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Research Paper

The Polymorphism of Indomethacin: An Analysis by Density Functional Theory Calculations

Clare Aubrey-Medendorp,[1] Matthew J. Swadley,[1] and Tonglei Li[1,2,3]

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Purpose. Indomethacin exhibits conformational polymorphism. Crystal structures of two polymorphs have been solved bearing different molecular conformations. Herein, the conformational variance in the crystals was examined by density functional theory (DFT) calculations in order to understand the mutual influence between electronic structures and crystal packing.
Methods. Electronic structures of the two polymorphs and the single molecule of indomethacin were calculated with quantum mechanical methods. Electronic properties based upon conceptual density functional theory were thereby analyzed. A potential energy surface was generated with regard to the conformational flexibility, which was identified by the electronic analysis. Lattice energies of the two polymorphs were further calculated with an empirically augmented DFT method.
Results. Electronic properties, including electronic and nuclear Fukui functions, provided a fundamental understanding of the energetic competition in the indomethacin molecule between delocalization of *p*-orbitals of two aromatic rings and steric repulsions. Two dihedral angles (the τ_1 and τ_2 in Fig. 1) were found playing a crucial role in affecting such competition and determining the variation of molecular conformations. The existing polymorphs, α- and γ-forms, were located in local minima on the energy surface based on the two dihedral angles of their molecular conformations. Calculated lattice energies suggest the α-form is more stable than the γ-form at the zero K.
Conclusions. The polymorphism of indomethacin lies in various meta-stable conformations of the molecule that are results of different orientations between the two aromatic indole and phenyl rings. The analysis of electronic and nuclear Fukui functions permits the revelation of local energy barriers that determine the conformational diversity and, for the case of indomethacin, the conformational polymorphism.

KEY WORDS: crystal packing; density functional theory; electronic calculation; Fukui function; indomethacin; polymorphism; quantum mechanics.

INTRODUCTION

Indomethacin (Fig. 1) is known to form polymorphs (1); two of them, the α- and γ- forms, have been structurally solved (2–5). It can also form solvates (6), and its amorphous properties have been extensively studied (7). Formation of different polymorphs and solvates is well known to be caused by varying experimental conditions including growth media, solute concentrations and environmental temperature. However, understanding the origin of indomethacin's polymorphism is scarcely discussed. Current polymorph prediction efforts rely on a brute-force approach (trying) to sort out all possible packing motifs of molecules in energy space so as to identify low-energy forms (8–10), unable to take into account the role of growth conditions. Lacking of reliable energies models for evaluating molecular interactions and also due to a monstrous number of combinations of crystal packing, limited success has been achieved (11).

In our earlier report (12), we have shown that the difference in the chemical reactivity of indomethacin with ammonia between the α- and γ- forms lies in the electronic structures of molecules in the two crystal forms, particularly the electronic properties including nuclear Fukui functions that are derived based upon conceptual density functional theory (13,14). In addition, we have found that conformational variance of the molecules was decided by the dislodgement between the two aromatic rings (indole and phenyl) because of steric hindrance. Calculations of electronic structures and nuclear Fukui functions were able to identify the local tensions in the molecules with regard to the energetic competition between the maximization of aromatic structures and nuclear–nuclear repulsions. The two dihedral angles, τ_1 and τ_2 (Fig. 1), were shown determining different degrees of the local tensions because of this competition. There appears to be a connection between the nuclear Fukui function and conformations of indomethacin molecules in the crystals. Herein, we report further studies of

[1] Pharmaceutical Sciences, University of Kentucky, Lexington, KY 40536, USA.
[2] 514 College of Pharmacy, University of Kentucky, 725 Rose Street, Lexington, KY 40536-0082, USA.
[3] To whom correspondence should be addressed. (e-mail: tonglei@uky.edu)

