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Research Paper

Study of Crystal Packing on the Solid-State Reactivity of Indomethacin with Density Functional Theory

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Purpose. Solid-state reactions are highly anisotropic. Different polymorphs of the same compound may have remarkably different chemical reactivities. It was reported that two polymorphs of indomethacin single crystals, α- and γ-forms, reacted with ammonia gas at dramatically different rates. In this study, the effect of crystal packing on their difference in chemical reactivity was investigated by examining the electronic structures and properties of the crystal forms.
Methods. *Ab initio* methods, including density functional theory, were used to calculate electronic structures of the α- and γ-forms of indomethacin. In particular, nuclear Fukui functions were obtained to elucidate how a molecule in a crystal may respond to an electronic perturbation that can be caused by a chemical reaction.
Results. Different conformers in the two polymorphs showed different electronic structures. The carboxylic group of one symmetrically different molecule in the α-form had significantly larger nuclear Fukui functions than those of other molecules of either the α- or γ-form, supporting the experimental observation that the α-form was much more reactive with ammonia than the γ-form. In addition, the large nuclear Fukui functions associated with atoms other than those from the carboxylic group were attributed to the tension of two dislodged aromatic rings.
Conclusions. Electronic calculations were able to provide insightful glimpses into the effect of crystal packing on the solid-state reaction of indomethacin. The nuclear Fukui function, which characterizes the physical stress on an atom due to perturbation in electron density, may provide a powerful means of studying the solid-state reactions of organic crystals at the electronic level.

KEY WORDS: crystal packing; density functional theory; electronic perturbation; indomethacin; nuclear Fukui function; polymorphism; quantum mechanics; solid-state reaction.

INTRODUCTION

The solid-state stability of pharmaceutical materials affects formulation and production, and casts a huge impact on the performance of drugs. Any degradation or chemical incompatibility in active ingredients and excipients may result in serious consequences for both manufacturers and consumers. Because most solid pharmaceutical materials are crystalline, the chemical reactivity of organic crystals has been a focus of both research and development (1,2).

The chemical reactivity of an organic crystal with a gas, a liquid, or another crystalline phase is further complicated by solid-state properties, including crystal structure, growth morphology, and particulate properties, in addition to the molecular structure of the compound. A four-step process was suggested for a solid-state reaction: (1) loosening of molecules on crystal surfaces; (2) chemical reaction; (3) formation of solid solution; and (4) phase separation of product (3–9). It is well regarded that molecular mobility in the solid state determines the loosening of molecules, and, thus, decides the reactivity of crystals (10–13). Current knowledge about solid-state reaction mechanisms of organic crystals is largely credited to studies made by the Curtin and Paul group three decades ago (3–9). Few studies of solid-state reactivity of organic crystals, however, have been conducted at the electronic level.

Many examples have been reported where polymorphs of the same compound show different chemical reactivities (10,14,15). The reactivity of the same polymorph can also be highly anisotropic with respect to crystal faces where chemical moieties are different. It is often observed that certain crystal faces are attacked preferentially by gases, and reactions propagate along specific directions. The role of crystal packing in affecting molecular mobility and consequent reactivity has been mainly investigated based on geometric analysis, including the topochemical postulate and reaction cavity (16,17). Clearly, solid-state reactions are much more complex than liquid reactions. Kinetics of solid-state reactions can be considerably affected by polymorphism and growth morphology. Because of relatively weak intermolecular interactions, organic crystals are prone to form

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multiple polymorphs (18). Both crystal structure and growth morphology of organics are highly sensitive to growth conditions such as solvents, additives, impurities, temperature, and concentrations. Thus, our aim is to understand the interconnection between the molecular/crystal packing of different polymorphs and the chemical reactivity of organic crystals at the electronic level.

Quantum mechanics (QM) and density functional theory (DFT) have been widely applied for studying molecular systems, including chemical reactivity. A huge interest in developing conceptual DFT has recently produced many enlightening concepts and results (19,20), including one report that employed DFT-based concepts to investigate the explosive mechanism of hexahydro-1,3,5-trinitro-1,3,5-triazine (RDX) (21). In the study, nuclear Fukui functions of the RDX molecule that were calculated provided significant insights into the reaction mechanisms of highly symmetric molecules, such as RDX. Nevertheless, the research was focused on the single molecule of RDX, and not the crystalline state of the explosive.

