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Quantitative Analysis of Weak Intermolecular Interactions in the Crystal Structures of Some Indole Derivatives

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Abstract: *A quantitative analyses of the intermolecular interactions in the crystal structures of some indole derivative have been performed. Analysis of the nature of intermolecular interactions is of utmost importance in the field of crystal engineering to facilitate the design of new materials with desirable properties and for crystal structure prediction of a given set of molecules. To get a better understanding of the contribution of intermolecular interactions to the crystal packing, it is important to get a quantitative evaluation of these interactions. A better understanding of these interactions and their influence on the crystal packing can be obtained by evaluating the energetics associated with these interactions. The lattice energy of all the compounds has been calculated by using PIXELC module in Coulomb London Pauli (CLP) package and is partitioned into corresponding coulombic, polarization, dispersion and repulsion contributions. The decomposition of the interaction energies obtained for different molecular pairs clearly demonstrated that the nature and strength of interactions present in a given molecular pair is directly correlated with the strength of the donor or/and acceptor atom present in the molecule. In order to throw some more light on the crystallographic structures vis-a-vis interaction energies, we have identified from the literature a series of some indole derivatives and extracted molecular pairs from the crystal packing providing maximum stability to their crystal structures.*
Keywords: *Hydrogen bonding, Indole, Intermolecular interactions, Lattice energy, PIXEL.*

I. Introduction

Studying intermolecular interactions in molecular crystals has been a very important aspect of supramolecular chemistry [1]. Both strong and weak intermolecular interactions have been observed to be responsible for the 3D arrangement of molecules in a crystal [2] and hence a detailed analysis of their nature is very important. Strong intermolecular interactions such as N-H…O/N, O-H…O/N [3] have been well studied and documented in the literature. In the past few years, in addition to strong interactions, weak interactions such as C-H…O/N [4], C-H…X (X=-F, -Cl, -Br, -I) [5-6], C-H…π [7], lp…π [8], X…X(X =F, Cl, Br, I) [9] has garnered attention across the world. Apart from this, various studies have also been performed to understand the interplay between strong and weak interactions within the same molecule in the crystal [10-11]. Along with experimental analysis, detailed computational studies have also become an important tool in delineating the strength and nature of intermolecular interactions [5, 12-13].

Bicyclic heterocyclic compounds containing pyrole ring with benzene ring fused to α,β-position are known as indoles. These derivatives are excellent drug intermediates for many pharmaceutical products and also for the synthesis of many biological active compounds [14-16]. These are quite commonly used as antiviral [17], anticancer [18], antifungal [19], antimicrobial [20-21], antiHIV [22-23], antioxidant agents [24-25] etc. In view of the immense biological importance of indole derivatives and their applications in the fields of biological, chemical and physical sciences, we have identified few known indole derivatives and calculated theoretically their lattice energies and their contribution towards the understanding of the molecular geometry and the different intermolecular interactions which control crystal packing. The quantification of the energetics associated with the formation of different "molecular pairs" is important to recognize the hierarchy of intermolecular interactions present in the crystal. The Crystallographic Information File (CIF) for each compound was obtained through the CSD licensed access.

All the molecular pairs involved in the crystal packing were extracted and their energies were computed using PIXEL [26]. Calculations were performed in order to estimate the nature and energies associated with the intermolecular interactions which enabled us to explore the role of these interactions in the stabilization of the crystal lattice. The present study can help us in designing different biologically active derivatives of Indole by changing the strength of donor and/or acceptor atom which can give rise to interactions of different strength and nature which in turn can help in identifying binding capabilities of such molecules with enzymes. A representative illustration of the atomic numbering scheme used for the present work is shown in Figure 1. The chemical name, molecular code, position of the substituent(s) for each compound is presented in Table 1 and its precise crystallographic data are presented in Table 2.

II. Theoretical calculation

To get a better understanding of the contribution of intermolecular interactions to the crystal packing, it is important to get a quantitative evaluation of these interactions. Calculation of the lattice energy not only offers a possible way for polymorph prediction but may also help to understand the supramolecular chemistry and self-assembly during the nucleation and crystal growth processes and help to predict the melting and solubility behavior of the compounds. The lattice energies of all the compounds were calculated by PIXELC module in Couloumb-London-Pauli (CLP) computer program package (version 13.2.2012) [26]. The program PIXEL provides the advantage of partitioning the total interaction energy for the different molecular pair's into the corresponding coulombic, polarization, dispersion and repulsion components respectively (Table 3). In CLP, the coulombic terms are handled by Coulomb's law while the polarization terms are calculated in the linear dipole approximation, with the incoming electric field acting on local polarizabilities and generating a dipole with its associated dipole separation energy; dispersion terms are simulated in London's inverse sixth power approximation, involving ionization potentials and polarizabilities; repulsion is presented as a modulated function of wavefunction overlap. The symmetry operator and centroid–centroid distance along with coulombic, polarization, dispersion, repulsion and total interaction energies between the molecular pairs are presented in Table 4. The molecular pairs are arranged in decreasing order of their stabilization energies. The PIXEL method has been preferred for the quantification of intermolecular interactions, primarily because of the following reasons: (i) It is computationally less demanding [26]. (ii) It allows partitioning of total interaction energy into corresponding coulombic, polarization, dispersion, and repulsion contribution which facilitates a better understanding of the nature of intermolecular interactions contributing towards the crystal packing [13]. (iii) The energies obtained from PIXEL calculation are generally comparable with high level quantum mechanical calculations [27-28].