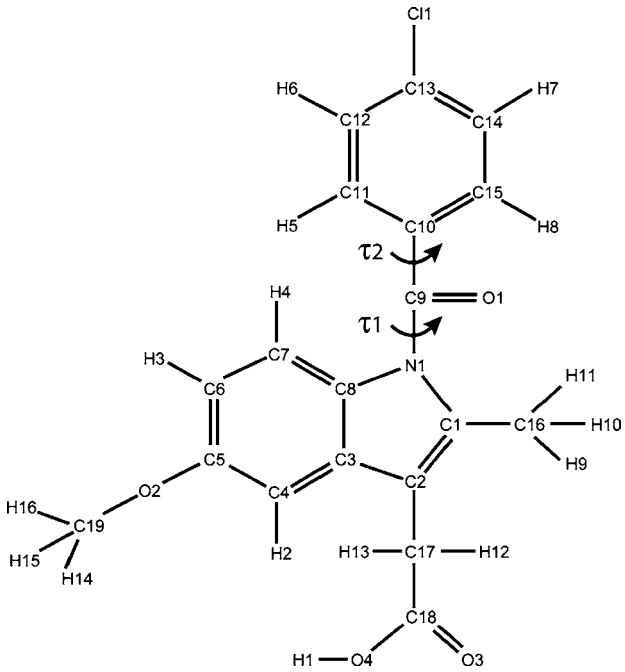

Fig. 1. Indomethacin molecule with atoms indexed. Two dihedral angles are marked by τ_1 (C1-N1-C9-O1) and τ_2 (O1-C9-C10-C15).

electronic calculations of indomethacin crystals and molecules. In addition to the nucleophilic nuclear Fukui functions that were reported (12), electrophilic nuclear Fukui functions were calculated. Moreover, electronic Fukui functions were calculated and analyzed to uncover the conformational diversity and polymorphism of the crystal. Energies of single molecules were analyzed with regard to the two dihedral angles. Lattice energies of the two polymorphs were calculated as well. The results suggest that the polymorphism of indomethacin stems from several metastable energy states that are associated with various combinations of the two dihedral angles.

METHODS

Electronic structures of the α- and γ-forms of indomethacin were calculated with periodic Hartree–Fock (HF) and density function theory (DFT) methods by solving Bloch functions that are of the periodicity of crystal lattice and have their local functions assembled by linear combinations of Gaussian-type basis sets (15). The α-form [$P2_1$, a=5.462, b=25.310, c=18.152 Å, and β=94.38° (2)] and γ-form [$P\bar{1}$, a=9.310, b=10.810, c=11.000 Å, α=105.77, β=93.00, and γ=122.48° (4)] were optimized with the restricted HF/6-21G prior to the final calculations with B3LYP/6-21G. The structural optimizations were carried out with the lattice parameters held constant while allowing fractional coordinates of all atoms to adjust. A periodic ab initio program, Crystal 03 (15), was used for the optimizations and electronic calculations. Energy convergence for the calculations was set as 10^{-7} Hartree. Root-mean-squares (RMS) of the energy gradient and atomic displacement were set to 0.0001 and 0.0003 atomic units, respectively. All calculations were performed on a Linux cluster in which parallel versions of Crystal 03 and Gaussian 03 were deployed.

From the calculated electronic structures of the two crystal forms, nuclear Fukui functions were evaluated in the same way as reported earlier (12,16). In brief, the number of electrons in a unit cell was increased or decreased by one, and electronic structures of the crystal were re-evaluated. The finite differences in Hellmann–Feynman forces, $\mathbf{F}_i$, were calculated as the nuclear Fukui functions (17):

$$\begin{aligned} \mathbf{\Phi}_i^+ &= \mathbf{F}_i^+ - \mathbf{F}_i^0 \\ \mathbf{\Phi}_i^- &= \mathbf{F}_i^0 - \mathbf{F}_i^- \end{aligned} \tag{1}$$

where $\mathbf{\Phi}_i^+$ and $\mathbf{\Phi}_i^-$ are nucleophilic and electrophilic nuclear Fukui functions, respectively, with the superscript indicating the increase (+), decrease (−) or no change (0) in the number of electrons in the unit cell; the subscript, i, indicates the i-th nucleus. In the calculations of indomethacin, one electron was added to or removed from one unit cell of the α-form that had six molecules, and one 3×1 super-cell of the γ-form that also had six molecules, respectively.