In this report, we illustrate that nuclear Fukui function may be able to characterize the difference in the chemical reactivity of two polymorphs of indomethacin (1-(4-chlorobenzoyl)-5-methoxy-2-methyl-1*H*-indole-3-acetic acid). Our results show that crystal packing of the polymorphs of indomethacin has a profound influence on the electronic structures and properties of molecules in the crystals, leading to variation in the chemical stability.

METHODS

We applied QM and DFT to study the difference in the chemical reactivity of two polymorphs, α- and γ-forms, of indomethacin reacting with ammonia gas. Both periodic structures of two polymorphs and single molecules were calculated, respectively. Lattice parameters of the monoclinic α-form (mp 152–154°C, $P2_1$) are a = 5.462, b =25.310, c = 18.152 Å, β = 94.38°, and Z = 6 (14); lattice parameters of the triclinic γ-form (mp 160–161°C, $P\bar{1}$) are a = 9.31, b = 10.81, c = 11.00 Å, α = 105.77, β = 93.00, γ = 122.48°, and Z = 2 (22). The crystal structures of two forms, as shown in Fig. 1, were optimized with the lattice parameters fixed prior to the calculations of electronic structures and properties. A periodic *ab initio* program, Crystal 03 (23), was used for the optimization and single-point electronic calculation. Hartree–Fock (HF) and DFT with B3LYP exchange-correlation functional (24,25) were used for structural optimization and electronic calculation, respectively. Pople's 6-21G basis sets were used for each calculation method. In addition, single molecule of indomethacin was calculated with the Gaussian 03 code package (Gaussian, Inc., Wallingford, CT, USA).

To study the effect of crystal packing on electronic structures of different polymorphs, particularly on chemical reactivity, we calculated and compared nuclear Fukui functions of atoms in the α- and γ-forms of indomethacin. Nuclear Fukui function has been developed according to the conceptual DFT. DFT states that the electron density is the fundamental quantity for describing atomic and molecular ground states, and energy is a functional of electron density (26–28). As a molecular system changes from a ground state to another because of perturbations in electron population or

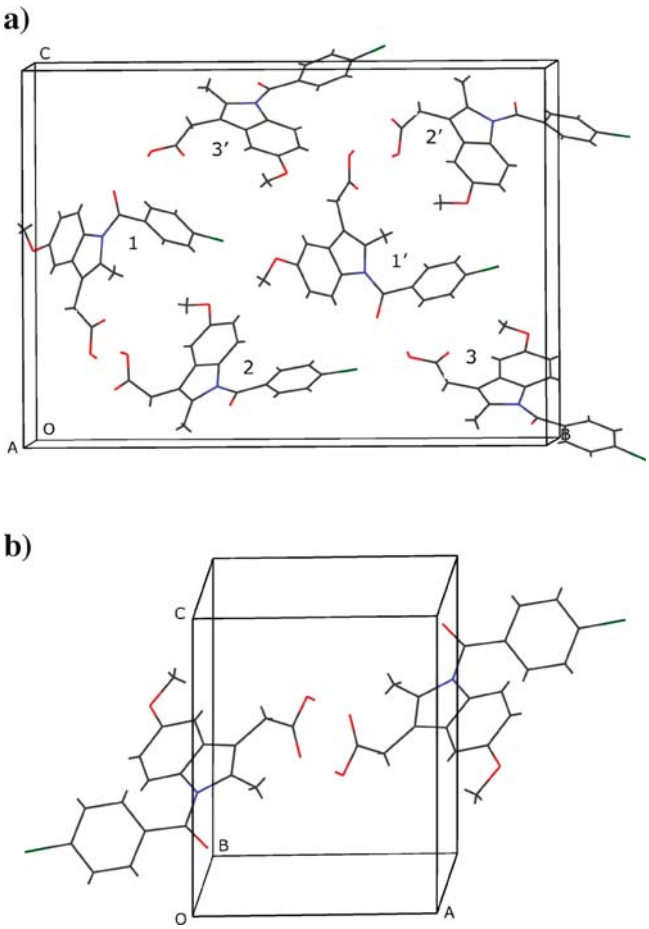

Fig. 1. Crystal structures of the (a) α- and (b) γ-forms of indomethacin. Six molecules in each unit cell of the α-form are divided into three symmetrically different pairs as marked.