III. Results and Discussion

3.1 *(5-Methoxy-1H-indol-3-yl)acetonitrile (M-1)*

Molecular pairs of M-1 (1-6) extracted from crystal structure along with their respective interaction energies are shown in Figure 2. The maximum stabilization to the crystal structure comes from N–H…O intermolecular interaction involving H1A with O1. The stabilization energy of the pair is -8.91 Kcal mol^{-1} (Motif 1) obtained using PIXEL. Another molecular pair (Motif 2) have an interaction energy of -7.15 Kcal mol^{-1} involves C-H…π intermolecular interaction involving H10A with centre of gravity of benzene ring. Motif 3 involves N1 and C10 with stabilization energy being -5.54 Kcal mol^{-1} and is dispersive in nature. The next two stabilized pairs show C-H…N intermolecular interaction. Motif 4 involves H11C interacting with N2 atom and in motif 5 H1B interact again with N2. The stabilization energies of these two pairs being -3.92 Kcal mol^{-1} and -2.63 Kcal mol^{-1}, respectively (Table 4). Last molecular pair 6 involves the interaction of O1 and C4. This pair also involves the interaction of H11A with N2 and C2 having an interaction energy of -2.15 Kcal mol^{-1} contributing towards the stability of crystal packing.

3.2 *2-(7-Methyl-1H-indol-3-yl)acetonitrile (M-2)*

The most stabilized molecular pairs (1-6) of M2 along with their stabilization energies are shown in Figure 3. The most stabilized molecular pair in M-2 shows the presence of C-H…π (involving H1B with C5 and C10 of phenyl ring) and provides stabilization of -7.81 Kcal mol^{-1}. The next most stabilized pair involves N-H…N hydrogen bonding (involving H1A with N2) having an interaction energy of -7.38 Kcal mol^{-1} and the stabilization mainly comes from the coulombic component. The next stabilized pair shows C-H…π (involving H11B interacting with C9 atom of the phenyl ring) resulting in a stabilization energy of -4.99 Kcal mol^{-1}. Additional stabilization to the structure comes from motif 4 which shows the presence of C-H…N (involving H9A with N2) forming dimer having an interaction energy of -3.97 Kcal mol^{-1}. Molecular pairs 5 and 6 having interaction energies -3.42 Kcal mol^{-1} and -2.72 Kcal mol^{-1} respectively, also contribute towards the stability of crystal packing.

3.3 *2-(4-Methoxy-1H-indol-3-yl)acetonitrile (M-3)*

The extracted molecular pairs (1-5) of M-3 are shown in Figure 4 along with their stabilization energies. The most stabilized molecular pair in M-3 shows the presence of N-H…N hydrogen bonding (involving N2 acceptor with H1A) with an interaction energy of -8.58 Kcal mol^{-1} and interaction is mainly columbic in nature. The next most stabilized pair shows the presence of C-H…N (involving H11C with N1) and C-H…π (involving H3B with C8 atom of the phenyl ring) intermolecular interactions and hence form dimer having an interaction energy of -6.55 Kcal mol^{-1} with major contribution from dispersion component. Molecular pair 3 shows the presence of bifurcated donor atom (involving H3A interacting with N2 and C4) and C-H…π interaction (involving H1B with centre of gravity of phenyl ring) and resulting in a stabilization energy of -5.42

Kcal mol^{-1}. Another C-H…N (involving H8A with N2) and C-H…C interactions (involving H11C with N1 and H11A with C4) generates a molecular pair having an interaction energy of -3.01 Kcal mol^{-1}. Finally the least stabilized pair shows C-H…C interaction (involving H11A with C4) having an interaction energy of -2.68 Kcal mol^{-1} which provides additional stabilization to the crystal packing.

3.4 *2-(6-Chloro-1H-indol-3-yl)acetonitrile (M-4)*

Molecular pairs of M-4 (1-6) extracted from crystal structure along with their respective interaction energies are shown in Figure 5. The maximum stabilization to the crystal involves molecular stacking to generate dimers and C-H…Cl hydrogen bonding (involving H3A with Cl1). The stabilization energy of this pair is -7.98 Kcal mol^{-1} obtained using PIXEL and the combined nature of these interactions is mainly dispersive in nature. Another molecular pair (Motif 2) shows the presence of N-H…N hydrogen bonding (involving H1A with N2) having an interaction energy of -7.74 Kcal mol^{-1} and is columbic in nature. Another C-H…N interaction (involving H3B with N1) generates a molecular pair having an interaction energy of -6.88 Kcal mol^{-1}. The next most stabilized pair in M-4 shows the presence of bifurcated acceptor atom Cl interacting with H1A and H7A forming dimer related by centre of symmetry with an interaction energy of -6.38 Kcal mol^{-1}. Molecular pair 5 having an interaction energy of -3.23 Kcal mol^{-1} shows C-H…Cl hydrogen bonding (involving H1B with Cl1) and hence contribute towords the stability of crystal packing. Molecular pair 6 involves H7A interacting with C10 also provide additional stabilization to the crystal structure.

3.5 *2-(4-Bromo-1H-indol-3-yl)acetonitrile (M-5)*

The molecular pairs (1-6) which provide maximum stabilization to the packing in M-5 are shown in Figure 6. The most stabilized molecular pair in M-5 involves Br…N interaction and C-H…N intermolecular interaction, (involving H9A with N1 and H8A with N2) having an interaction energy of -9.18 Kcal mol^{-1} with major contribution from dispersion component. The next most stabilized pair involves N-H…C hydrogen bonding (involving H1A with C4) resulting in a stabilization energy of -7.50 Kcal mol^{-1}. Molecular pair 3 shows the presence of C-H…N (involving H3 and N2) and C-H…π (involving H1B with centre of gravity of phenyl ring) having an interaction energy of 6.36 Kcal mol^{-1}. The next two most stabilized pairs shows C-H…C hydrogen bonding, motif 4 involves H7A interacting with C4 resulting in interaction energy of -4.92 Kcal mol^{-1} whereas in motif 5 acceptor atom C9 interacting with H9A forming dimer having an interaction energy of -3.97 Kcal mol^{-1}. Last stabilized pair involves C-H…Br (involving Br1 with H3A) interaction forming a dimer having an interaction energy of -3.20 Kcal mol^{-1}.