From the Hellmann–Feynman theorem (18,19), $\mathbf{F}_i$, originates from the electronic structure (i.e., electron density) of the molecular system in addition to nuclear–nuclear repulsions. The electrostatic forces, $\{\mathbf{F}_i\}$, provide a straightforward and pictorial model for understanding molecular conformation and chemical process based upon the underlying electronic structure (20,21). Defined as the response of Hellmann–Feynman force to electronic perturbation as indicated by Eq. 1, the nuclear Fukui function has been shown to measure how much a conformational change or displacement of each atom contributes to the variance in electronic chemical potential of a molecular system (22). The physical meaning is further underlined by $\mathbf{\Phi}_i$ as a "condensed" index of electronic Fukui function, $f(\mathbf{r})$, integrated around nucleus i in accordance to the definitions of the Hellmann–Feynman force and nuclear Fukui function:

$$\mathbf{\Phi}_i = \left(\frac{\partial \mathbf{F}_i}{\partial N}\right)_v = Z_i \int f(\mathbf{r}) \frac{\mathbf{R}_i - \mathbf{r}}{|\mathbf{R}_i - \mathbf{r}|^3} d\mathbf{r} \tag{2}$$

where N is the number of electrons, $v(\mathbf{r})$ is the external potential determined by nuclear charges $\{Z_i\}$ and their positions $\{\mathbf{R}_i\}$ at position $\mathbf{r}$ in space. It is thus suggested that a nucleus surrounded by a large density distribution of electronic Fukui functions tends to have a large value of its nuclear Fukui function. The connection between nuclear and electronic Fukui functions is signified by the physical meaning of electronic Fukui function, which is defined as the change in charge density, $\rho(\mathbf{r})$, upon a change in the electronic population (23–25):

$$f(\mathbf{r}) = \left(\frac{\partial \rho(\mathbf{r})}{\partial N}\right)_v \tag{3}$$

Similar to the finite-difference calculations of nuclear Fukui functions by Eq. 1, nucleophilic and electrophilic electronic Fukui functions, $f^+(\mathbf{r})$ and $f^-(\mathbf{r})$, can be calculated from the difference in charge densities between the neutral and anionic or cationic molecular systems. It has

been indicated that $f(\mathbf{r})$ is directly associated with local polarizability or softness of a molecular system (26–28). One relationship is given by (29):

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

where α and S are the global polarizability and softness, respectively. The softness, a DFT concept, can be dated back to Pearson's HSAB (hard and soft acids and bases) principle (30–34), and may be utilized to characterize intermolecular interactions (35,36). In addition, $S\ f(\mathbf{r})$ is defined as local softness (37). Thus, we believe a local region of a molecular system that has strong electronic Fukui functions can contribute greatly to the intramolecular and intermolecular interactions, because the van der Waals energy, a dominant component of the lattice energy of organic crystals, is determined by polarizabilities of interacting atoms and molecules (in addition to their distances) (38). It is worth noting that electrostatic interactions also control how molecules interact (36,39), but may not be as important as van der Waals energies in this system. For the purpose of this study, we further postulate that a large distribution of local electronic Fukui functions controls the conformational diversity or flexibility of the molecule, since the transformation from one stable conformer to another needs to overcome the energy barrier defined by the molecular region that has a large distribution of electronic Fukui functions. Given the relationship between the nuclear and electronic Fukui functions (Eq. 2), examining nuclear Fukui functions may allow us to identify those molecular moieties that are pivotal for the conformational multiplicity. With regard to the polymorphism of indomethacin, therefore, the analysis of Fukui functions is believed to reveal the functional groups that regulate the conformational diversity, and consequently determine the variation of crystal packing. To further elaborate, two dihedral angles, τ_1 and τ_2 (Fig. 1), were identified crucial in determining the conformation of the indomethacin molecule (12). An energy surface was then produced by calculating the total energy of the single molecule as a function of the two dihedral angles. The single molecule was initially optimized, followed by varying τ_1 and τ_2 from −180 to 180° with the step size of 2.5°, respectively. All other bond lengths and bond angles were kept constant. The calculations were conducted with the B3LYP/6-311G** by Gaussian 03 (Gaussian, Wallingford, CT).

