Communication

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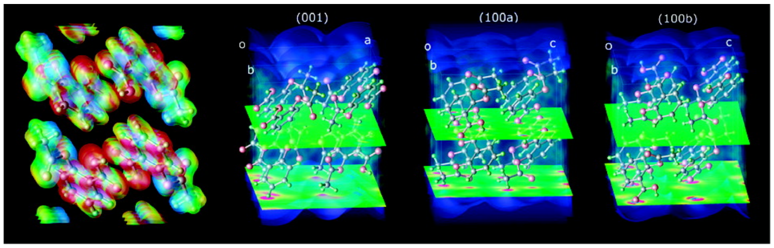

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Face-Integrated Fukui Function: Understanding Wettability Anisotropy of Molecular Crystals from Density Functional Theory

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Molecular crystals make up the majority of pharmaceutical materials and a significant amount of fine chemicals. Since chemical moieties exposed on different growth faces are varied, physical, chemical, and mechanical properties of a growth face can be highly anisotropic. Among all surface properties, wettability plays a fundamental role in every interfacial phenomenon where a liquid phase is involved. For pharmaceuticals, not only does wettability affect the drug development process but also it controls the dissolution and final therapeutic effects. Because wettability is anisotropic, a crystal with different shapes or polymorphs may have its overall wettability greatly changed. Understanding and controlling it are essential in the industry, as well as in basic science research.[1]

Wettability is often characterized by the contact angle of a liquid droplet residing on a surface. When a liquid, such as water, is in contact with a crystal, solid−liquid interactions will solely determine the wettability difference among individual surfaces. A stronger interaction between the solid and liquid will predictably result in a smaller contact angle. Due to the very nature of intermolecular interaction, it may be possible to apply Pearson's HSAB (hard and soft acids and bases) Principle[2] to describe their interactions between a liquid and different faces of a molecular crystal. As demonstrated by density functional theory (DFT), interactions between a Lewis acid and a base consist of electrostatic, covalent, and polarization contributions.[3] It has been shown that for the hard−hard type of interaction, the electrostatic contribution is dominant. For the soft−soft type of interaction, however, the covalent and polarization components are more significant. Therefore, the HSAB Principle applies to molecular systems where the Lewis acid−base interaction is maximized. DFT further shows that the global hardness of a molecular system can be approximated by Klopman's frontier orbital theory, indicating the resistance to charge transfer.[4] Conversely, the global softness (the inverse of hardness) of a molecule signifies the polarizability of its electron clouds. In this Communication, we apply the HSAB Principle with DFT-based concepts and propose using the face-integrated Fukui function to understand the wettability anisotropy of molecular crystal surfaces.

In DFT,[4] the system energy, E, of a molecular system is a functional of the total charge density, $\rho(\mathbf{r})$. The charge density is confined by the external potential, $v(\mathbf{r})$, which is defined by nuclear charges and positions. As a local response of the energy to the simultaneous perturbation in the number of electrons, N, and the external potential field, the Fukui function is defined by[5]

$$f(\mathbf{r}) = \left[\frac{\delta^2 E}{\delta v(\mathbf{r})\partial N}\right] = \left[\frac{\delta \mu}{\delta v(\mathbf{r})}\right]_N = \left(\frac{\partial \rho(\mathbf{r})}{\partial N}\right)_v \tag{1}$$

where μ is the electronic chemical potential, opposite of the electronegativity.[6] The local Fukui function (e/Bohr^3) can be calculated from the change of the charge density as a response to the change of the number of electrons in a molecular system.[7] It describes the sensitivity of a molecular system to the electronic and nuclear perturbations. The function is directly proportional to local softness, $s(\mathbf{r})$:[8]

$$s(\mathbf{r}) = Sf(\mathbf{r}) \tag{2}$$

where S is the global softness. Hence, of the same crystal, Fukui functions are able to characterize the variation in softness among different faces. Because of soft−soft type interactions that are dominant between water (and organic liquids) and molecular crystals, Fukui functions are believed to be capable of describing the wettability anisotropy. For this purpose, we propose to integrate the local Fukui function over a crystallographic face and to use the integrated value to characterize the relative softness of the face:

$$F(\mathbf{p}) = \int_{\mathbf{p}} f(\mathbf{r})\mathrm{d}\mathbf{r}/A(\mathbf{p}) \tag{3}$$

where $\mathbf{p}$ denotes a specific crystallographic face and its relative position in the unit cell. The normalization by $A(\mathbf{p})$, the surface area of the integrated face, is to make the quantity comparable among different crystallographic faces. In practical calculations, the integration is replaced by summation of discrete data points. Resolutions of data points on different faces are kept the same for the purpose of comparison.