the number of electrons, dN, as well as the external potential defined by atomic positions and nuclear charges, $\delta v(\boldsymbol{r})$, the expansion of the system energy change to second order may be expressed as (29,30):

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

where $\boldsymbol{r}$ is the position vector, μ is the electronic chemical potential [the opposite of the electronegativity (31)], characterizing electron's escape tendency from the equilibrium, $\rho(\boldsymbol{r})$ is electron density, η is hardness, $f(\boldsymbol{r})$ is the Fukui function, and $\beta(\boldsymbol{r}, \boldsymbol{r}')$ is the linear response function. The Fukui function may be capable of describing the sensitivity of a molecular system to electronic and nuclear perturbations (32,33). The hardness is related to Klopman's frontier

molecular orbital theory (34), calculated by the energy gap between ionization potential, I, and electron affinity, A (35):

$$\eta = \frac{1}{2}\left(\frac{\partial^2 E}{\partial N^2}\right)_v = \frac{1}{2}\left(\frac{\partial \mu}{\partial N}\right)_v \cong \frac{I-A}{2} \quad (2)$$

The inverse of hardness is softness, S (36). It is believed that hardness indicates a resistance to charge transfer, whereas softness measures ease of transfer and is associated with polarizability (27). Consequently, the dependence of hardness on molecular deformation, named as the nuclear stiffness, may be relevant in characterizing the chemical reactivity (21,37):

$$\boldsymbol{G}_i = \left(\frac{\partial \eta}{\partial \boldsymbol{Q}_i}\right)_N \quad (3)$$

where $\boldsymbol{Q}_i = \boldsymbol{R}_i - \boldsymbol{R}_{i,0}$ is the displacement vector of atom i from its equilibrium position, $\boldsymbol{R}_{i,0}$. Similarly, the nuclear reactivity index is defined as the derivative of electronic chemical potential with respect to the displacement of an atom (38):

$$\boldsymbol{\Phi}_i = -\left(\frac{\partial \mu}{\partial \boldsymbol{Q}_i}\right)_N \quad (4)$$

Their contributions to the global hardness and chemical potential can be expressed as:

$$\begin{aligned} \eta &= \eta_0 + \sum_i \left(\frac{\partial \eta}{\partial \boldsymbol{Q}_i}\right)_N \cdot \boldsymbol{Q}_i = \eta_0 + \sum_i \boldsymbol{G}_i \cdot \boldsymbol{Q}_i \\ \mu &= \mu_0 + \sum_i \left(\frac{\partial \mu}{\partial \boldsymbol{Q}_i}\right)_N \cdot \boldsymbol{Q}_i = \mu_0 - \sum_i \boldsymbol{\Phi}_i \cdot \boldsymbol{Q}_i \end{aligned} \quad (5)$$

where η_0 and μ_0 are the hardness and chemical potential of undeformed molecules at equilibrium. As a reaction occurs, contributions of $\boldsymbol{G}_i$ and $\boldsymbol{\Phi}_i$ to the decrease in hardness and chemical potential may be revealed from their scalar products with atomic displacements (i.e., $\boldsymbol{G}_i \cdot \boldsymbol{Q}_i$ and $\Phi_i \cdot \boldsymbol{Q}_i$), likely to predict which atoms are involved in the reaction, whether the molecule accepts or donates electron(s), and whether the reacting bond is shortened or stretched (37). It has been shown that large absolute values of $\boldsymbol{G}_i$ and $\boldsymbol{\Phi}_i$ can be used to identify those atoms and bonds that are involved in a chemical reaction (21).

Furthermore, the nuclear stiffness and nuclear reaction index can be calculated by atomic or Hellmann–Feynman forces (38):

$$\begin{aligned} \boldsymbol{G}_i &= -\tfrac{1}{2}\left(\boldsymbol{F}_i^+ + \boldsymbol{F}_i^-\right) \\ \boldsymbol{\Phi}_i &= \tfrac{1}{2}\left(\boldsymbol{F}_i^+ - \boldsymbol{F}_i^-\right) \end{aligned} \quad (6)$$