Lattice energies of the α- and γ-forms of indomethacin were calculated with an empirically augmented density functional theory method that we tested on dozens of organic crystals (40,41). The method was demonstrated to be satisfactory in reference to the comparisons with experimental values. Without reiterating the method, only the extension of considering the chloride atom in calculating the empirical part of lattice energy is given here. The original method was able to handle only C, N, O and H atoms. The atomic dispersion coefficient and effective number of electrons of Cl were taken from the Halgren's report as 1,427 kcal/mol·Å^3 and 5.1, respectively (42). The van der Waals radius of Cl was assigned to 1.75 Å according to the literature (43). The optimized crystal structures of the two polymorphs of indomethacin were used for both empirical and DFT calculations of the lattice energy.

RESULTS AND DISCUSSION

Nucleophilic and electrophilic nuclear Fukui functions, $\mathbf{\Phi}_i^+$ and $\mathbf{\Phi}_i^-$, of the three symmetrically different molecules of the α-form and the one molecule of the γ-form of indomethacin were calculated. Their magnitudes are listed in Table I. The most notable trend in the nuclear Fukui function, $|\mathbf{\Phi}_i^+|$, is the high stress on C9 and O1 of the carbonyl group and its surrounding atoms (N1 and C10) as we reported earlier (12). It should be noted that nuclear Fukui function values are not normalized (to keep the average electronic perturbation one molecule per electron as they were in the last report). As illustrated in Fig. 1, the carbonyl group bridges the two aromatic systems, the indole and phenyl rings. Ideally all the *p*-orbitals from the carbonyl and two aromatic rings would delocalize and form one single aromatic plane to lower the system energy. Due to the steric repulsion between two hydrogen atoms on the phenyl ring (H5 and H8) and the H4 atom and methyl group (C16 and H9–H11) on the indole ring, however, the indomethacin molecule is forced to twist at the carbonyl offsetting the two aromatic rings. Clearly, the dislodgement of the two aromatic rings is vividly illustrated by the nucleophilic nuclear Fukui functions.

Large values of $|\mathbf{\Phi}_i^-|$ can be seen associated with part of the indole ring (N1, C3–C6 and C8) and the C9 and O2 atoms. Although rankings of $|\mathbf{\Phi}_i^-|$ on these atoms vary, it appears that N1 has the largest values in the three molecules of the α-form, and has the third largest value in the γ-form. $|\mathbf{\Phi}_i^-|$ on C9 are also significant, being the second, the sixth and the fifth in the α-form and the fifth in the γ-form. Interestingly, among the three molecules in the α-form, the $|\mathbf{\Phi}_i^-|$ values in #3 molecule are considerably larger than those in other two molecules. Once again, the rankings of the electrophilic nuclear Fukui functions indicate the twisting of the two aromatic rings where the linkage atoms experience large physical stress, highlighting the molecular propensity to be in a planar conformation. As indicated earlier (12), the difference in the rankings of $|\mathbf{\Phi}_i^+|$ and $|\mathbf{\Phi}_i^-|$ is likely led by the separation of the frontier orbitals between the indole and phenyl rings.

The different values of the nuclear Fukui functions, as they were calculated in the two crystal forms, suggest that the energetic competition between the delocalization of the *p*-orbital surrounding the indole, phenyl and carbonyl groups and the steric repulsion is affected by the conformational difference of the molecules in the crystals. Table II lists the two dihedral angles, τ_1 and τ_2, that control the relative orientation between the indole and phenyl rings. Both experimental and optimized molecular structures in the α- and γ-forms were examined. The small changes (less than 10°) by the structural optimization may indicate the validity of the optimization approach (40). Values of the optimized single molecule are also listed. The data show that indomethacin exhibits conformational diversity in the two crystal forms. There are even three different conformations in the α-form as compared to just one in the γ-form. Consequently, an energy surface was generated with the plot of total energy of single indomethacin molecules as a function of τ_1 and τ_2.