IV. Figures and Tables

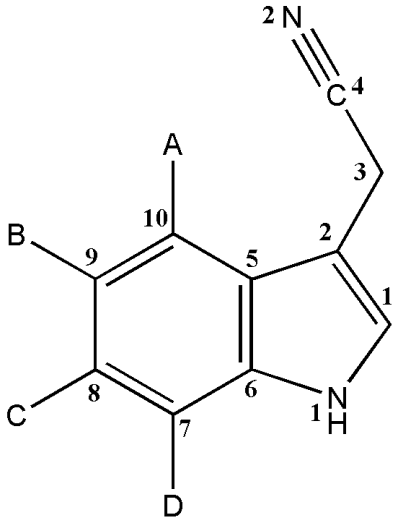


Figure 1. Chemical structure of the indole moiety indicating the atomic numbering scheme.

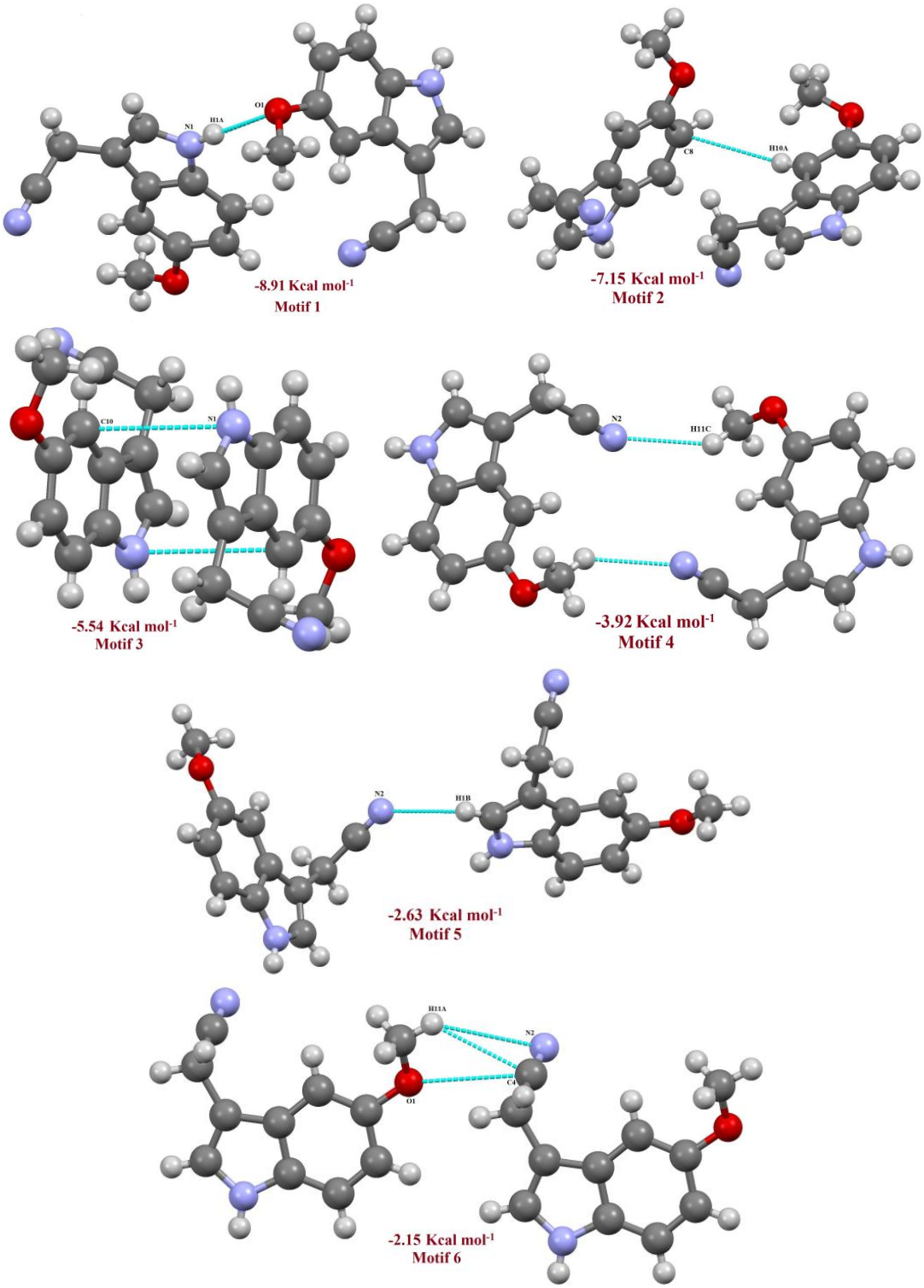


Figure 2. Molecular pairs (I-VIII in Table 3) along with their interaction energies calculated with PIXEL (values in red) in M-1.

