QUANTITATIVE ANALYSIS OF WEAK INTERMOLECULAR INTERACTIONS IN COUMARIN-3-CARBOXYLATE DERIVATIVES

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The study of nature of intermolecular interactions and their control is extremely important in the area of crystal engineering, in order to design a new material of desirable properties and also for crystal structure prediction. A better understanding of these interactions and their influence on the crystal packing can be obtained by evaluating the energetics associated with these interactions. In this regard, we have identified from the literature a series of coumarin-3-carboxylate derivatives and extracted molecular pairs from the crystal packing providing maximum stability to the crystal structure. The lattice energy of all the compouds have been calculated by using PIXELC module in Coulomb-London-Pauli (CLP) package and is partitioned into corresponding coulombic, polarization, dispersion and repulsion contributions. It is found that the weak intermolecular interactions like C-H…O, π…π and C-H…π play an important role in the stabilization of the crystal packing.

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Introduction

Coumarins (2H-1-benzopyran-2-ones) belong to the family of lactones containing benzopyrone skeletal framework that have enjoyed isolation from plant as well as total synthesis in the laboratory.[1] Coumarins have been extensively investigated due to their applications in the fields of biological, chemical and physical sciences.[2,3] Coumarin in itself possess broad range of biological activities namely antioxidant,[4,5] cytostatic,[6] anti-hyperglycemic,[7] casein kinase 2 inhibitor,[8] vasorelaxant,[9] and antitubercular[10] activities. In view of the immense biological importance of coumarins, we have identified from the literature a few Coumarin-3-carboxylate derivatives and calculated theoretically their lattice energies. 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 determined using PIXEL.[11] PIXEL calculations were performed in order to estimate the nature and energies associated with the intermolecular interactions which will enable us to explore the role of these interactions in the stabilization of the crystal lattice. A representative illustration of the coumarin moiety indicating the atomic numbering scheme used for the present work is shown in Fig.1.
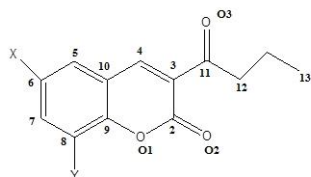

Figure 1. Coumarin moiety and the numbering scheme used

The chemical name, molecular code, position of the substituent(s) and precise crystallographic data for each compound are presented in Table 1a and 1b, respectively.

Table 1a. List of compounds and the position of substituent(s)

Chemical name	Substituent	
	X	Y
Ethyl-2H-benzopyran-2-oxo-3-carboxylate (M-1)[12]	H	H
Ethyl 6-chloro-2-oxo-2H-chromene-3-carboxylate (M-2)[13]	Cl	H
Ethyl 6-bromo-2-oxo-2H-chromene-3-carboxylate (M-3)[13]	Br	H
Ethyl 8-methoxy-2-oxo-2H-chromene-3-carboxylate (M-4)[14]	H	OCH3

Table 1b. Precise crystal data for coumarin-3-carboxylate derivatives

Data	M-1	M-2	M-3	M-4
	$C_{12}H_{10}O_4$	$C_{12}H_9ClO_4$	$C_{12}H_9BrO_4$	$C_{13}H_{12}O_5$
M, g mol^{-1}	218.20	252.64	297.10	248.23
Crystal System	Monoclinic	Monoclinic	Monoclinic	Monoclinic
Space Group	P21/c	P21/c	P21/c	P21/n
a(Å)	7.916(1)	5.7982(5)	5.8432(6)	6.8572(14)
b(Å)	15.736(2)	13.0702(12)	13.2073(14)	10.644(2)
c(Å)	8.737(8)	15.5540(12)	15.6959(15)	15.780(3)
α(°)	90	90	90	90
β(°)	108.11(6)	108.191(3)	109.327(3)	100.153(14)
γ(°)	90	90	90	90
Z	4	4	4	4
R	0.0696	0.055	0.045	0.044

Theoretical calculations

The lattice energies of all the compounds were calculated by PIXELC module in Couloumb-London-Pauli (CLP) computer program package (version 13.2.2012).[11] The total lattice energy is partitioned into its coulombic, polarization, dispersion and repulsion contributions (Table 2).