Fig. 2 shows the energy surface. There are eight valleys of energy minima marked with M1–M4 and M1′–M4′ with

Table I. Magnitudes of Nuclear Fukui Functions of Three Conformationally Different Molecules in the **α**-form and One Molecule of the **γ**-form

	α-Form						γ-Form	
	#1		#2		#3			
	Φ_i^+	Φ_i^-	Φ_i^+	Φ_i^-	Φ_i^+	Φ_i^-	Φ_i^+	Φ_i^-
Cl1	0.156	0.056	0.118	0.018	0.056	0.091	0.093	0.008
O1	1.144	0.148	0.851	0.106	0.343	0.318	0.836	0.129
O2	0.142	0.248	0.084	0.441	0.045	1.117	0.031	0.478
O3	0.081	0.099	0.076	0.034	0.114	0.194	0.032	0.039
O4	0.099	0.117	0.062	0.054	0.321	0.258	0.033	0.071
N1	0.611	0.306	0.363	0.436	0.154	1.119	0.343	0.511
C1	0.427	0.066	0.316	0.208	0.106	0.472	0.278	0.123
C2	0.352	0.042	0.286	0.087	0.105	0.253	0.215	0.153
C3	0.285	0.180	0.234	0.300	0.090	0.555	0.180	0.205
C4	0.132	0.158	0.102	0.355	0.039	0.996	0.056	0.562
C5	0.152	0.259	0.098	0.387	0.041	1.104	0.064	0.633
C6	0.078	0.232	0.039	0.274	0.022	0.471	0.032	0.132
C7	0.105	0.187	0.039	0.296	0.018	0.617	0.018	0.202
C8	0.328	0.234	0.182	0.406	0.090	0.839	0.231	0.294
C9	1.227	0.290	1.012	0.318	0.460	0.974	0.991	0.459
C10	0.785	0.021	0.705	0.040	0.330	0.114	0.740	0.060
C11	0.373	0.024	0.377	0.026	0.141	0.066	0.328	0.028
C12	0.246	0.024	0.069	0.020	0.142	0.032	0.182	0.025
C13	0.118	0.077	0.211	0.027	0.086	0.111	0.097	0.029
C14	0.129	0.026	0.318	0.017	0.030	0.055	0.197	0.011
C15	0.394	0.014	0.322	0.016	0.186	0.051	0.342	0.038
C16	0.058	0.021	0.019	0.033	0.016	0.034	0.019	0.013
C17	0.064	0.074	0.040	0.007	0.032	0.051	0.021	0.188
C18	0.120	0.136	0.131	0.051	0.293	0.318	0.034	0.044
C19	0.038	0.150	0.032	0.201	0.030	0.454	0.062	0.122
H1	0.010	0.089	0.019	0.063	0.269	0.035	0.027	0.011
H2	0.026	0.094	0.011	0.013	0.008	0.076	0.009	0.027
H3	0.014	0.013	0.008	0.008	0.011	0.013	0.007	0.006
H4	0.030	0.012	0.029	0.018	0.013	0.031	0.022	0.016
H5	0.045	0.013	0.036	0.012	0.024	0.057	0.034	0.008
H6	0.029	0.032	0.049	0.018	0.034	0.011	0.010	0.001
H7	0.036	0.031	0.021	0.009	0.013	0.008	0.032	0.039
H8	0.030	0.010	0.025	0.009	0.016	0.036	0.008	0.022
H9	0.012	0.011	0.037	0.019	0.008	0.028	0.043	0.008
H10	0.030	0.015	0.018	0.023	0.015	0.033	0.008	0.011
H11	0.045	0.008	0.020	0.009	0.015	0.034	0.011	0.014
H12	0.022	0.145	0.011	0.003	0.020	0.019	0.015	0.016
H13	0.011	0.035	0.008	0.004	0.005	0.031	0.002	0.021
H14	0.009	0.030	0.014	0.018	0.005	0.059	0.028	0.028
H15	0.006	0.011	0.014	0.016	0.007	0.030	0.011	0.012
H16	0.007	0.028	0.016	0.038	0.004	0.060	0.004	0.041