where $\boldsymbol{F}_i^+$ and $\boldsymbol{F}_i^-$ are forces acting on the same atom i when the number of molecular electrons has increased (+) or decreased (−), respectively. Thus, from their relationship with electronic forces on ionized species, $\boldsymbol{G}_i$ and $\boldsymbol{\Phi}_i$ may be able to reveal how much an atom participates in a reaction. A large force on an atom indicates a large displacement, resulting in a bond breaking, shortening, or conformational change. As a first-order derivative of the system energy with respect to the number of electrons (Eq. 1), the nuclear reactivity index may be better for describing the reactivity than the nuclear stiffness. In fact, the concept of nuclear reactivity index has been extended into so-called nuclear Fukui function (38):

$$\begin{aligned} \boldsymbol{\Phi}_i^+ &= \boldsymbol{F}_i^+ - \boldsymbol{F}_i^0 \\ \boldsymbol{\Phi}_i^- &= \boldsymbol{F}_i^0 - \boldsymbol{F}_i^- \end{aligned} \quad (7)$$

to characterize a nucleophilic or electrophilic attack, respectively. Because a chemical reaction is driven by the change in system energy, and is accompanied by the electron transfer and atomic displacement, the nuclear Fukui function, a local function to describe system sensitivity to a simultaneous perturbation in the number of electrons, N, and the nuclear position, $\boldsymbol{R}$, may be useful for characterizing the reactivity of crystals with respect to crystal packing. For a molecule in equilibrium, $\boldsymbol{F}_i^0$ is close to zero; $\boldsymbol{F}_i^+$ or $\boldsymbol{F}_i^-$ alone may be sufficient to study the reactivity of respective atoms in a nucleophilic or electrophilic reaction (39).

In this study, $\boldsymbol{\Phi}_i^+$ was calculated for the analysis of the reactivity difference in the two polymorphs of indomethacin because the molecule deprotonates during the reaction with ammonia. $\boldsymbol{F}_i^0$ and $\boldsymbol{F}_i^+$ of each atom were obtained from calculations of the neutral and anionic species of a crystal structure, respectively. The molecular structure of the anionic species was kept the same as its neutral counterpart, whereas an extra electron was introduced to the unit cell during the calculation. The energy convergence of the structural optimizations and single-point electronic calculations was set as 10^{-7} Hartree. The root mean squares (RMS) of energy gradient and atomic displacement were set to 0.0003 and 0.0012 atomic units, respectively. All calculations were performed on a 16-CPU Linux cluster.

RESULTS AND DISCUSSION

Two polymorphs of indomethacin (α- and γ-forms) were reported to react with ammonia gas at different reaction rates (14). The α-form reacted much faster than the γ-form. Within 1 h, the α-form picked up 3.7–3.8% of ammonia gas (4.76% for complete reaction), quickly becoming opaque. The reaction involved deprotonation of the carboxylic group of the molecule, resulting in the formation of ammonium indomethacin. On the other hand, the γ-form was inert to ammonia gas, showing little reactivity within 24 h. Clearly, the two polymorphs showed a significant difference in their chemical reactivities.

To study the influence of crystal packing on the chemical reactivity of indomethacin, we calculated the electronic structures and nuclear Fukui functions, $\boldsymbol{\Phi}_i^+$, of the α- and γ-forms. The crystal structures of the two forms are shown in Fig. 1, indicating that the α-form has three symmetrically different molecules, whereas the γ-form has only one. Figure 2 illustrates the scales and directions of nuclear Fukui functions of each conformer of the two polymorphs. Values of the functions are listed in Table I. Because the reaction mainly involved deprotonation of the carboxylic group of indomethacin when reacting with ammonia, the comparison of nuclear Fukui functions in both Fig. 2 and Table I indicates that the –COOH group of molecule #3 of the α-form has significantly larger values than those of other two molecules, #1 and #2, of the α-form, and the molecule of the γ-form. H1 of the molecule #3 has a value (1.6141 nN) that is at least 1 order of magnitude larger. O4, C18, and O3 of the –COOH are also much larger than