Table 2. Lattice energy from CLP (in kcal mol^{-1})

Molecule	E_{Cou}	E_{Pol}	E_{Disp}	E_{Rep}	E_{Tot}
M-1	-11.08	-4.11	-28.15	17.13	-26.22
M-2	-12.35	-4.34	-31.59	19.26	-29.039
M-3	-12.64	-4.2065	-31.09	19.33	-28.58
M-4	-14.86	-5.47	-35.25	25.40	-30.18

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 All the stabilizing molecular pairs involved in crystal packing were selected from the mlc output file, which is generated after PIXEL energy calculations and were analysed with their interaction energies. 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 3. 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: (1) It is computationally less demanding.[11] (2) 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.[15,16] (3) The energies obtained from PIXEL calculation are generally comparable with high level quantum mechanical calculations.[17,18]

Results and discussion

Ethyl-2H-benzopyran-2-oxo-3-carboxylate (M-1)

Molecular pairs of M-1 (a-i) extracted from crystal structure along with their respective interaction energies are shown in Fig. 2. The maximum stabilization to the crystal structure comes from C–H…π intermolecular interaction involving H12 with C8 and C9 of Cg2 (where Cg2 is the centroid of benzene ring) and C-C molecular stacking forming dimer related by centre of symmetry. The stabilization energy of the pair is -10.25 kcal mol^{-1} (Fig. 2a) obtained using PIXEL.

Another molecular pair (Fig. 2b) involves molecular stacking to generate dimers across the centre of symmetry having an interaction energy of -8.41 kcal mol^{-1}. The next two stabilized pairs show the presence of bifurcated

C-H…O hydrogen bonding. Motif c involves bifurcated donor atom H8 interacting with O1 and O2 (Fig. 2c) whereas in motif d, acceptor atom O2 (interacting with H6 and H7) and donor atom H6 (interacting with O2 and O3) is bifurcated (Fig. 2d). The stabilization energy of the two pairs being -7.05 kcal mol^{-1} and -4.73 kcal mol^{-1} respectively and the stabilization mainly comes from the coulombic component (Table 3). Motif e shows the presence of C–H…π (involving H13 and C6 of Cg2 ring) and provides stabilization of -2.08 kcal mol^{-1} (Fig. 2e). Additional stabilization to the structure comes from molecular pair (Fig. 2f) showing the presence of C-H…H-C (involving H5 and H13) with H…H distance being 2.478 Å, forming dimer having an interaction energy of -1.98 kcal mol^{-1}. Molecular pairs g, h and i having interaction energies -1.79, -1.38 and -1.31 kcal mol^{-1}, respectively, also contribute towards the stability of crystal packing.
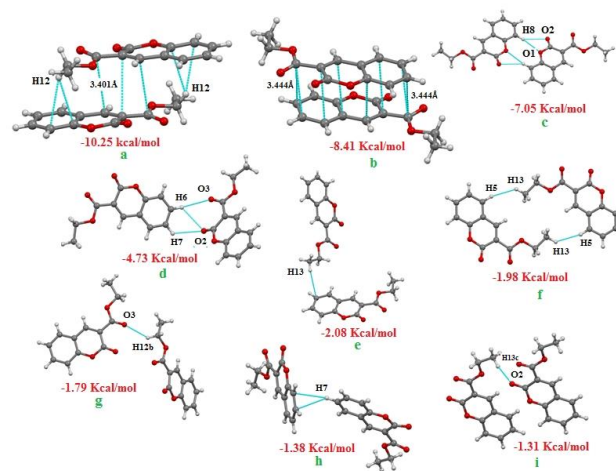

Figure 2. Molecular pairs (a-i in Table 3) along with their interaction energies calculated with Pixel (values in red) in M-1.