Unit: nN

M1 being the lowest. Because of the twofold rotational symmetry by the phenyl ring along the C10–C9 axis, the energy minima M1–M4 should be identical with the M1′–M4′, correspondingly. For each identical pair (e.g., M1 vs M1′), their τ_2 have a difference of 180° and τ_1 are the same. The slight difference in the total energy on the surface between each identical pair was due to other bond lengths and bond angles being fixed when τ_2 was varied. Particularly the phenyl ring was not perfectly planar, resulting in two theoretically identical conformers (τ_2 and τ_2+180°) slightly different in their conformations (and energies) with respect to the phenyl moiety. Additionally, there are two energy maximum peaks. The smaller one is due to the close contact between H4 and H5/H8; the larger one is between the methyl group (C16 and H9–H11) and H5/H8. Locations of the two dihedral angles that are associated with the molecules (both experimental and optimized) in the α- and γ-forms are noted on the energy surface. It appears on Fig. 2 that the conformations of the molecules in the crystals coincide with the energy minima that are identified by the energy space spanned by τ_1 and τ_2 of single molecules. The γ-form has its molecules residing in M1, close to the global minimum calculated on the single molecule. One of the three molecules, #2, of the α-form is also in M1; another two are in the vicinity of other minima (#1 close to M4 and #3 close to M2′). It is worth pointing out that energy surface shown in Fig. 2 is an approximation of the energy space spanned by the two dihedral angles because the whole molecule is "frozen" during the generation of the

Table II. Dihedral Angles, τ_1 and τ_2, of the α- and γ-forms of Both Experimental (Exp) and Optimized (Opt) Structures as well as of the Optimized Single Molecule

	α-Form						γ-Form		Molecule
	#1		#2		#3				
	Exp	Opt	Exp	Opt	Exp	Opt	Exp	Opt	
τ_1	−159.74	−158.58	−23.23	−24.48	21.39	29.49	−26.17	−32.42	−29.84
τ_2	52.92	51.80	−51.88	−41.51	50.00	43.32	−40.32	−23.25	−29.55

Unit: degree

energy surface except for τ_1 and τ_2. Only the starting structure (marked by a cross in Fig. 2) was fully optimized serving as the global minimum. In addition, the energy surface is of single molecule calculated in gas phase, not in the crystals. As such, M1 is more reliable while other local minimum regions may be shifted if full optimizations are conducted for all points in Fig. 2. Nonetheless, the calculations were not meant to produce an accurate energy surface, but rather to reveal the local minima and their relative positions; the most interesting result is the residency of the molecules of the α- and γ-forms in or close to the energy minimum regions, indicating that the polymorphism of indomethacin stems from the conformational variance of the molecule itself. Furthermore, there is another local minimum region, M3, that may offer potential candidates of molecular structures for new polymorphs of indomethacin. The three molecular structures in each asymmetric unit of the α-form come from three of the four local minimum regions (M1, M2 and M4), suggesting that there could be more new polymorphs. The energy surface produced by varying just two dihedral angles, τ_1 and τ_2, seems to reveal the conformational polymorphism of indomethacin.

The analyses of both nuclear Fukui functions (Table I) and the energy surface (Fig. 2) point to the same chemical moiety, manifested by τ_1 and τ_2, that determines the conformational diversity and, most likely, leads to the polymorphism of indomethacin. The large values of nuclear Fukui functions in the two polymorphs, as suggested by Eqs. 2–4, indicate large distributions of nucleophilic electronic Fukui functions around the carbonyl group (C9 and O1) and electrophilic electronic Fukui functions around the N1 atom and the phenyl part of the indole ring, respectively. This is clearly illustrated by Fig. 3 in which $\mathbf{\Phi}_i$ and isosurfaces of $f(\mathbf{r})$ are plotted concurrently. For the reason that a large region of electronic Fukui functions suggests the surrounded chemical moiety is softer or more polarizable, such a region is believed to contribute considerably to the interatomic interactions of organic molecules and, within the context of this study, to the relative stabilities of indomethacin's conformations. Since different conformers of the same molecule are local minima with regard to the molecular energy, when one conformer transforms to another, an energy barrier must be overcome. If a local conformational minimum is bounded by large energy barriers, the conformation is likely to be a major conformer and the molecule should be relatively stable when taking the