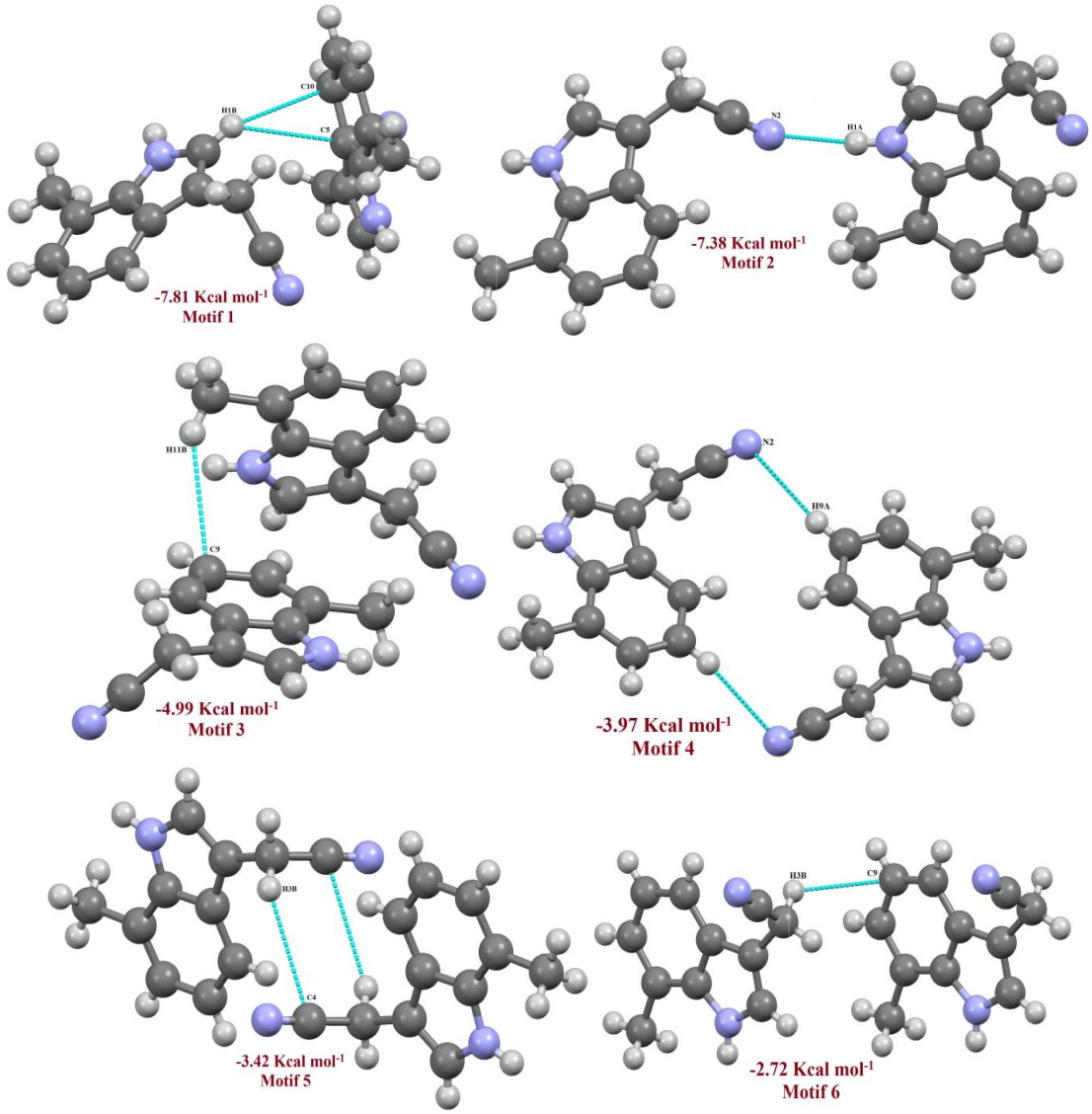
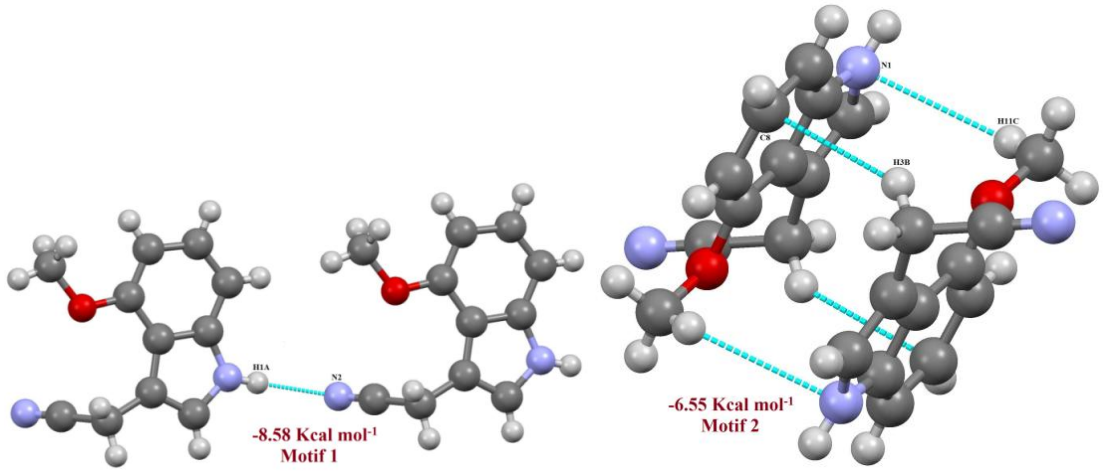


Figure 3. Molecular pairs (I-VI in Table 3) along with their interaction energies calculated with PIXEL (values in red) in M-2.



