respectively. Because an isosurface of electron density is generally regarded as the confinement or shape of a molecule, these figures clearly illustrate that different regions of the aspirin molecule in the crystal have different sensitivities to the perturbation in electronic population and external potential or, in other words, have different local polarizabilities. Fukui functions are significantly larger around the carboxyl dimer region where hydrogen bonds are formed. The phenyl ring shows relatively large values as well, particularly around the para-hydrogen with regard to the carboxyl group; however, around the acetyloxy group, Fukui functions are small. The difference in the Fukui function may uncover the relative interacting strength between molecules. The hydrogen bonds between adjacent carboxyl groups certainly play the major role in binding molecules in the crystal. Equally important is the phenyl group, which may contribute considerably to the intermolecular interaction. In addition, it can be seen from Fig. 1 that there is only one way to expose the (0 0 1) surface, but there are two possible truncates for the (1 0 0) surface—one

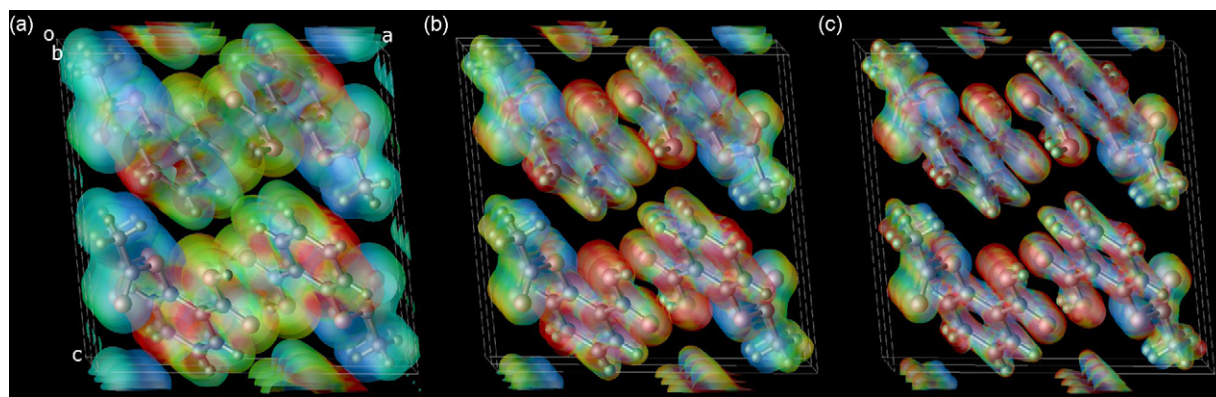


Fig. 1. Fukui functions mapped on isosurfaces of electron density of aspirin bulk structure. Values of isosurfaces are 0.03 (a), 0.1 (b) and 0.17 e/Bohr³ (c), respectively. The Fukui functions are color-coded linearly from blue (0.0) to green and to red (0.0004 e/Bohr³). A movie of continuous change in the isosurface is available. Another movie displays the rotation of the 0.1 e/Bohr³ isosurface.

going through acetyl groups, denoted as (1 0 0a), and another through hydrogen bonds between carboxyl groups, denoted as (1 0 0b). It is highly possible that the (1 0 0a), not the (1 0 0b), is the exposed (1 0 0) face of aspirin crystals.

Slab models of the (0 0 1), (1 0 0a), and (1 0 0b) were calculated, and their Fukui functions were derived. Shown in Fig. 2, the Fukui functions have large values at both ends of each model. Except for the (1 0 0a), the middle region has values close to zero. This may indicate that the surface of a molecular crystal is much more sensitive to the electronic perturbation than the bulk; moreover, the surface of the (1 0 0b) slab seems to have larger Fukui functions as compared to the (1 0 0a) and (0 0 1) faces, especially around the oxygen of the carboxyl group on the surface. The relatively larger Fukui functions in the middle of the (1 0 0a) also suggest that the (1 0 0b) has larger values on the surface than the (1 0 0a) since they have the same size of 2-D unit cells for the distribution of one extra electron (when calculating $f^+(\mathbf{r})$). Thus, the (1 0 0b) is the softest and may be dominant over the (1 0 0a) when interacting with a polar liquid such as water. With regard to how solvents affect the growth morphology of aspirin, it is believed

that the morphology change is a result of the difference in the softness of solvents. A better match between solvent molecules and a crystal face may impede the growth rate of the face much more, leading it to a major face.