Ethyl-6-chloro-2-oxo-2H-chromene-3-carboxylate (M-2)

The extracted molecular pairs (a-f) of M-2 are shown in Fig.3 along with their stabilization energies. The most stabilized molecular pair in M-2 shows the presence of bifurcated acceptor C-H…O hydrogen bonding (involving O3 with H4 and H5) forming dimers related by centre of symmetry with an interaction energy of -10.27 kcal mol^{-1} (Fig. 3a) and the interaction is mainly coulombic in nature (Table 3). The next most stabilized pair involves C=O…π and C–H…π intermolecular interaction, involving O3 with Cg1(centre of gravity of pyrone ring) and H12a with Cg2 (centre of gravity of benzene ring) and hence form dimer having an interaction energy of -10.04 kcal mol^{-1} (Fig. 3b). The combined nature of these interactions is mainly dispersive in nature (Table 3). Molecular pair c shows the presence of C-H…O interaction involving bifurcated acceptor atom O2 with H7 and H8 and donor atom H13a with O1 resulting in a stabilization energy of -5.73 kcal mol^{-1} (Fig. 3c). Another C-H…O (involving H4 and O2) interaction generates a molecular pair having an interaction energy of -4.8 kcal mol^{-1} (Fig.3d). Another molecular pair (Fig. 3e) involves the interaction of carbon atom C2 of carbonyl bond of Cg1 with chlorine atom Cl1 of another molecule with C…Cl distance being 3.456Å.

Table 3. PIXEL interaction energies (I.E.) (kcal/mol) 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			
a	3.788	-4.66	-1.649	-4.756	7.98	-10.25	2-x,-y,2-z	C12-H12…π, stacking
b	4.237	-3.18	-1.12	-12.78	8.65	-8.41	1-x,-y,2-z	Stacking
c	8.117	-4.92	-1.36	-3.44	2.67	-7.05	1-x,-y,1-z	C8-H8…O1, C8-H8…O2
d	9.188	-3.25	-0.95	-2.605	2.08	-4.73	1-x,1/2+y,1.5-z	C6-H6…O2, C6-H6…O3, C7-H7…O2
e	9.366	-0.54	-0.21	-2.05	0.74	-2.08	2-x,-1/2+y,2.5-z	C13-H13…C6(π)
f	8.722	0.19	-0.597	-3.94	2.36	-1.98	2-x,-y,3-z	C5-H5…H13-C13
g	8.513	-0.43	-0.88	-2.007	1.52	-1.79	x,1/2-y,-1/2+z	C12-H12b…O3
h	9.494	-0.09	-0.33	-2.31	1.36	-1.38	x,-1/2-y,1/2+z	C7-H7…π
i	8.737	-0.64	-0.19	-0.59	0.12	-1.31	x,y,1+z	C13-H13c…O2
					M-2			
a	6.251	-8.84	-2.72	-6.91	8.22	-10.27	2-x,-y,1-z	C4-H4…O3, C5-H5…O3
b	4.463	-3.72	-1.69	-13.69	9.05	-10.04	1-x,-y,1-z	C11=O3… Cg1, C12-H12a…Cg2
c	8.787	-3.89	-1.17	-4.08	3.41	-5.73	-x,1/2+y,1/2-z	C7-H7…O2, C8-H8…O2, C13-H13a…O1
d	5.798	-1.05	-0.78	-5.4	2.44	-4.8	-1+x,y,z	C4-H4…O2
e	7.569	-0.382	-0.525	-5.97	2.92	-3.97	1-x,1/2+y,1/2-z	C6-Cl1…C2=O2
f	13.070	-0.47	-0.215	-2.46	1.21	-1.96	x,-1+y,z	C12-H12b…Cl1, C13-H13c…Cl1
					M-3			
a	6.437	-8.67	-2.6	-7.07	7.88	-10.46	2-x,-y,1-z	C4-H4…O3, C5-H5…O3
b	5.437	-3.75	-1.60	-13.26	8.55	-10.06	1-x,-y,1-z	C11=O3… Cg1, C12-H12a…Cg2
c	9.147	-3.91	-1.19	-4.08	3.37	-5.80	-x,1/2+y,1/2-z	C7-H7…O2, C8-H8…O2, C13-H13a…O1
d	5.843	-1.05	-0.78	-5.37	2.53	-4.68	1+x,y,z	C4-H4…O2
e	7.59	-0.54	-0.43	-5.73	2.89	-3.8	1-x,-1/2+y,1/2-z	C6-Br1…C2=O2
f	13.207	-0.50	-0.167	-2.22	1.12	-1.76	x,1+y,z	C12-H12b…Br1, C13-H13c…Br1
					M-4			
a	4.906	-6.59	-2.31	-14.77	12.97	-10.71	2-x,-y,1-z	π… π , C14-H14…O3
b	4.726	-3.991	-1.745	-15.6	10.8	-10.54	1-x,-y,1-z	π… π , C14-H14…O4
c	9.037	-4.25	-1.57	-5.8	4.34	-7.26	-1/2+x,1/2-y, 1/2+z	C13-H13…O5, C12-H12…O5, C14-H14a…O4, C14-H14b…O2
d	7.194	-4.37	-1.72	-4.63	3.53	-7.19	1.5-x, -1/2+y, 1/2-z	C4-H4…O3, C5-H5…O3, C12-H12…O2
e	8.830	-0.07	-0.215	-1.5	0.76	-1.07	1/2-x,1/2+y, 1/2 -z	C13-H13…C5
f	12.228	0.12	-0.26	-1.81	0.95	-1.003	1.5-x, -1/2+y,1.5-z	C14-H14…π, C6-H6…C14