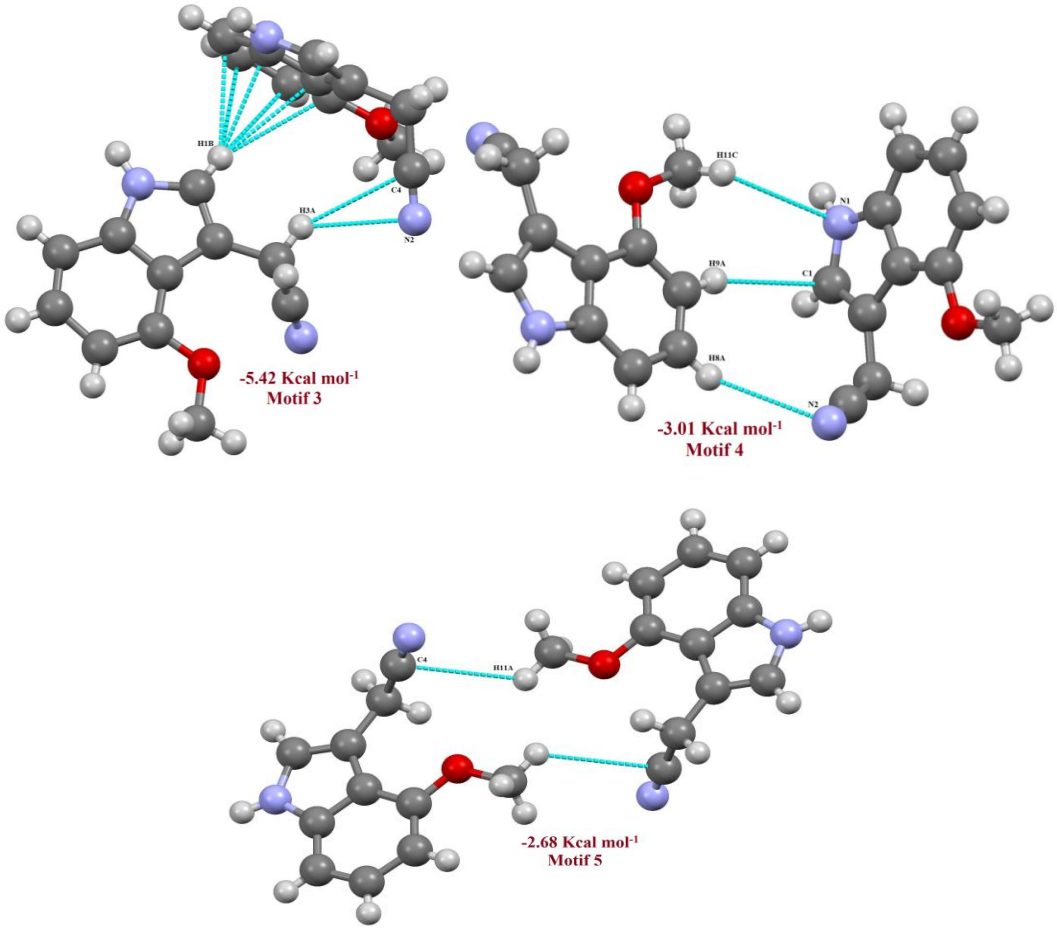
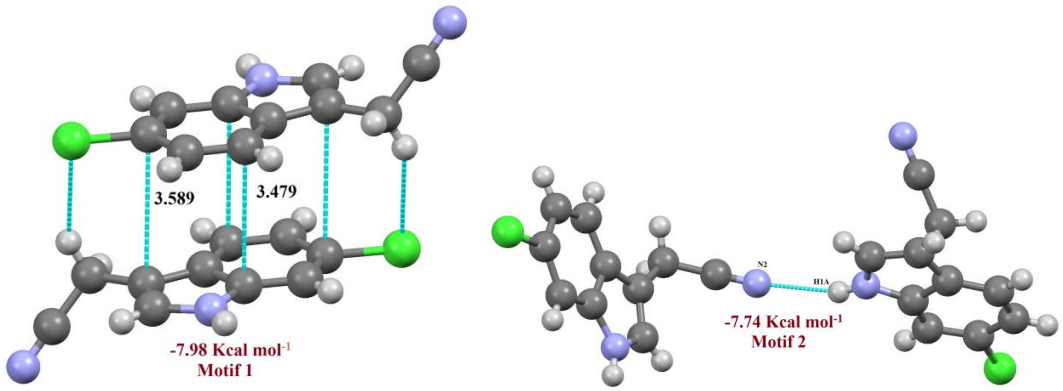


Figure 4. Molecular pairs (I-V in Table 3) along with their interaction energies calculated with PIXEL (values in red) in M-3.



