Quantitative Evaluation of Intermolecular Interaction Energies in Crystal Structures of 4-hydroxy-3-nitrocoumarin and 4-chloro-3nitrocoumarin : Insights from PIXEL

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ABSTRACT

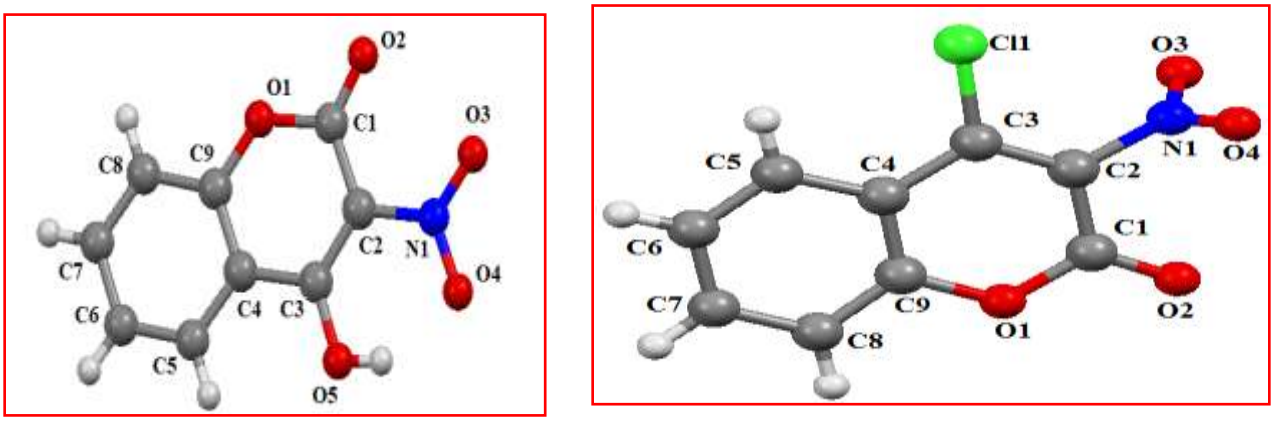
Weak intermolecular interactions such as hydrogen bonding, cation–π interaction, stacking and ionic interactions play an important role in molecular recognition and crystal structure prediction and is also of utmost importance in the field of Crystal Engineering. Crystal packing is not simply determined by a small number of strong interactions, but by the cooperation and competition of a large number of strong and weak interactions. In the present work, analysis has been done on the basis of molecular conformation and supramolecular packing of the molecules in the solid state in crystal structures of two nitrocoumarin derivatives namely 4-hydroxy-3-nitrocoumarin and 4-chloro-3nitrocoumarin. The lattice energy of the two compounds has been computed using PIXEL method. In order to have better understanding of the nature of non-covalent interactions, the interaction energy associated with molecular pairs playing an important role in crystal stabilization has also been calculated. Analysis of molecular motifs shows that C-H…O and π…π stacking are the major contributors towards the stabilization of the structures. Furthermore, short C-Cl…O=C/N contact also make significant contributions in the stabilization of 4-chloro-3nitrocoumarin.

Keywords: Coumarin, Hydrogen Bonding, Lattice Energy, Pixel

INTRODUCTION

Critical analysis of scientific literature reveals that coumarin derivatives possess diverse biological activities [1][2][3]. A series of 3-nitrocoumarins have been reported to possess antimicrobial activity and are potent inhibitors of phospholipase C [4] [5]. The wide range of biological activities is due to different substituent attached to the parent coumarin nucleus and their involvement in different kinds of intermolecular interactions. Quantitative estimation of these interactions is essential in determining their role in stabilizing crystal structure. Keeping in view the important applications of this class of compounds in pharmaceutical industry and the role of intermolecular interactions, the crystal structure of two nitrocoumarin derivatives namely 4-hydroxy-3-nitrocoumarin and 4-chloro-3nitrocoumarin have been analyzed. The Crystal structures of these two compounds were already reported [6] [7]. Pixel Calculations were performed to calculate the lattice energy and interaction energies of the molecular pairs of these two compounds. The key input for performing Pixel Calculations is the Crystallographic information file (CIF) which for the above mentioned compounds is obtained from CSD (Cambridge Structural Data Base). The schematic structure of the two compounds indicating the

atomic numbering scheme is shown in figure 1 and their precise crystallographic details are presented in Table 1.



