

## ANALYSIS OF WEAK INTERMOLECULAR INTERACTIONS THROUGH PIXEL AND HIRSHFELD SURFACE IN HYDROUS AND ANHYDROUS CRYSTAL STRUCTURES OF 7-HYDROXY-4-METHYL COUMARIN

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**ABSTRACT.** The crystal structures of anhydrous and solvated forms of 7-hydroxy-4 methyl coumarin have been analyzed on the basis of energies responsible for holding the moiety in a 3D pattern through weak intermolecular interactions. The lattice energy as well as intermolecular interaction energies of the stabilizing molecular pairs extracted from crystal packing for both structures have been evaluated using PIXEL method. The energies are further split into coulombic, dispersion, repulsion and polarization components, which facilitates in analyzing the stabilizing roles of weak interactions. Lattice energy calculations show that anhydrous form is more stable than hydrous form. Moreover, Hirshfeld surfaces and fingerprint plots were generated using Crystal Explorer 3.0. Critical analysis of Hirshfeld surfaces and fingerprint plots provides essential inputs about the differences in crystal packing of structures and associated intermolecular interactions.

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### 1. INTRODUCTION

A number of reviews pertaining to the biological activities of coumarins have been well documented [1,2,3,4]. Literature survey reveals that coumarin compounds possess potent applications in the field of Pharmaceutical Sciences. A series of 7-hydroxy coumarin (umbelliferone) derivatives possesses different biological activities such as antioxidants [5] and inhibition of acetylcholinesterase and monoamine oxidase [6,7]. 7-hydroxy coumarin is also the parent compound of a large number of structurally more complex coumarins [8]. In view of the immense biological applications of 7-hydroxy coumarin, crystal structures of hydrous and anhydrous forms of 7-hydroxy -4-methyl coumarin have been investigated. The crystal structures of these compounds have already been reported in 2007 [9,10]. In the present manuscript, the main aim is to present a comparative study based on molecular geometry, energies of stabilizing molecular pairs holding the moiety in 3D pattern and lattice energies of two structures. The structure of the title compound indicating the atomic numbering scheme is shown in Fig.1. The Lattice energies and energies of molecular pairs are determined using the PIXEL method as the results obtained by this method are comparable with those

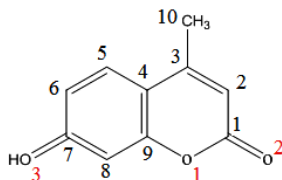


FIGURE 1. 7-hydroxy-4-methyl coumarin

involving complex quantum computations [11,12,13,14]. The study is further supported by Hirshfeld surfaces [15] and fingerprint plots [16] which are generated using crystal explorer 3.0 [17].

## 2. THEORETICAL CALCULATIONS

The lattice energies of the compounds have been computed using the Semiclassical Density Sum method (PIXEL approach) in Coulomb London Pauli (CLP) module [13,18]. The crystallographic information file (CIF) which is a prerequisite for performing such calculations, for above mentioned compounds are obtained from CSD (Cambridge Structural Database). The positions of Hydrogen atoms determined by X-ray crystallography are uncertain and hence are normalized to standard bonding distances determined by neutron diffraction (e.g. C-H bond distances are normalized to 1.08Å) before performing the calculations. This method enables the partitioning of lattice energies of the structures and interaction energies of molecular motifs into coulombic, polarization, dispersion and repulsion contributions. The coulomb energies are calculated using Coulomb's law, while the polarization energies are calculated in linear dipole approximation, in which dipole moment is induced in a molecule (polarized) due to the electric field exerted by surrounding molecules. The dispersion energies are calculated using London's formula and repulsion energies between two molecules are computed by an overlap of their electron densities. The lattice energies of the compounds and stabilizing energies of important motifs selected from crystal packing are presented in Table 1 and 2 respectively.

TABLE 1. Lattice energy of compounds (kcal mol<sup>-1</sup>)

Structure	$E_{\text{Cou}}$	$E_{\text{Pol}}$	$E_{\text{Disp}}$	$E_{\text{Rep}}$	$E_{\text{Tot}}$
7-hydroxy-4-methyl coumarin	-22.96	-9.83	-25.38	30.95	-27.24
Hydrous 7-hydroxy-4-methyl coumarin	-22.03	-9.52	-16.57	27.48	-20.64

## 3. HIRSHFELD SURFACES

Hirshfeld surfaces are important visual tools for exploring packing modes and analyzing intermolecular interactions between molecules in the crystal structure [19]. The information about all the intermolecular interactions is encoded on the surface. It facilitates to compare the structures in terms

TABLE 2. Molecular pairs along with their interaction energies (kcal mol<sup>-1</sup>)