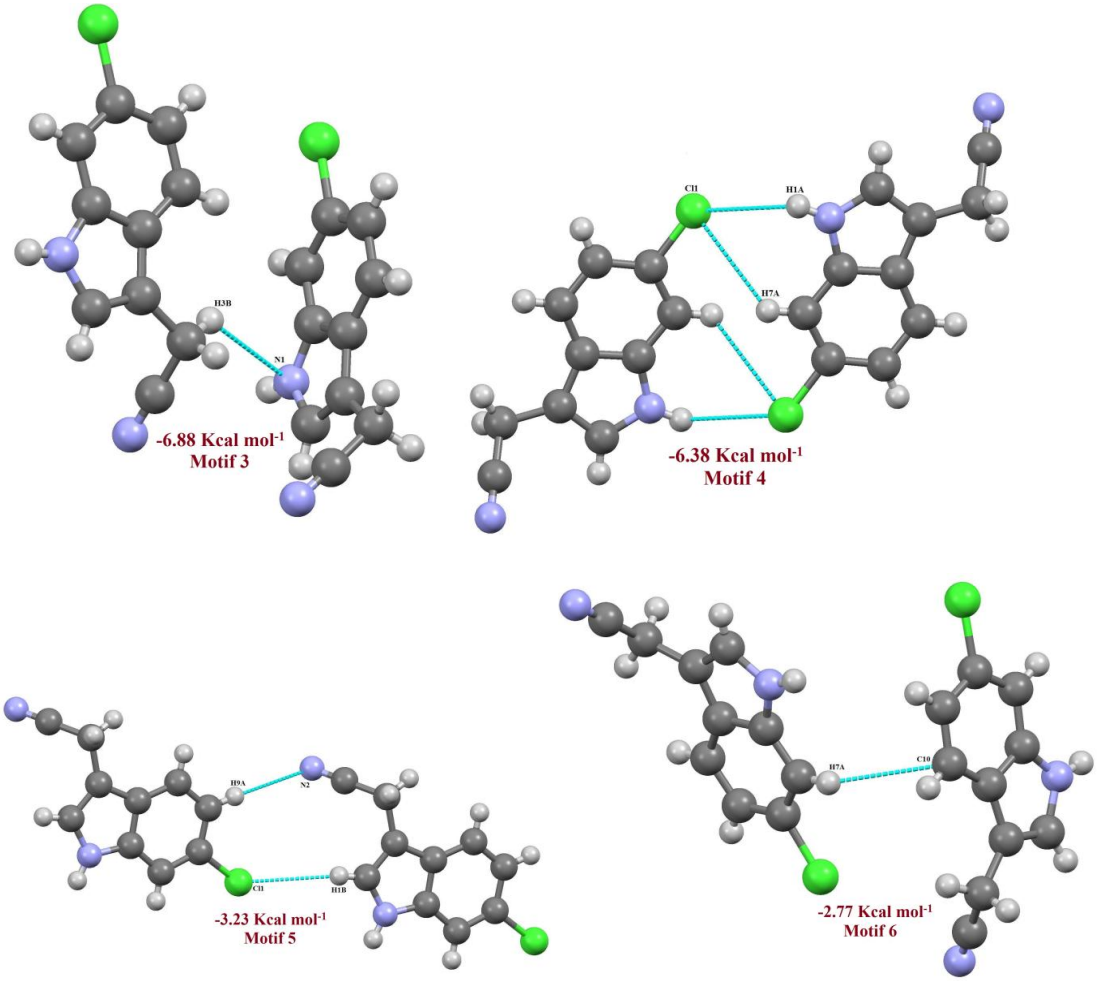
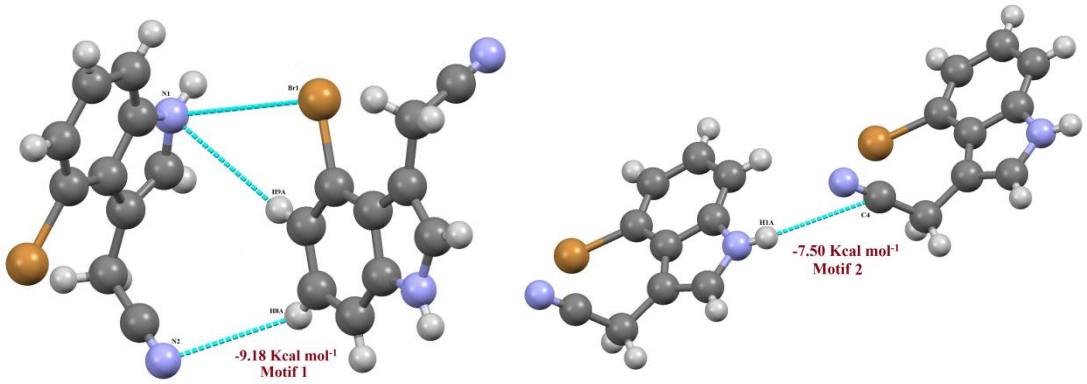


Figure 5. Molecular pairs (I-VI in Table 3) along with their interaction energies calculated with PIXEL (values in red) in M-4.