(a) (b)

Figure 1.Schematic structure of (a) 4-hydroxy-3-nitrocoumarin (b) 4-chloro-3nitrocoumarin

Data	**4-hydroxy-3 nitro coumarin**	**4-chloro-3 nitro coumarin**
Formula	$C_9H_5NO_5$	C9H4ClNO4
Formula weight	207.14	225.59
Crystal System	orthorhombic	Monoclinic
Space group	*Pc*21*b*	P21/c
a(Å)	18.5990(3)Å	8.5110 (4)Å
b(Å)	5.0250(10)Å	13.526 (1)Å
c(Å)	8.871(2)Å	8.6612 (5)Å
α(°)	90	90
β(°)	90	114.119 (5)
γ(°)	90	90
Z	4	4
R	0.0543	0.0471

Table -1. Precise Crystallographic data of two nitrocoumarin derivatives

Theoretical Calculations

The lattice energies of the two structures have been calculated by PixelC module in Coulomb-London-Pauli (CLP) model [8] [9] [10]. This method requires one ab initio molecular orbital calculations, to prepare the molecular electron density which is essential for performing calculations. It allows the total energy to be partitioned into coulombic, polarization, dispersion and repulsion energies. The total lattice energy partitioned into these components is presented in table 2. The interaction energies of the selected molecular pairs extracted from the crystal packing (after performing PIXEL calculations) partitioned into different components along with the involved intermolecular interactions are presented in table 3. Molecular motifs and crystal packing diagrams were generated using Mercury software[11]. The geometrical restrictions imposed on the intermolecular contacts in the selected molecular pairs are the sum of van der waals radii +0.4 Å and the directionality is greater than 110°.

Molecule	E_{Cou}	E_{Pol}	E_{Disp}	E_{Rep}	E_{Tot}
4-hydroxy-3 nitro coumarin	-11.20	-3.25	-24.20	14.69	-23.98
4-chloro-3 nitro coumarin	-9.79	-3.15	-24.58	14.83	-22.69

Table-2 Lattice energy of two compounds obtained from CLP (Kcal mol^{-1})

Motif	**Centroid Distance (Å)**	**E_{Coul}**	**E_{Pol}**	**E_{Disp}**	**E_{Rep}**	**E_{Tot}**	**Symmetry**	**Important interactions**
4-hydroxy-3 nitro coumarin								
1	5.783	-4.20	-1.12	-3.89	2.60	-6.59	1-x,-y,-1/2+z	C8-H8…O3, O2…π
2	6.243	-3.48	-1.03	-3.67	3.58	-4.63	1-x,1-y,1/2+z	O5-H5O…O2, O4…π
3	9.504	-2.75	-0.78	-2.41	1.86	-4.08	-1/2+x,-y,z	C6-H6…O2,C7-H7…O2, C7-H7…O3
4	5.025	0.69	-0.64	-6.24	2.98	-3.20	x,-1+y,z	C-C Stacking, O…π
5	7.582	-0.16	-0.21	-3.34	1.55	-2.19	1.5-x,y,-1/2+z	C-C Stacking
6	9.096	-0.07	-0.47	-2.36	1.48	-1.43	1.5-x,-1+y, 1/2+z	C-7-H7…O5
4-chloro-3 nitro coumarin								

1	5.080	-3.56	-1.17	-10.94	6.85	-8.81	-x,1-y,1-z	π...π
2	5.250	-3.65	-1.00	-7.72	4.54	-8.79	1-x,1-y,1-z	C5-H5…O4, Cl…π
3	8.788	-2.10	-0.84	-2.79	2.32	-3.39	-x,-1/2+y,1/2-z	C6-H6…O1, C6-H6…O2
4	5.938	-0.93	-0.91	-3.68	2.32	-3.22	x,1/2-y,-1/2+z	O…π
5	7.773	-2.55	-0.62	-2.58	2.58	-3.17	1-x,-1/2+y,1.5-z	Cl…O (lone pair)
6	9.338	-0.91	-0.55	-2.58	1.05	-2.96	-1+x,y,-1+z	C7-H7…Cl1, C8-H8…O3, C8-H8…O4
7	7.341	-1.69	-0.28	-1.74	0.97	-2.77	1-x,1-y,2-z	Cl…O (lone pair)