Current quantum mechanical computation methods (e.g., Hartree–Fock and DFT that is based on local density approximation or generalized gradient approximation) cannot fully consider the dispersion energy, limiting their applications in organic crystals. By demonstrating the electron sensitivity analysis of aspirin bulk and surface structures in this study, however, we believe that, among all DFT-based electron properties (Eq. (1)), the Fukui function permits us to comprehend the dispersion energy and thereby to study the spatial variations and relative magnitudes of intermolecular interactions of a molecular crystal. Being a local property, the Fukui function describes the sensitivity of a molecular system to the electronic perturbation that may be caused by interacting with other molecules, providing a powerful tool to analyze the electronic structure and interpret intermolecular (as well as intramolecular) interactions of an organic crystal. In particular, the Fukui function may shed light on the origin

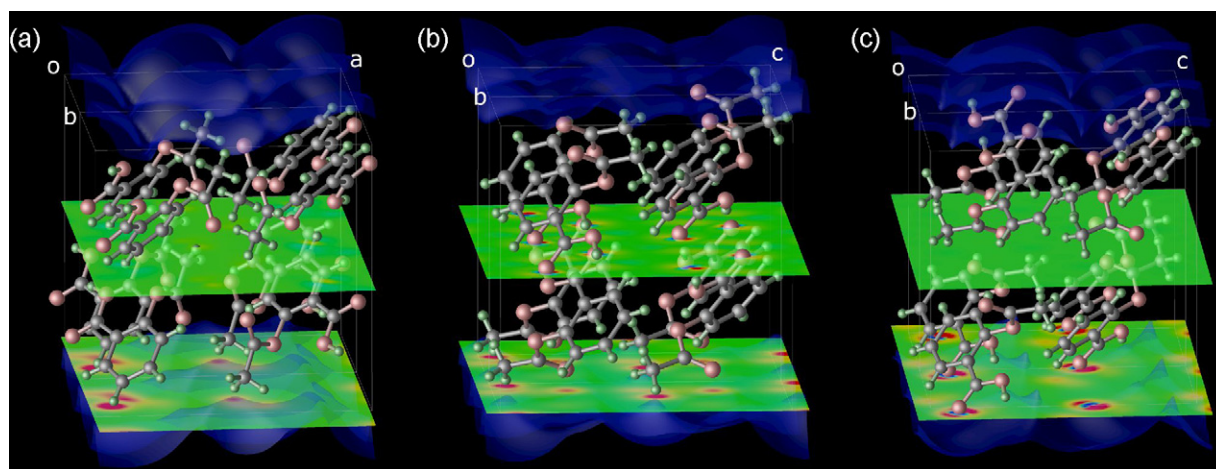


Fig. 2. Slab models of aspirin surfaces where periodic boundary conditions apply horizontally (0 0 1) (a), (1 0 0a) (b), and (1 0 0b) (c). Fukui functions were calculated and mapped to two planes of each model. Iso-surfaces of electron density of 10^{-4} e/Bohr³ are shown at both ends of each slab. The Fukui functions are color-coded linearly from blue (−0.002) to green and to red (+0.002 e/bohr³). Only complete molecules are shown. Three movies of Fukui functions mapped on isosurfaces of electron density are available for the slabs.

of polymorphism because of its relationship to the softness and polarizability. As the intermolecular interaction of organic crystals is mainly of dispersion energy, the lattice energy of organic crystals is much smaller than those of ionic, covalent and metallic crystals. This renders organic molecules susceptible to forming various types of packing motifs in solid state. The polymorphs by the same molecule are clearly a result of the locality or regional selectivity of intermolecular interactions with regard to the molecular structure, in particular, the anisotropy and distribution of functional groups. As such, understanding and applying the Fukui function underline perhaps a new direction taken by our group for studying the polymorphic formation of organics.

Supporting information available

Movies of Fukui functions of aspirin bulk structure and (1 0 0) and (0 0 1) surfaces are available.

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Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at [doi:10.1016/j.jmgm.2007.08.001](https://doi.org/10.1016/j.jmgm.2007.08.001).

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