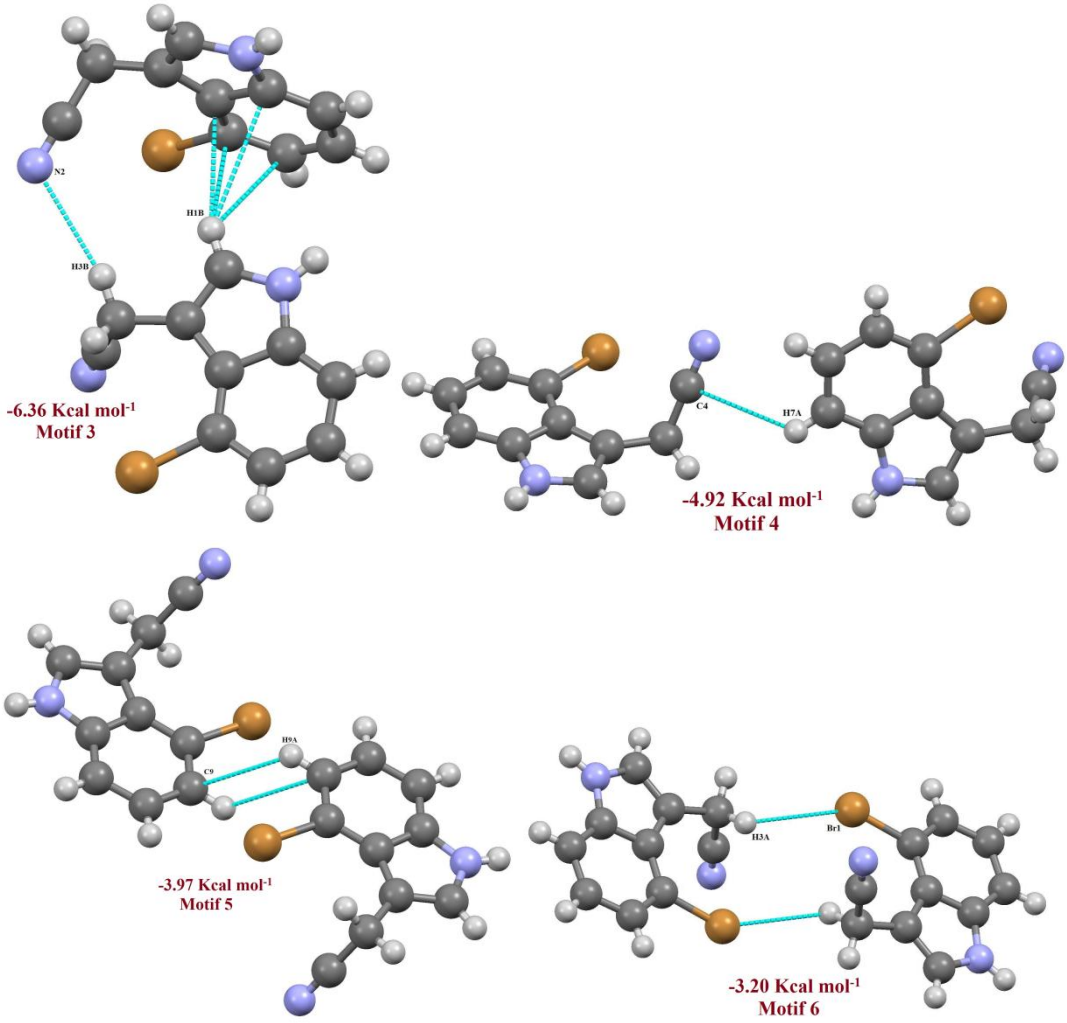


Figure 6. Molecular pairs (I-VI in Table 3) along with their interaction energies calculated with PIXEL (values in red) in M-5.

Table 1. List of compounds, molecular code and the position of substituent(s).

Chemical Name	Molecule Code	Substituent				Reference No.
		A	B	C	D	
(5-Methoxy-1H-indol-3-yl)acetonitrile	M-1	H	OCH_3	H	H	[29]
2-(7-Methyl-1H-indol-3-yl)acetonitrile	M-2	H	H	H	CH_3	[30]
2-(4-Methoxy-1H-indol-3-yl)acetonitrile	M-3	OCH_3	H	H	H	[31]
2-(6-Chloro-1H-indol-3-yl)acetonitrile	M-4	H	H	Cl	H	[32]
2-(4-Bromo-1H-indol-3-yl)acetonitrile	M-5	Br	H	H	H	[33]

Table 2. Precise crystal data for indole derivatives.

Data	M-1	M-2	M-3	M-4	M-5
Formula	$C_{11}H_{10}N_2O$	$C_{11}H_{10}N_2$	$C_{11}H_{10}N_2O$	$C_{10}H_7ClN_2$	$C_{10}H_7BrN_2$

Formula weight	186.21	170.21	186.21	190.63	235.09
Crystal System	Monoclinic	Monoclinic	Monoclinic	Monoclinic	Monoclinic
Space group	$P2_1/n$	$P2_1/c$	$P2_1/c$	$P2_1/c$	$P2_1/c$
a(Å)	8.9242 (18)	6.9962 (14)	8.3182 (17)	9.761 (2)	8.3971 (17)
b(Å)	11.461 (2)	8.9445 (18)	13.062 (3)	11.205 (2)	11.237 (2)
c(Å)	9.889 (2)	15.406 (3)	9.3867 (19)	8.7791 (18)	9.979 (2)
β(°)	110.77 (3)	97.97	101.53 (3)	100.39 (3)	104.82
V(Å^3)	945.7 (3)	954.7 (3)	999.3 (3)	944.4 (3)	910.2 (3)
Z	4	4	4	4	4
S	1.01	1.05	1.07	1.05	1.09
R	0.0696	0.055	0.088	0.110	0.073

Table 3. Lattice energy from CLP (in Kcal mol^{-1}).

Molecule	**E_{Coul}**	**E_{Pol}**	**E_{Disp}**	**E_{Rep}**	**E_{Tot}**
M-1	-15.46	-6.72	-28.97	21.68	-29.47
M-2	-13.86	-5.33	-23.92	16.75	-26.36
M-3	-15.30	-6.45	-23.90	18.16	-27.48
M-4	-14.82	-6.12	-26.19	18.09	-29.04
M-5	-12.45	-4.66	-28.08	16.90	-28.27

Table 4. PIXEL interaction energies (I.E.) (kcal mol^{-1}) between molecular pairs related by a symmetry operation and the associated intermolecular interactions in the crystal.