Table -3. Interaction energies of the molecular pairs along with the associated intermolecular interactions

Results and Discussion

4-hydroxy-3 nitro coumarin:

The principal structural motifs (1-6) contributing maximum stabilization to the structure are shown in figure 2. The most stabilized molecular pair 1 involves C(sp^2)-H…O (H8 with O3) hydrogen bonding along with O…π interaction, resulting in a total interaction energy of -6.59

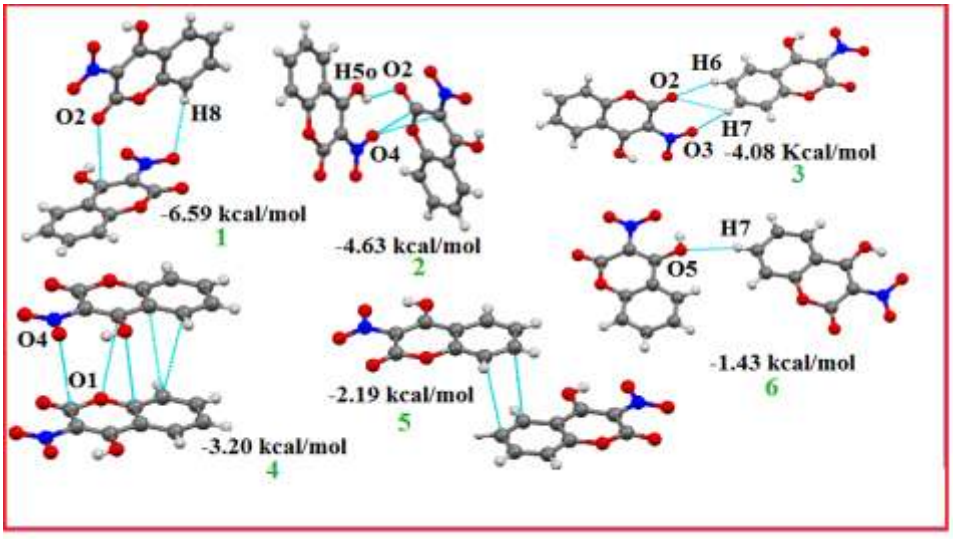


Figure-2. Molecular pairs (1-6) along with their interaction energies in 4-hydroxy-3-nitro coumarin

Kcal mol^{-1}. The next stabilized pair 2 contributing -4.63 Kcal mol^{-1} towards crystal stabilization, shows the presence of O-H…O (H5O with O2) and O…π (lone pair electrons of O4 interacting with the π electron cloud of pyran ring) interaction. The third most stabilized pair having energy -4.08 Kcal mol^{-1} involving bifurcated C-H…O hydrogen bonding forms a chain along a axis. The chains so formed are then stacked along b axis via means of molecular pair 4 (-3.20 Kcal mol^{-1}) as shown in figure 3. Additional stabilization to the structure is imparted by pairs 5 (C…C stacking) and 6 (C(sp^2)-H…O) having interaction energies of -2.19 Kcal mol^{-1} and -1.43 Kcal mol^{-1} respectively.