Motif	Centroid Distance (Å)	$E_{\text{cou}}$	$E_{\text{pol}}$	$E_{\text{Dis}}$	$E_{\text{Rep}}$	$E_{\text{Tot}}$	Symmetry	Important Interactions
<b>7-hydroxy-4-methyl coumarin</b>								
I	8.524	-14.81	-6.24	-3.03	14.97	-9.11	$-x-\frac{1}{2}, -y, -z-\frac{1}{2}$	O3-H3...O2 C8-H8...O2
II	6.468	-1.91	-0.84	-5.29	4.35	-3.68	$x-\frac{1}{2}, -y+\frac{1}{2}, -z+1$	C5-H5... $\pi$
III	8.630	-2.66	-1.05	-2.53	2.63	-3.64	$x-\frac{1}{2}, -y+\frac{1}{2}, -z$	C3-H3...O2
IV	5.229	-0.77	-1.77	-5.81	4.31	-3.42	$x+1, y, z$	C11-H11... $\pi$
V	6.276	-0.21	-0.84	-3.01	1.65	-2.42	$-x, y+\frac{1}{2}, -z+\frac{1}{2}$	C11-H11b...O1
VI	7.471	-0.98	-0.66	-2.96	2.44	-2.15	$-x+\frac{1}{2}, -y, z+\frac{1}{2}$	O3... $\pi$
<b>Hydrous 7-hydroxy-4-methyl coumarin</b>								
I	5.300	-17.18	-7.65	-3.01	18.80	-9.02	$x+\frac{1}{2}, -y+\frac{1}{2}, z+\frac{1}{2}$	O3-H3...Ow
II	5.448	-9.28	-3.21	-1.94	8.59	-5.84	$-x, -y, -z+1$	Ow-Hw2...O2
III	7.684	-3.61	-0.72	-2.15	0.79	-5.67	$x+\frac{1}{2}, -y+\frac{1}{2}, z+\frac{1}{2}$	C11-H11A...O2
IV	6.173	-9.93	-3.80	-1.82	10.43	-5.12	$x, y, z$	Ow-Hw1...O2
V	3.159	-1.22	-1.51	-11.24	9.42	-4.54	$-x, -y+1, -z+1$	$\pi$ ... $\pi$
VI	4.493	-1.84	-1.19	-9.59	8.52	-4.11	$-x+1, -y+1, -z+1$	$\pi$ ... $\pi$
VII	7.188	-0.91	-0.41	-3.28	1.48	-3.11	$-x+\frac{1}{2}, y+\frac{1}{2}, -z+\frac{1}{2}$	C5-H5... $\pi$ , C6-H6... $\pi$
VIII	5.320	-1.65	-0.41	-1.27	0.93	-2.42	$x, y+1, z$	C6-H6...Ow
IX	8.818	-1.60	-0.69	-2.58	2.53	-2.34	$x-\frac{1}{2}, -y+\frac{3}{2}, z-\frac{1}{2}$	C5-H5...O3

of the whole molecule approach rather than the limited number of short contacts between atoms. Hirshfeld surfaces mapped with normalized contact distance  $d_{\text{norm}}$  (equation 1) using red white blue colouring scheme have been used for the analysis of intermolecular interactions.

$$(1) \quad d_{\text{norm}} = \frac{d_i - r_i^{\text{vdW}}}{r_i^{\text{vdW}}} + \frac{d_e - r_e^{\text{vdW}}}{r_e^{\text{vdW}}}$$

where  $d_e$  and  $d_i$  are the distances from the Hirshfeld surface to the nearest nucleus outside and inside the surface,  $r_i^{\text{vdW}}$  and  $r_e^{\text{vdW}}$  are the van der Waals (vdW) radii of internal and external atoms. For contacts smaller than vdW separation,  $d_{\text{norm}}$  is negative and is represented by red colour whereas blue colour indicates contacts larger than vdW separation ( $d_{\text{norm}}$  is positive) and white colour is for contacts around vdW separation.