Motif	**Centroid Distance (Å)**	**E_{Coul}**	**E_{Pol}**	**E_{Disp}**	**E_{Rep}**	**E_{Tot}**	**Symmetry**	**Important interactions**
				M-1				
1	6.520	-6.50	-3.03	-6.19	6.81	-8.91	1/2-x, -1/2+y, 3/2-z	N1-H1A…O1
2	5.677	-3.25	-0.88	-5.59	2.58	-7.15	1/2+x, 1/2-y, 1/2+z	C10-H10A… π(C8)
3	4.485	-0.91	-1.53	-12.91	9.77	-5.54	1-x, 1-y, 2-z	N1…C10
4	7.946	-3.20	-1.05	-2.27	2.60	-3.92	1-x, -y, 2-z	C11-H11C…N2
5	9.428	-1.77	-0.72	-1.43	1.29	-2.63	3/2-x, -1/2+y, 3/2-z	C1-H1B…N2
6	8.924	-0.26	-0.67	-3.08	1.86	-2.15	-1+x, y, z	O1…C4 C11-H11A…N2 C11-H11A…C4
				M-2				
1	5.495	-3.97	-1.46	-6.62	4.25	-7.81	-x, 1/2 +y, 1/2 -z	C1-H1B…π(C10,C5)
2	8.679	-7.96	-2.65	-2.25	5.47	-7.38	x, 3/2-y, -1/2+z	N1-H1A…N2
3	6.222	-1.84	-0.86	-5.99	3.73	-4.99	1-x, 1/2+y, 1/2-z	C11-H11B…π(C9)
4	6.984	-1.70	-0.64	-2.82	1.17	-3.97	1-x, 1-y, 1-z	C9-H9A…N2
5	7.430	-0.62	-0.52	-3.30	1.05	-3.42	-x, 1-y, 1-z	C3-H3B…C4
6	6.996	-0.45	-0.41	-3.75	1.91	-2.72	1+x, y, z	C3-H3B…C9
				M-3				
1	8.318	-8.77	-2.94	-3.30	6.43	-8.58	-1+x, y, z	N1-H1A…N2
2	4.187	-1.09	-1.29	-10.47	6.31	-6.55	1-x, 1-y, -z	C11-H11C…N1 C3-H3B…π(C8)
3	5.771	-2.89	-1.62	-6.19	5.28	-5.42	x, 3/2-y, -1/2+z	C3-H3A…N2 C3-H3A…C4 C1-H1B…π
4	6.964	-0.31	-0.72	-3.99	2.01	-3.01	1-x, 1/2+y, 1/2-z	C11-H11C…N1 C9-H9A…C1 C8-H8A…N2
5	7.817	-0.52	-0.41	-2.94	1.17	-2.68	-x, 1-y, -z	C11-H11A…C4
				M-4				
1	4.067	-2.72	-1.62	-12.21	8.60	-7.98	1-x, -y, -z	C3-H3A…Cl1
2	9.482	-8.34	-2.70	-2.17	5.47	-7.74	2-x, 1/2+y, 1/2-z	N1-H1A…N2
3	5.328	-2.84	-1.17	-6.98	4.09	-6.88	x, 1/2-y, 1/2+z	C3-H3B…N1
4	7.100	-2.77	-0.96	-4.89	2.25	-6.38	1-x, -y, 1-z	N1-H1A…Cl1 C7-H7A…Cl1
5	9.761	-1.55	-0.62	-2.27	1.22	-3.23	-1+x, y, z	C1-H1B…Cl1 C9-H9A…N2

6	6.239	0.19	-0.57	-3.54	1.17	-2.77	1-x, 1/2+y, 1/2-z	C7-H7A…C10
				M-5				
1	4.635	-3.58	-1.31	-13.09	8.79	-9.18	2-x, 2-y, -z	Br1…N1 C9-H9A…N1 C8-H8A…N2
2	8.397	-5.59	-1.67	-3.23	3.01	-7.50	-1+x, y, z	N1-H1A…C4
3	6.303	-2.60	-1.89	-5.97	4.11	-6.36	x, 3/2-y, -1/2+z	C3-H3B…N2 C1-H1B…π
4	6.128	-1.82	-0.79	-4.64	2.32	-4.92	2-x, -1/2+y, 1/2-z	C7-H7A…C4
5	6.820	-1.60	-0.43	-3.82	1.89	-3.97	2-x, 2-y, 1-z	C9-H9A…C9
6	6.470	-0.86	-0.52	-4.33	2.51	-3.20	1-x, 2-y, -z	C3-H3A…Br1

V. Conclusion

In this study, we have quantitatively analyzed the intermolecular interactions present in the crystal structures of some indole derivatives. Molecular organization and molecular interactions are the basis of functional properties of organic molecules and a detailed understanding of non-covalent chemistry is therefore fundamental to interpreting and predicting relationships between chemical structure and function. Analysis of different structural motifs shows that C-H…O, C-H…π and π…π intermolecular interactions are the major contributors that stabilizes the crystal. A better understanding of these interactions and their influence on the crystal packing can be obtained by evaluating the energetic associated with these interactions. A proper quantitative evaluation of intermolecular interaction energies is a prerequisite for an understanding of molecular aggregation modes in condensed phases, and hence for prediction and control of structural, thermodynamic, and physical properties of materials. PIXEL calculations suggest the presence of different key structural motifs which aid in the stabilization of crystal packing. The present study can help us in designing different biologically active derivatives of Indole by changing the strength of donor and/or acceptor atom which can give rise to interactions of different strength and nature which in turn can help in identifying binding capabilities of such molecules with enzymes. The crystal structure analysis and computation of lattice energies has been undertaken to make a possible correlation between the crystal packing effects and the crystal structure. Though the analysis is empirical in nature, yet it is useful in the sense that synthetic chemists can devise strategies while making derivatives of similar looking compounds. In summary, the results demonstrated that the calculation of lattice energies is a useful approach to assess the stability of molecular crystals in which dispersion type interactions make up an essential part of the intermolecular interactions.

Acknowledgements

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