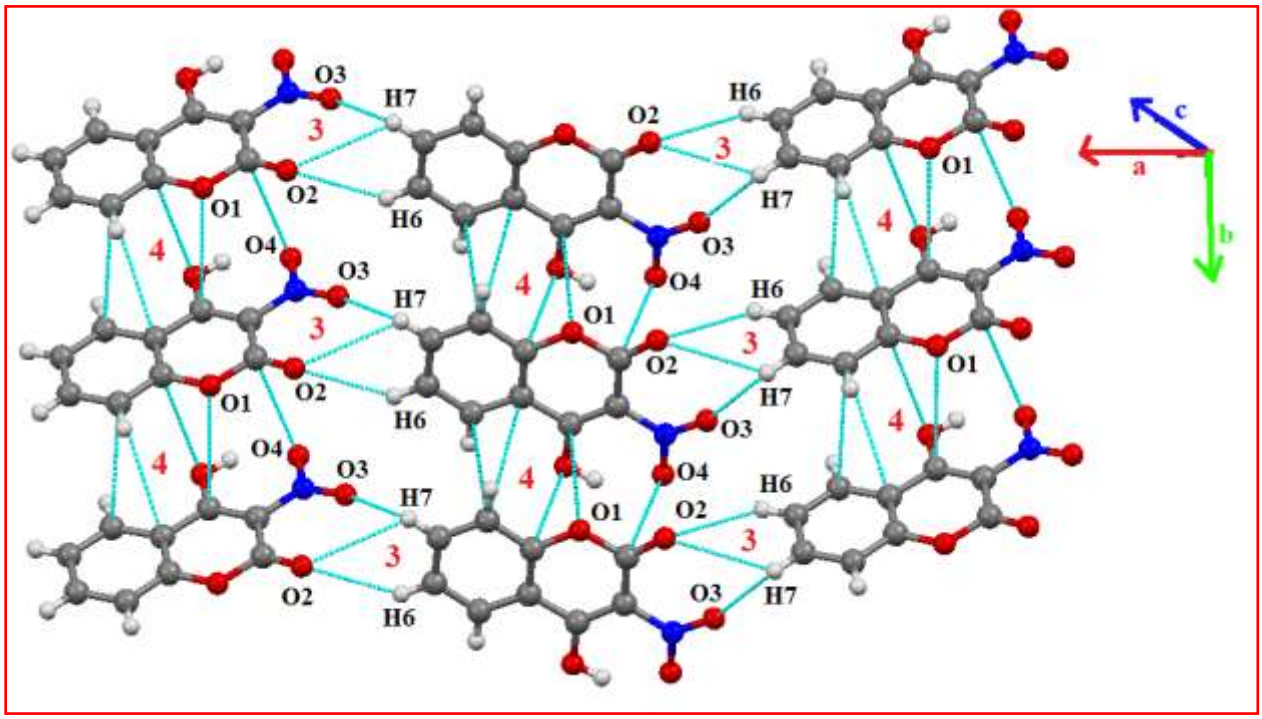


Figure-3. Crystal packing depicting formation of chains in the ab plane in 4-hydroxy-3-nitro coumarin

4-chloro-3 nitro coumarin:

The molecular pairs (1-7) extracted from the crystal structure of 4-chloro-3 nitro coumarin along with their interaction energies are shown in Figure 4. The crystal packing displays the stacking of the molecules along the crystallographic c axis utilizing motif 1 and 2. Motif 1 having the highest energy stabilization of – 8.81 Kcal mol^{-1} (70% contribution to net stabilization from dispersion component) shows the presence of π...π stacking, whereas dimeric C(sp^2)-H5…O4 and Cl…π binds the molecules in motif 2 (-8.79 Kcal mol^{-1}). The molecular stacks are then interlinked via motif 6 and 7 forming layers in the ac plane as shown in figure 5. Molecular pair 6 involves bifurcated donor C(sp^2)-H…O hydrogen bonding (involving H8 with O3 and O4) and C(sp^2)-H7…Cl1 interaction and contributes -2.96 Kcal mol^{-1} towards crystal stabilization. The molecules in pair 7(-2.77 Kcal mol^{-1}) are interlinked by nonbonding dimeric Cl1…O3

interaction. The packing in the crystal also involves the formation of molecular chains in the bc plane via molecular pairs 3, 5 and 6 as depicted in figure 6. Molecular pair 3(-3.39 kcal mol^{-1}) shows bifurcated donor $C(sp^2)$-H…O (involving H6 with O1 and O2) hydrogen bonding and molecular pair 5 (-3.17 Kcal mol^{-1}) shows non bonding short Cl1…O2 interaction in which Cl1 interacts with the lone pair electrons of O2.