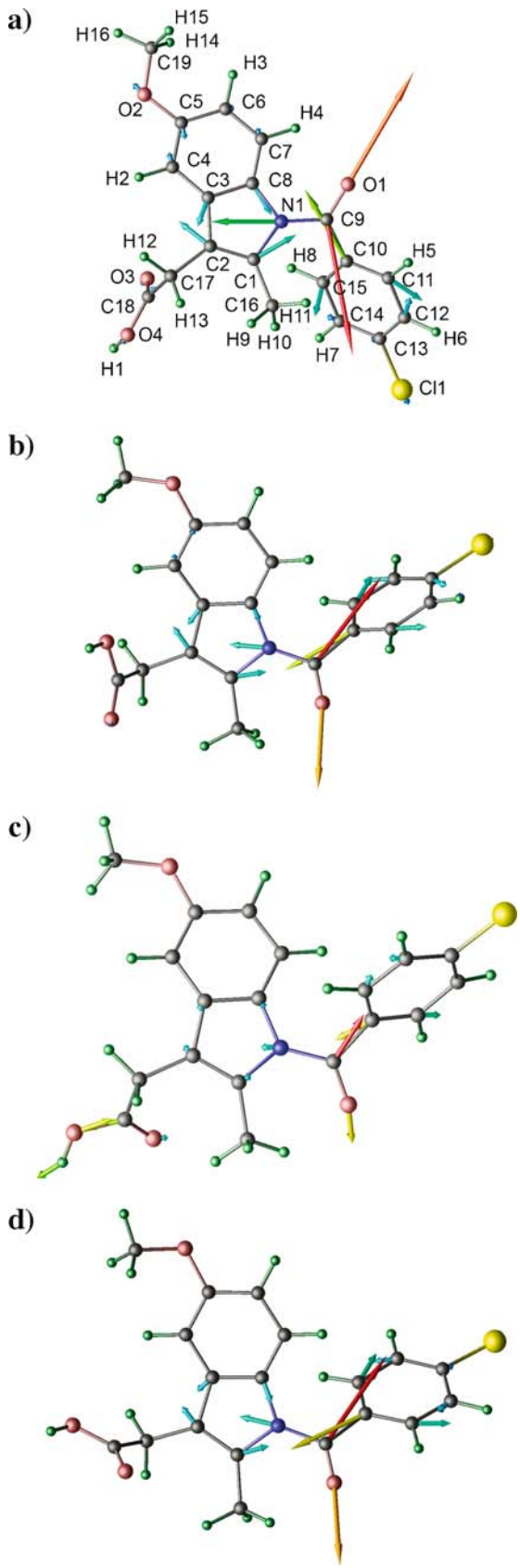

Table I. Nuclear Fukui Functions of Three Symmetrically Different Molecules of the α-Form, #1, #2, and #3, and the Molecule of the γ-Form of Indomethacin Calculated with Crystal 03 by B3LYP/6-21G//HF/6-21G (unit: nN)

	α-Form			
	#1	#2	#3	γ-Form
Cl1	0.9378	0.7086	0.3383	0.5586
O1	6.8662	5.1087	2.0575	5.0163
O2	0.8548	0.5050	0.2703	0.1887
O3[a]	0.4831	0.4549	0.6817	0.1920
O4[a]	0.5910	0.3730	1.9279	0.1959
N1	3.6679	2.1758	0.9255	2.0602
C1	2.5647	1.8948	0.6373	1.6706
C2	2.1143	1.7131	0.6289	1.2922
C3	1.7117	1.4023	0.5397	1.0827
C4	0.7913	0.6135	0.2329	0.3369
C5	0.9144	0.5906	0.2446	0.3811
C6	0.4677	0.2335	0.1348	0.1907
C7	0.6296	0.2313	0.1080	0.1109
C8	1.9673	1.0921	0.5419	1.3883
C9	7.3603	6.0740	2.7619	5.9478
C10	4.7073	4.2288	1.9776	4.4399
C11	2.2388	2.2612	0.8471	1.9671
C12	1.4776	0.4129	0.8492	1.0943
C13	0.7060	1.2687	0.5165	0.5826
C14	0.7753	1.9105	0.1810	1.1790
C15	2.3670	1.9317	1.1132	2.0512
C16	0.3456	0.1158	0.0936	0.1149
C17	0.3814	0.2402	0.1941	0.2051
C18[a]	0.7193	0.7854	1.7558	0.3729
C19	0.2272	0.1925	0.1799	0.1237
H1[a]	0.0617	0.1155	1.6141	0.1616
H2	0.1551	0.0659	0.0466	0.0530
H3	0.0835	0.0492	0.0638	0.0408
H4	0.1812	0.1727	0.0796	0.1305
H5	0.2683	0.2142	0.1450	0.2024
H6	0.1748	0.2962	0.2039	0.0579
H7	0.2183	0.1251	0.0755	0.1914
H8	0.1811	0.1480	0.0939	0.0491
H9	0.0734	0.2203	0.0484	0.2558
H10	0.1784	0.1069	0.0876	0.0502
H11	0.2688	0.1201	0.0896	0.0677
H12	0.1309	0.0642	0.1222	0.0915
H13	0.0666	0.0463	0.0308	0.0128
H14	0.0523	0.0828	0.0276	0.1689
H15	0.0357	0.0846	0.0391	0.0630
H16	0.0440	0.0986	0.0215	0.0233