#### 4. RESULTS AND DISCUSSION

The lattice energy of the anhydrous form of the compound is 6.6 kcal mol<sup>-1</sup> greater than the hydrous form. Partitioning of lattice energy into different components (Table 1) indicates that coulombic and polarization contributions are the same for both the structures and it is dispersion component (larger in anhydrous form) which results in a larger value of lattice energy in anhydrous form. The important molecular pairs responsible for holding the moiety in the 3D pattern have been selected from crystal packing (Table 2) and subsequently analyzed based on inputs from PIXEL (interaction energies of pairs) and Hirshfeld surfaces. The molecular pairs along with Hirshfeld surfaces mapped with  $d_{\text{norm}}$  and shape index property for

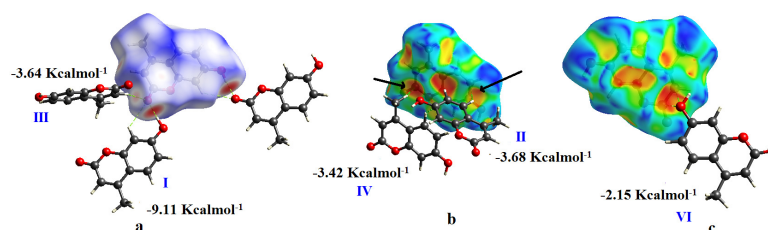


FIGURE 2. Hirshfeld surface mapped with (a)  $d_{norm}$  (b) & (c) shape index property along with PIXEL interaction energies in 7-hydroxy-4-methyl coumarin

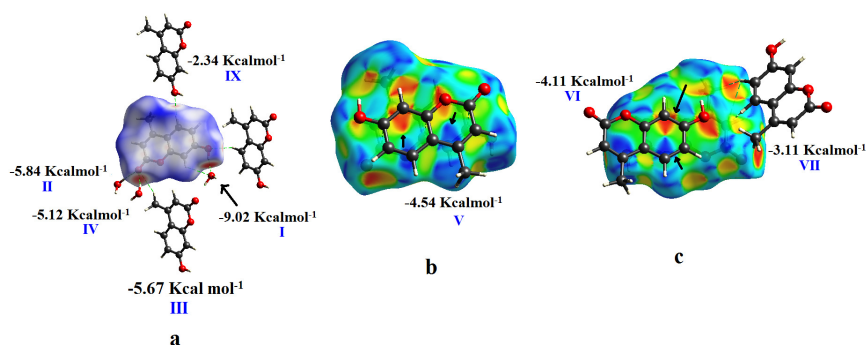


FIGURE 3. Hirshfeld surface mapped with (a)  $d_{norm}$  (b) & (c) shape index property along with PIXEL interaction energies in hydrous 7-hydroxy-4-methyl coumarin

both structures are presented in Figs. 2 and 3. Critical analysis reveals that stabilizing pairs in hydrous and anhydrous forms of the compound under investigation are different having varying interaction energies and hence are in a different crystal environment. The most stabilized molecular pair in anhydrous form (interaction energy I.E =  $-9.11 \text{ kcal mol}^{-1}$ ) involves short O3-H3...O2 along with weak C8-H8...O2 which is confirmed by the presence of two red spots on the Hirshfeld surface mapped with  $d_{norm}$  (Fig. 2a). Another faint red spot on the same surface reveals the presence of weak C3-H3...O2 interaction (Motif III, I.E. =  $-3.64 \text{ kcal mol}^{-1}$ ). Motif II (I.E. =  $-3.68 \text{ kcal mol}^{-1}$ ) and IV (I.E. =  $-3.42 \text{ kcal mol}^{-1}$ ) involve  $C-H \dots \pi$  interaction as indicated by red blue triangular regions marked by arrows on the shape index property (Fig. 2b). The 3D packing of the molecules also involves  $O \dots \pi$  interaction (lone pair on oxygen interacting with C2 and C3, Motif VI, I.E. =  $-2.15 \text{ kcal mol}^{-1}$ ) revealed by red blue regions on the shape index property (Fig. 2c).

The inclusion of solvent ( $H_2O$ ) molecule in the crystal structure (hydrous form) alters the crystal packing and results in the generation of different stabilizing pairs. The occurrence of O-H...O interaction between two host

molecules as present in anhydrous form (pair I) is eliminated by the presence of  $H_2O$  molecule which is involved in host-guest interaction by means of O-H...O hydrogen bonding. The most stabilized host-guest interaction involves strong O3-H3...Ow (Ow means O atom of a water molecule) hydrogen bonding (molecular pair- I, I.E =  $-9.02 \text{ kcal mol}^{-1}$ ) indicated by the presence of red spot on Hirshfeld surface mapped with  $d_{norm}$  (Fig. 3a). The water molecule is also interacting with the host molecule via means of motif II (I.E. =  $-5.84 \text{ kcal mol}^{-1}$ ) and IV (I.E. =  $-5.12 \text{ kcal mol}^{-1}$ ) again represented by the red spots on the same surface mapped with  $d_{norm}$  (Fig. 3a). It is also observed that the pairs interacting via host-guest interactions are comparatively more energetic than the interaction between two host molecules. It may be due to the fact that the solvent and host molecules are interacting via means of strong O-H...O hydrogen bond. The packing of the molecules also shows the presence of C...C stacking interaction between host molecules (motifs V and VI), a phenomenon which was not observed in anhydrous form. The presence of these interactions is confirmed by the presence of red blue triangular regions in the shape index property (Figs. 3b and 3c).