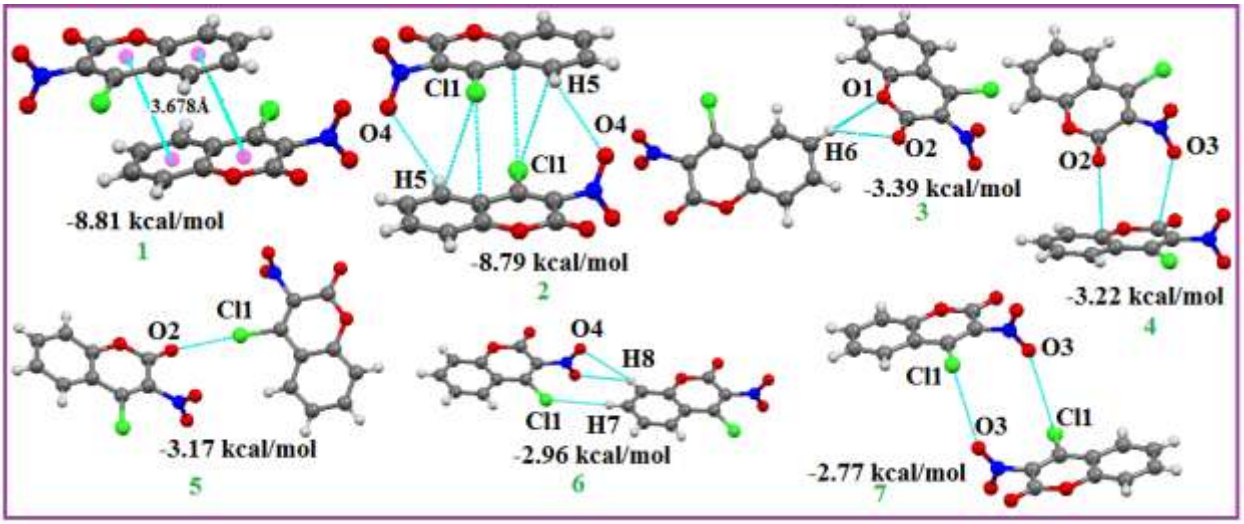


Figure-4. Molecular pairs (1-6) along with their interaction energies in 4-chloro-3-nitro coumarin