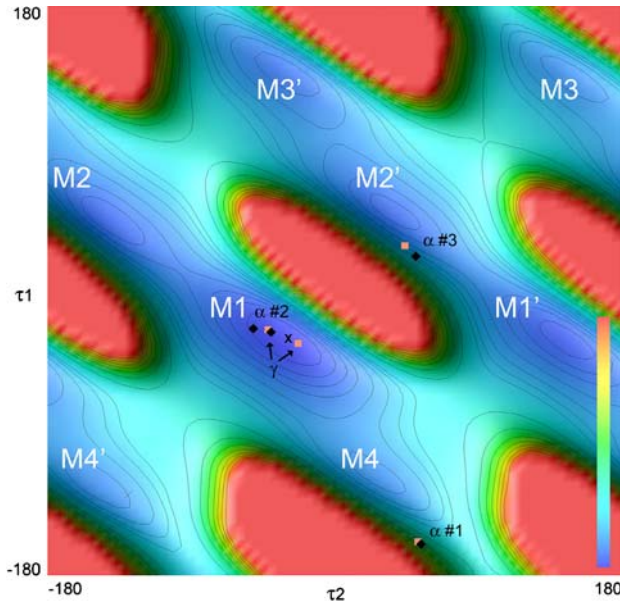

Fig. 2. Energy surface of single indomethacin molecule as a function of τ_1 and τ_2 with corresponding values of molecules in the α- and γ-forms marked. Experimental structures are shown as *dark diamonds*, and optimized structures are as pink squares. The global minimum (i.e., the fully optimized single molecule) is shown as an x. Four local minima are indicated by M1–M4. The color scheme (*inserted color bar*) changes linearly from blue to green to red, indicating the increase in the total energy from −1549.83 to −1549.73 hartrees.

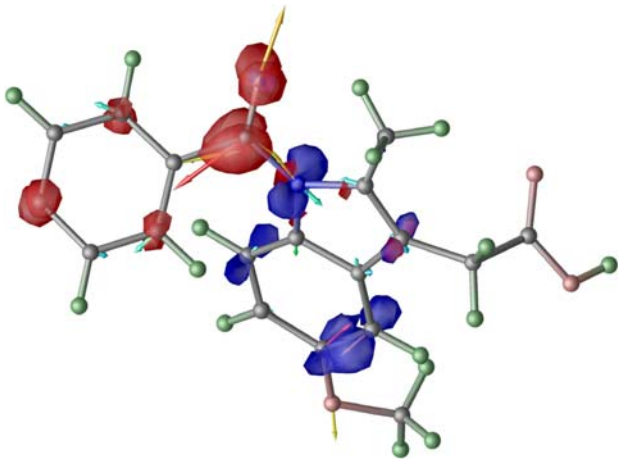

Fig. 3. Isosurfaces of electronic Fukui functions of a molecule in the **α**-form (*red* nucleophilic, *blue* electrophilic). The value of the isosurfaces is 0.001 e/bohr^3. Nucleophilic and electrophilic nuclear Fukui functions are also illustrated by arrows whose lengths are proportional to their magnitudes.

conformation. Therefore, the concurrence between the conformational flexibility around the carbonyl group (C9 and O1) and the large distribution of electronic Fukui functions (along with the large values of corresponding nuclear Fukui functions) suggests that the most important conformers of indomethacin are decided by the carbonyl and its surrounding moiety through the two dihedral angles τ_1 and τ_2.

The lattice energies of the two polymorphs, furthermore, were calculated with the empirically augmented DFT methods (40,41). With the medium damping function, the lattice energies of the α- and γ-forms are −113.90 and −101.25 kJ/mol, respectively, indicating the α-form is considerably more stable. Empirically calculated dispersion energies are −168.24 and −164.24 kJ/mol of the α- and γ-forms, respectively. The results indicate that the long-range van der Waals interaction is the determinant energy term in the crystal packing of indomethacin. The results also imply that the crystal system is enantiotropic because the γ-form is more stable than the α-form at room temperature (44), and the calculations were implicitly done at absolute zero. Although the conformation of single molecule in the γ-form is the most stable as compared to those in the α-form (Fig. 2), the lattice energy values seem to indicate the intermolecular interactions in the α-form are stronger, perhaps due to larger polarizabilities and/or more close contacts. Still, further studies are needed for understanding the relative stability since the α-form has lower melting point and lower heat of fusion but higher density than the γ-form.

In summary, we have calculated the electronic structures and lattice energies of the two polymorphs of indomethacin. Analysis of electronic properties, including electronic and nuclear Fukui functions, shows the conformational polymorphism of indomethacin is due to the energetic competition between delocalization of π systems and steric repulsion. The study further demonstrates the potential of using Fukui functions for conformational examination. As organic crystals are mainly held by the dispersion energy, this approach may be extended to understanding the packing polymorphism and even more complicated cases.

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