Cg1- centre of gravity of pyrone ring (O1-C2-C3-C4-C10-C9); Cg2- centre of gravity of benzene ring (C5-C6-C7-C8-C9-C10)

The stabilization energy of the pair is -3.97 kcal mol⁻¹ with major contribution from dispersion component (Table 3). Finally the least stabilized pair involves bifurcated C-H…Cl (involving Cl1 with H13c and H12b) interaction having an interaction energy of -1.96 kcal mol⁻¹ (Fig.3f).
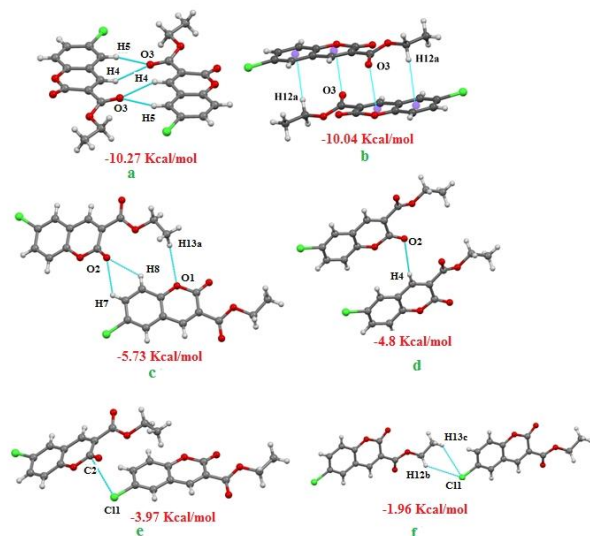

Figure 3. Molecular pairs (a-j in Table 3) along with their interaction energies calculated with Pixel (values in red) in M-2.

Ethyl 6-bromo-2-oxo-2H-chromene-3-carboxylate (M-3)

Molecular pairs (a-f) extracted from M-2 along with their respective interaction energies are shown in Fig. 4. The only difference between M-2 and M-3 is the presence of different halogen atom (Br in place of Cl). The packing features of M-3 were almost similar to those observed for M-1 and results in the generation of similar packing motifs. The energy of molecular pairs involving bifurcated C-H…O hydrogen bond (Fig. 4a,c) of M-3 were similar to those observed in M-1(Table 3).
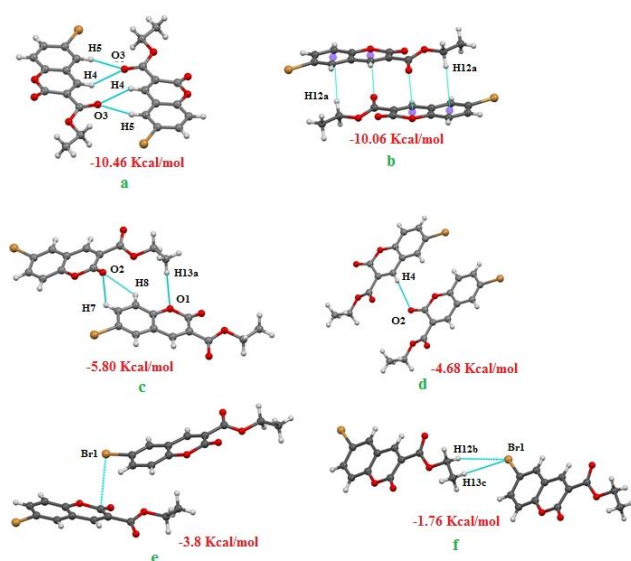