[a] Atoms of the carboxylic group.

their counterparts in other conformers. Because the nuclear Fukui function characterizes how much physical stress is applied to a nucleus due to the change or perturbation in electron density (Eq. 7), it is expected that large physical stresses on nuclei may lead to conformational change or even breaking of chemical bonds. The larger values of nuclear Fukui functions in the –COOH of molecule #3 may account

Fig. 2. Nuclear Fukui functions of three symmetrically different molecules of the α-form #1 (a), #2 (b), and #3 (c), and the molecule of the γ-form (d) of indomethacin represented as arrows originated from each atom. Arrows are color-coded continuously from red to green to blue indicating values from the largest to the smallest of each molecule.

for the reactivity difference between the α- and γ-forms of indomethacin. The opposite directions of nuclear Fukui functions of H1 and O4 of molecule #3 suggests that the chemical bond is stretched upon a nucleophilic attack, possibly leading to bond breaking. Other conformers, including the molecule of the γ-form, show little effects of physical stress applied to the carboxylic groups due to perturbation in electron density.

Nonetheless, the largest nuclear Fukui functions are associated with other atoms than the –COOH of all molecules of α- and γ-forms of indomethacin, as shown in Fig. 2 and Table I. C9, O1, and C10 are the top three ranking atoms in terms of nuclear Fukui functions, followed by the neighbor atoms (C11, N1, C15, and C1). The difference in nuclear Fukui functions between these atoms and –COOH is a few nN, except for molecule #3 of the α-form. Although these atoms are not directly involved in the acid–base reaction, it is thought that the large physical stress on these atoms due to the electronic perturbation may stem from energy-unfavorable conformations. As shown in Fig. 2, N1, C9, O1, and C10 bridge two aromatic rings of indomethacin molecule, the indole, and phenyl rings. Because the carbonyl group between the two rings also provides *p* orbitals, the ideal conformation for the molecule would be delocalization of all *p* orbitals (excluding those of the –COOH), forming one single aromatic plane by the indole, carbonyl, and benzoyl groups. The current conformations of indomethacin molecules in the α- and γ-forms are likely due to the steric repulsion between the chlorobenzoyl and the methyl of the indole ring. Table II lists two dihedral angels associated with the linkage atoms of the two aromatic rings. It is clear that the two rings are on two different planes, thereby forcing the separation of two local aromatic systems. To support this argument, molecular orbitals of isolated indomethacin molecule were calculated with Gaussian 03. As shown in Fig. 3, the HOMO is mainly delocalized on the indole ring, and not extending to the phenyl ring at all. On the other hand, the LUMO spreads over the chlorobenzoyl part of the molecule. The separation of the aromatic structures is likely the result of their conformations. Therefore, the balance between the steric repulsion and the tendency to form one aromatic system may be metastable and sensitive to any electronic perturbation, causing the two rings to realign their positions and/or to change their conformations. The large values of the nuclear Fukui functions of the atoms connecting the two ring structures may indicate the localization of the two aromatic systems, characterizing the tension between the steric repulsion and the inclination to form a single sharing of the *p* orbitals. These atoms may not be directly associated with the deprotonation; their large nuclear Fukui functions may simply indicate significant conformational changes of the indole and benzoyl groups if there is any perturbation in electron density. Such conformational changes may lower the total energy, making the molecule more stable rather than breaking chemical bonds of their atoms. In addition, it is interesting to note that the –COOH group of molecule #3 has the largest Fukui functions whereas the carbonyl group and its neighbor atoms between the two rings have the smallest nuclear Fukui functions as compared to other molecules of both forms. The values of the –COOH are close to those of the carbonyl C9 and O1 atoms. There may be a connection between the increase in nuclear Fukui functions of the –COOH and the decrease in other atoms. The conformation of molecule #3 allows a relatively small stress on the linkage atoms of the two rings, but puts the –COOH group under a significantly large physical stress when an electronic perturbation is introduced into the system.