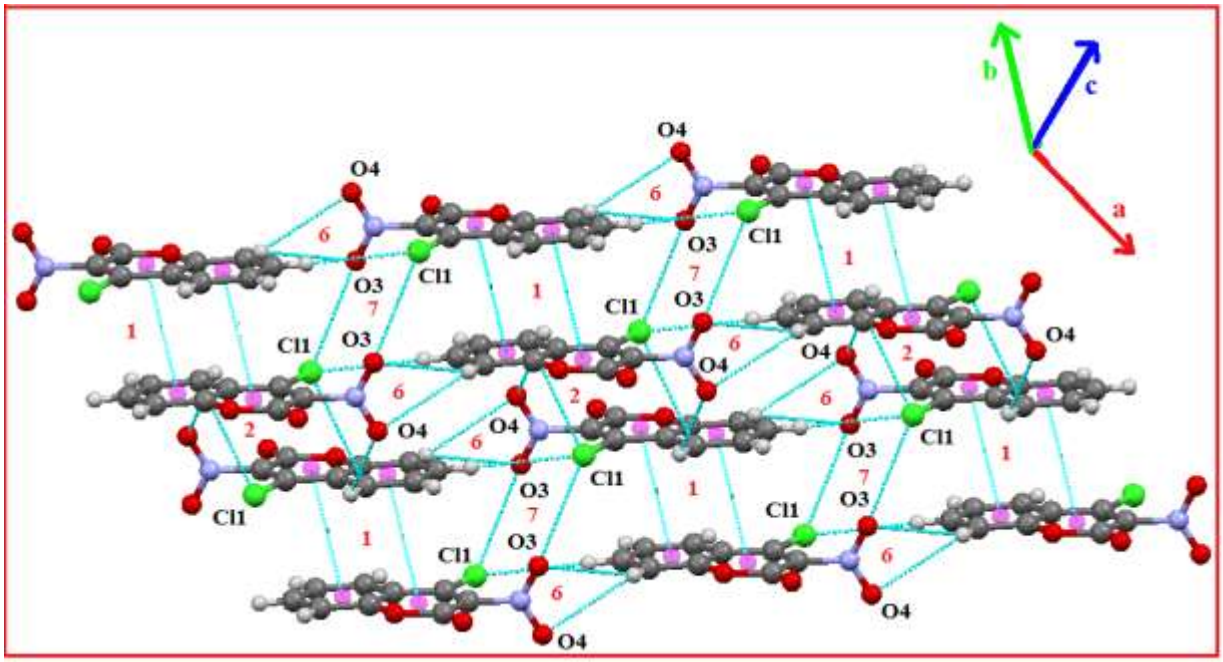


Figure-5. Molecular stacking in 4-chloro-3 nitro coumarin in the ac plane

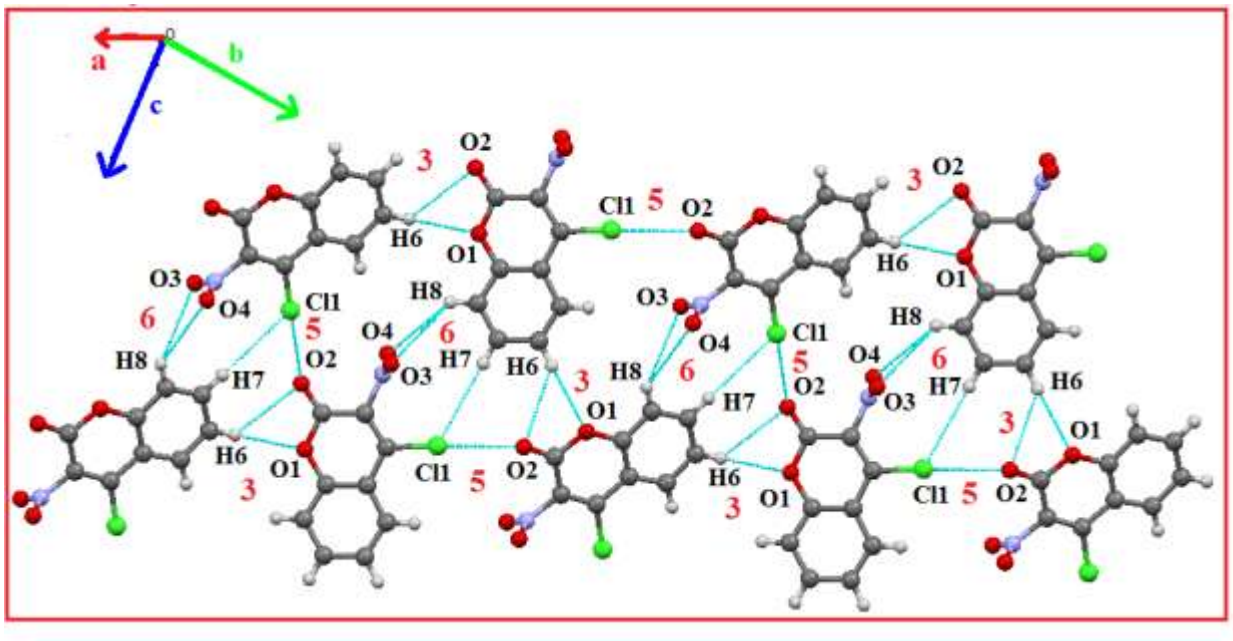


Figure-6. Packing of the molecules in 4-chloro-3 nitro coumarin in bc plane

CONCLUSION

In the present manuscript, the role of intermolecular interactions in two nitrocoumarin derivatives has been analyzed using PIXEL calculations. The total interaction energy (Lattice energy) of both the compounds are almost similar with energy of the order of -23 Kcal mol^{-1}. Analysis of key structural motifs essential for the stabilization of crystal structure suggests that C–H…O intermolecular contacts and O...π interactions are the most important contributors towards the stabilization of the crystal structure of 4-hydroxy -3 nitrocoumarin. π...π interaction imparts maximum contribution towards stabilization of 4-chloro-3-nitrocoumarin along with other weak intermolecular interactions like C-H…O, C-H…Cl and O...π. Non-bonding interaction involving short Cl…O contacts are also observed to stabilize the crystal structure of 4-chloro-3-nitrocoumarin. The energy of the molecular pairs involving short Cl …O contacts is almost of the order of -3 Kcal mol^{-1}.

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