The 2D fingerprint plots are graphical representations that represent all the intermolecular interactions contributing to Hirshfeld surfaces and are unique for a particular molecule. The comparison of fingerprint plots (Fig. 4) shows that plots for the two structures are distinct indicating different intermolecular interactions and packing motifs. There is distinct spike in such plots for the two structures. The spike in anhydrous form corresponds to O-H...O interaction between two molecules whereas the spike appearing in hydrous form corresponds to the same interaction (O-H...O) between host and guest ( $H_2O$ ) molecules. Complementary regions are appearing in the plots where  $d_e > d_i$  (molecule acts as donor) and  $d_e < d_i$  (molecule as

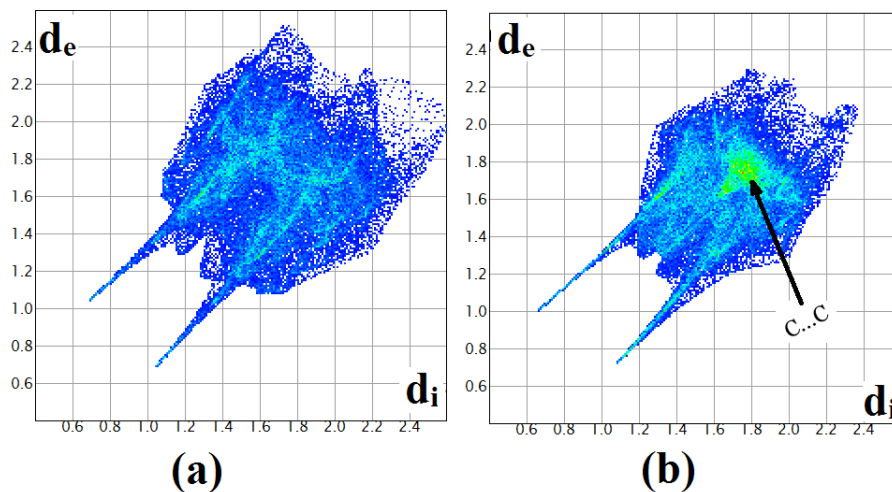


FIGURE 4. 2D Fingerprint Plots (a) 7-hydroxy -4-methyl coumarin (b) Hydrated 7-hydroxy -4-methyl coumarin

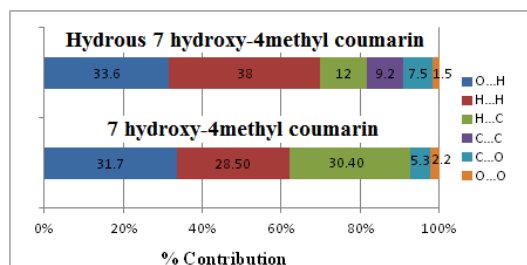


FIGURE 5. Percentage contribution to Hirshfeld surface from different intermolecular contacts

acceptor). The visible difference in the plots for the two structures is the presence of C...C stacking interaction in the hydrous form, indicated by the region marked by an arrow.

The decomposition of 2D-fingerprint plots enables to separate the relative contribution of different intermolecular interactions contributing towards the Hirshfeld surface. The relative percentage distribution of different intermolecular interactions present in the two structures are presented in Fig. 5. The major contribution towards Hirshfeld surface in anhydrous form is imparted by O...H contacts (31.7%) followed by H...C (30.4%) and H...H (28.5%) contacts while in hydrous structure the presence of the solvent molecule increases the relative contribution from O...H (33.6%) and H...H (38%) contacts. The presence of weak C...C interaction in hydrous form (9.2%) which is absent in anhydrous form results in a decrease in the contribution for C...H contacts.

## 5. CONCLUSIONS

PIXEL energy calculations show that the hydrous form of investigated structure is  $6.6 \text{ kcal mol}^{-1}$  less stable than the anhydrous form. Analysis of selected molecular pairs shows that the arrangement of molecules in three dimensions is different in both forms. This indicates that the molecules in two forms are in a state of different crystal environment. The interaction between host and guest molecules is slightly more energetic than the interaction between two host molecules. The molecular pairs interacting via O... $\pi$ ,  $\pi$ ... $\pi$  and C-H... $\pi$  are having a relatively higher dispersion component than the rest of the molecular pairs. The decomposed fingerprint plots show that the various interactions are contributing differently towards Hirshfeld surfaces in the two forms.

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