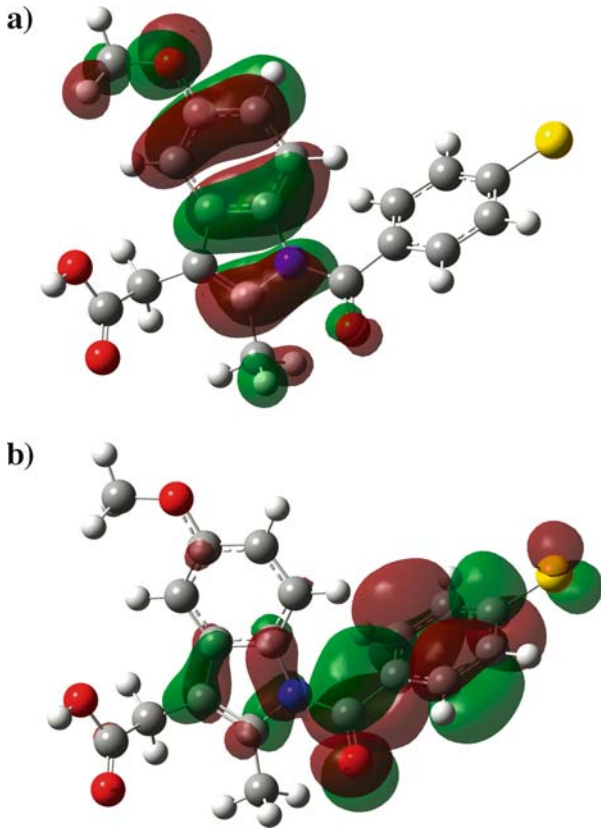

Fig. 3. Molecular orbitals (MO) of indomethacin single molecule calculated with Gaussian 03 by B3LYP/6-311G**//B3LYP/6-311**: (a) highest occupied molecular orbital (HOMO) and (b) lowest unoccupied molecular orbital (LUMO).

Table II. Dihedral angles of C1–N1–C9–O1 and O1–C9–C10–C15 of molecules of the α- and γ-forms of indomethacin that were optimized with Crystal 03 by HF/6-21G based on X-ray structural data (unit: degrees)

	α-Form			
	#1	#2	#3	γ-Form
C1–N1–C9–O1	−158.58	−24.48	29.49	−32.42
O1–C9–C10–C15	51.80	−41.51	43.32	−23.25

A positive value of *i–j–k–l* corresponds to the clockwise rotation of the *k–l* viewed along the *j–k* with the *i–j* being fixed and closer to the viewer. A negative value corresponds to the counterclockwise rotation.

In summary, we calculated the electronic structures of two polymorphs of indomethacin, α- and γ-forms, and employed nuclear Fukui functions to understand the influence of crystal packing on the chemical reactivity of their solid-state reactions with ammonia gas. Nuclear Fukui function allows the study of chemical reactivity from the point of view of physical stresses or forces applied to individual atoms when there is a change in electron density of the molecular system. Our results show that the two forms have significantly

different electronic structures and properties. The carboxylic group of molecule #3 of the α-form has considerably larger nuclear Fukui functions than those of other molecules of the same form as well as of the γ-form. Under a nucleophilic attack, the –OH bond of the carboxylic group of molecule #3 is likely to break, leading to deprotonation of the indomethacin molecule. Moreover, the large nuclear Fukui functions associated with the carbonyl group between the indole and phenyl rings and surrounding atoms are believed to be caused by the tension between the two aromatic systems that are forced to dislodge due to steric repulsions. It is very likely that the two aromatic rings will realign themselves to maximize the overlapping of their *p* orbitals as much as possible if there is any change in electronic structure. This study may provide convincing insights into the effect of crystal packing on the electronic structures of two polymorphs of indomethacin and on their difference in chemical reactivity, illustrating that *ab initio* calculations and DFT-based concepts can be used for studying crystal packing of organic crystals at the electronic level.

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