The face-integrated Fukui functions (e/Bohr^3) for two crystal systems, aspirin ($P2_1/c$; $a = 11.43$, $b = 6.591$, and $c = 11.395$ Å; $\beta = 95.68°$)[9] and *n*,*n*-octyl-D-gluconamide (OGA) ($P2_1$; $a = 5.252$, $b = 32.436$, and $c = 4.805$ Å; $\beta = 94.96°$)[10] were calculated in the present work. We have grown aspirin crystals from ethanol and obtained millimeter-sized, platelike crystals, which had (100) and (001) as major growth faces. The crystals were cleaved to expose clean (100) and (001) faces for the contact angle measurement by a video-based optical contact angle meter (OCA 15, DataPhysics). Contact angles by glycerol, water, and diiodomethane were 56, 57, and 36° on the (100) face, and 66, 65, and 41° on the (001) face, respectively. OGA is a polar crystal where contact angles of water on its dominant faces were reported as 43° on the (010) and 76° on the (0$\bar{1}$0).[11]

Shown in Figure 1 are two possible ways to expose the (100) face of aspirin, one cutting through hydrogen bonds between carboxylic groups, (100b), and another between methyl groups without breaking any hydrogen-bonded dimers, (100a). In contrast, there is only one way to expose the (001) face. Fukui functions were calculated from the charge density differences between the neutral form and anionic form (which had lower energy than that of the cationic counterpart). Fukui functions are shown significantly larger around the hydrogen-bonded region (Figure 1). Moreover, face-integrated Fukui functions were calculated from slab structures of the three surfaces (Figure 2). The functions have the largest value for the (100b) slab than for other two slabs. The large values along the (100b)

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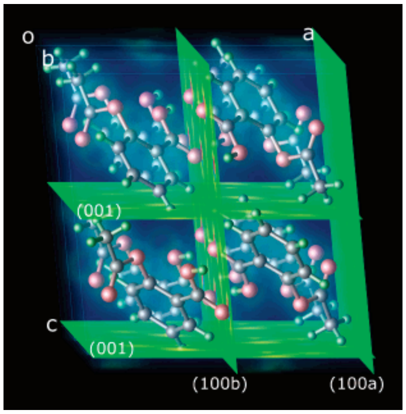

Figure 1. Two major faces of the aspirin crystal. Fukui functions (e/Bohr^3) are mapped on four selected planes. Charge densities are volume rendered. Only complete molecules are drawn in unit cells.

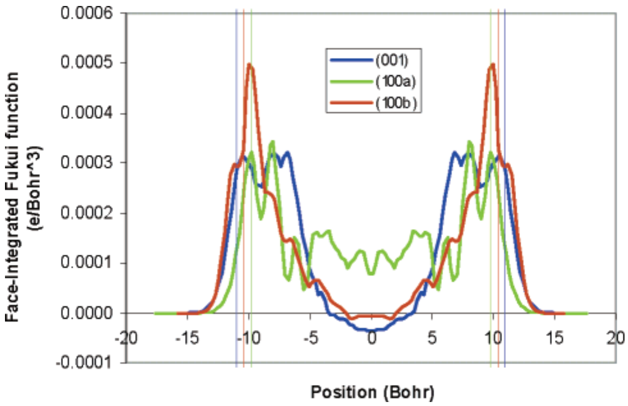

Figure 2. Face-integrated Fukui functions along three slabs of aspirin. Each value is a normalized integrand over a crystallographic face parallel to the slab surface. The position is relative to the center of each slab. Vertical lines denote outer surfaces of respective slabs.

slab are attributed to exposed carboxylic groups on the surface, indicating that the surface is softer than the other two cuts. For the same liquid, a softer face may accommodate stronger solid−liquid interactions and thus lead to smaller contact angles, as we have observed in the experiment. Since an actual (100) face may consist of both (100a) and (100b) and since it is likely that the (100b) is dominantly interacting with a liquid, the overall Fukui function or softness of the (100) face ought to be larger than that of the (001) face.

As a polar crystal, OGA is not centrosymmetric, and the octyl group points toward the $(0\bar{1}0)$ side and the gluconamide group toward the (010) side, as shown in Figure 3. Face-integrated Fukui functions, shown along the slab model in the same figure, were calculated from the charge density differences between the neutral and anionic forms (which were more stable than the cationic forms). Because of suspected coordinate error, three H atoms of the gluconamide moiety were removed in Cambridge Structural Database, including the one of the terminal −OH at the (010) surface. Two curves in Figure 3 were obtained on structures where the three H atoms were added, and their positions were optimized with a difference in positioning the H of the terminal −OH. A normal optimization resulted in the −OH pointing inward, forming hydrogen bonds with adjacent OGA molecules. Because it may form hydrogen bonds with liquid molecules, the H of the −OH was optimized further by putting a water molecule nearby, resulting in another structure with the −OH pointing outward, breaking the internal hydrogen bonds. In both cases, face-integrated Fukui functions have a peak on the (010) side higher than that on the $(0\bar{1}0)$ side. If the surface reconstructs itself to maximize interactions with liquids, the (010) has even larger Fukui functions. Thus, the gluconamide side or the (010) face seems significantly softer than that of the $(0\bar{1}0)$, allowing stronger solid−liquid interactions, leading to a smaller contact angle as confirmed by experiments