Figure 4. Molecular pairs (a-f in Table 3) along with their interaction energies calculated with Pixel (values in red) in M-3.

An important striking feature is that an interaction in which Cl is involved in M-2 is replaced by the similar interaction with Br in M-3. The molecular pairs in which Br1 is involved are motifs e and f with their stabilization energies being -3.8 and -1.76 kcal mol⁻¹ and are dispersive in nature.

Ethyl 8-methoxy-2-oxo-2H-chromene-3-carboxylate (M-4)

The molecular pairs (a-f) which provide maximum stabilization to the packing in M-4 are shown in Fig. 5. The two most stabilized pairs (a and b) show the presence of π…π interaction, a packing feature which is not observed in M-1, M-2 and M-3. Molecules in both the motifs are arranged in antiparallel manner and show the presence of double ring stacking (Cg1-Cg2). Along with this interaction both the pairs also involve C-H…O interaction and hence forming dimers(Fig. 5a,b) having stabilization energies of -10.71 and -10.54 kcal mol⁻¹ respectively. The combined nature of these interactions is mainly dispersive in nature. Molecular pair c involves the interaction of bifurcated acceptor atom O3 with H13 and H12. This pair also involves the interaction of H14a with O4 and H14b with O2 and hence resulting in a total stabilization energy of -7.26 kcal mol⁻¹ (Fig. 5c). The next stabilized interacting pair also interacts via C-H…O interaction (involving bifurcated acceptor atom O3 with H4 and H5 and O2 with H12) with an interaction energy of -7.19 kcal mol⁻¹ (Fig. 5d). Molecular pairs e and f having an interaction energy -1.07 and -1.003 kcal mol⁻¹ respectively provides additional stabilization to the crystal structure.
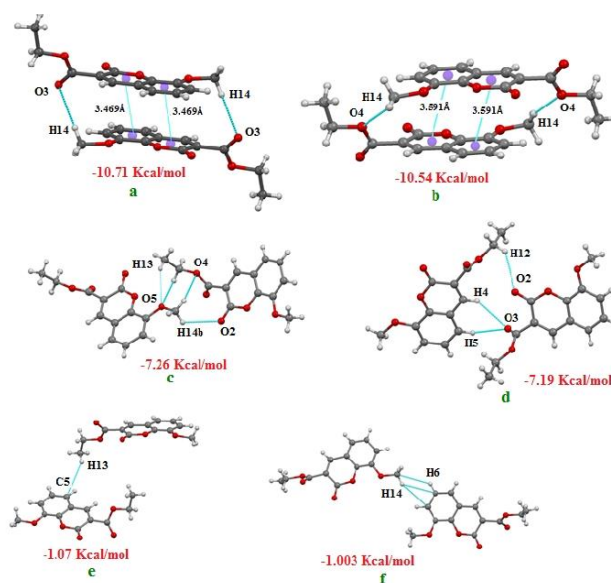

Figure 5. Molecular pairs (a-f in Table 3) along with their interaction energies calculated with Pixel (values in red) in M-4.

Conclusions

The field of investigation of the crystal and molecular structures has advanced to an extent wherein it is possible to exploit the role of weak intermolecular interactions which aid crystal packing. PIXEL calculations suggest the presence of different key structural motifs which aid in the

stabilization of crystal packing. Analysis of different structural motifs shows that C-H…O and π…π intermolecular interactions are the major contributors that stabilizes the crystal paking in addition to C-H…π and C-H…X (Cl or Br). It is of interest to extend such studies in other complex structures which will enable to exploit the role of intermolecular interactions.

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