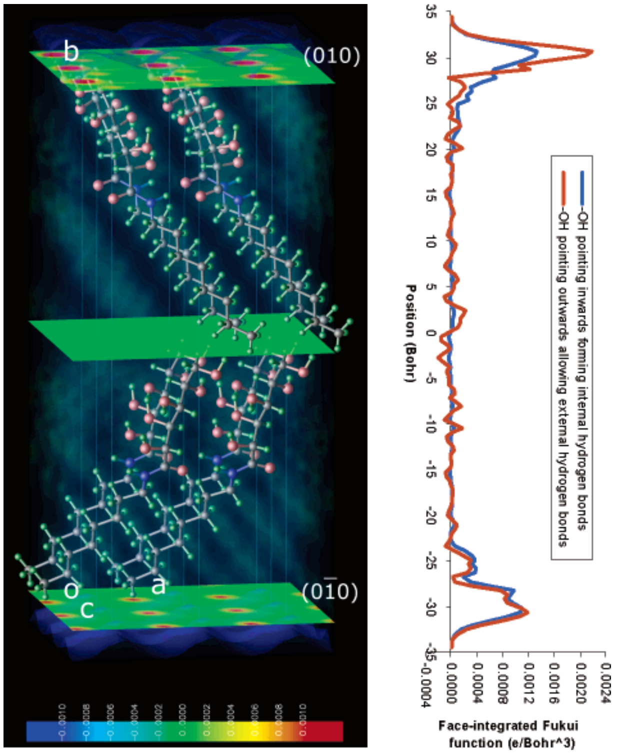

Figure 3. The (010) slab of the OGA crystal. Charge density is volume rendered and superimposed with the slab structure. Charge density isosurfaces of 10^{-4} e/Bohr^3 are shown at the (010) and $(0\bar{1}0)$ ends. Only complete molecules are drawn in the lattice. Fukui functions (e/Bohr^3) are mapped to three selected planes according to the color bar. The face-integrated Fukui functions are plotted on the right. Two curves show the influence by the terminal −OH group of OGA molecules at the (010).

In summary, the face-integrated Fukui function appears to be an appropriate tool for describing the relative softness among various faces of the same crystal, characterizing anisotropic interactions with liquids. The concept, as well as the method to apply the HSAB Principle with DFT-based concepts, may be useful for other anisotropic phenomena of the same nature for crystal materials.

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Supporting Information Available: Computational steps of Fukui functions (PDF). This material is available free of charge via the Internet at http://pubs.acs.org.

References

(1) Somorjai, G. A. *J. Phys. Chem. B* **2002**, *106*, 9201.
(2) (a) Pearson, R. G. *J. Am. Chem. Soc.* **1963**, *85*, 3533. (b) Pearson, R. G. *Science* **1966**, *151*, 172.
(3) Parr, R. G.; Yang, W. *Density Functional Theory of Atoms and Molecules*; Oxford University Press: Oxford, 1989
(4) (a) Parr, R. G.; Yang, W. *Annu. Rev. Phys. Chem.* **1995**, *46*, 701. (b) Kohn, W.; Becke, A. D.; Parr, R. G. *J. Phys. Chem.* **1996**, *100*, 12974. (c) Geerlings, P.; De Proft, F.; Langenaeker, W. *Chem. Rev.* **2003**, *103*, 1793.
(5) (a) Fukui, K. *Science* **1982**, *218*, 747. (b) Parr, R. G.; Yang, W. *J. Am. Chem. Soc.* **1984**, *106*, 4049.
(6) Parr, R. G.; Donnelly, R. A.; Levy, M.; Palke, W. E. *J. Chem. Phys.* **1978**, *68*, 3801.
(7) De Proft, F.; Liu, S.; Geerlings, P. *J. Chem. Phys.* **1998**, *108*, 7549.
(8) Yang, W.; Parr, R. G. *Proc. Natl. Acad. Sci. U.S.A.* **1985**, *82*, 6723.
(9) Kim, Y.; Machida, K.; Taga, T.; Osaki, K. *Chem. Pharm. Bull.* **1985**, *33*, 2641.
(10) Zabel, V.; Mullerfahrnow, A.; Hilgenfeld, R.; Saenger, W.; Pfannemuller, B.; Enkelmann, V.; Welte, W. *Chem. Phys. Lipids* **1986**, *39*, 313.
(11) (a) Wang, J. L.; Leiserowitz, L.; Lahav, M. *J. Phys. Chem.* **1992**, *96*, 15. (b) Muster, T. H.; Prestidge, C. A. *J. Pharm. Sci.* **2002**, *91*, 1432.

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