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# Intramolecular resonance assisted $N-H\cdots O=C$ hydrogen bond and weak noncovalent interactions in two asymmetrically substituted geminal amido-esters: Crystal structures and quantum chemical exploration



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# ABSTRACT

asymmetrically substituted geminal amido-esters, namely ethyl (2E)-2-[(2,5-dimethoxy Two phenyl)carbamoyl]-3-[(4-nitrophenyl)amino] prop-2-enoate (I) and ethyl (2E)-2-[(9,10-dioxo-9,10dihydroanthracen-1-yl)carbamoyl]-3-(phenylamino) prop-2-enoate (II) were synthesized and the nature and strength of intramolecular resonance assisted hydrogen bond (RAHB) and non-RAHB was studied. X-ray analysis revealed that intramolecular N-H···O, and C-H···O interactions lead to the formation of angularly fused pseudo tricyclic (A-C) motif in compound I and fused pseudo pentacyclic (A-E) motif in compound II. Intramolecular RAHB; non-RAHB interactions are characterized and quantified by Bader's quantum theory of atoms-in-molecules approach (QTAIM). In both compounds, ring A was found to exhibit intramolecular RAHB characteristics. Crystal structures of I and II are stabilized by weak intermolecular C-H···O, C-H··· $\pi$ , and  $\pi \cdots \pi$  interactions. Intermolecular interaction energies for different molecular dimers in I and II have been quantified by using the PIXEL, QTAIM, and DFT methods. The pseudoring stacking interaction is observed only in compound II whereas no such stacking interactions are seen in compound I. Hirshfeld surface (HS) analysis suggested that the H···H and O···H contacts are the first and second dominant contacts in both crystal structures. The theoretical charge density analysis revealed that the C-H···O and C-H···C( $\pi$ ) interactions produce closed-shell characteristics. Further, the crystal packing of compounds I and II analyzed based on the energy frameworks.

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# 1. Introduction

Resonance-assisted hydrogen bond (RAHB) [1,2] is shorter and more robust than the classical hydrogen bond (HB), observed in the system that is conjugated with the multiple  $\pi$ -bonds in the neutral molecules. The concept of RAHB was proposed by Gilli and co-workers for the first time, using enol form of  $\beta$ -diketone compounds, and more significant developments took place in the last two decades of the 20<sup>th</sup> century [2]. As Gilli and co-workers stated, the more robust and shorter nature of the RAHB has justified that partial charges on the oxygen atom arising out of resonance of the carbonyl (C=O) group enhance the proton acceptor characteristic. As a result, both proton donor and acceptor functionalities have moved closer to each other to yield a strong HB [3]. Thus the strong stabilization energy for the RAHB arises due to the partial delocalization of the  $\pi$ -electrons [4-6]. Since the proposal on RAHB, both intramolecular and intermolecular RAHB have been extensively studied in a wide range of molecules with different kinds of O-H···O, N-H···O, O-H···N, and O-H···S interactions [1, 2,7-15]. Over the past few decades, several experimental and theoretical approaches have been explored to understand the originating point for the RAHB and its importance in the wide range of molecules established. The RAHB phenomenon has received the most attention because it drastically influenced molecular prop-

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Scheme 1. Chemical structures of symmetrically substituted geminal amido ester (1-8) studied earlier and asymmetrically substituted geminal amido ester (I and II) used in the present study.

erties, such as electronic energies, geometrical parameters, vibrational frequencies, and downfield shifted <sup>1</sup>H NMR signals [16,17]. The RAHB phenomena play a crucial role in protein folding and DNA pairing [18].

After Gilli's proposal on RAHB, different researchers proposed other possible explanations on the originating point for the RAHB. Fonseca Guerra and co-workers suggested that the donor-acceptor orbital interactions comparably dominate in the stabilization of RAHB with  $\pi$ -polarization effects (partial delocalization of the  $\pi$ -electrons) [19,20]. Further, Gora and co-workers made computational studies (valence bond and atoms-in-molecules computations) and suggested that the partial charges generated by resonance can enhance RAHB [21]. Several other theoretical approaches, such as energy decomposition analyses [22], blocklocalized wavefunction analyses [23], and coupling constants [24], suggested that the effects of RAHB originated from geometric constraints of the  $\sigma$ -framework [3]. Recently, we demonstrated the crystal packing modulation of the strength of RAHB using a series of geminal amido esters 1-8 with symmetrical substituents (Scheme 1) [25]. In our previous report, we described the effect of crystal packing on the strength of intramolecular RAHBs in symmetrically substituted amido-ester derivatives based on Xray and theoretical models with the aid of Bader's QTAIM approach [25]. Two intramolecular N-H···O hydrogen bonds (RAHB and non-RAHB) and one intramolecular C-H···O interaction generate fused pseudo tricyclic (S(6), S(6), S(6)) motifs in the symmetrically substituted geminal amido esters 1 - 8 (Scheme 1). We also noted that the strength of intramolecular RAHB (N-H···O interaction) varied in a wide range (6.9 to 11.4 kcal mol<sup>-1</sup>) due to crystal packing constraints arising out of different aromatic ring substitutions. Further, this effect was less significant for non-resonance assisted intramolecular N-H···O hydrogen bond (8.2 to 9.9 kcal mol<sup>-1</sup>). Another interesting packing motif observed in our previous study was the strong resonance-assisted pseudo ring stacking interaction and this motif acted as a basic motif in geminal amido ester derivatives [25]. Similar stacking dimers were observed between an aromatic ring and a pseudo planar five/six-membered hydrogen-bridged rings; [26,27], between two planar hydrogenbridged rings [28-31] and between two resonance-assisted hydrogen bond (RAHB) rings [2, 21,30-34].

In the present work, we synthesized two asymmetrically substituted amido ester (I and II; Scheme 1) derivatives to investigate the effect of crystal packing on the strength of N–H···O RAHB and non-RAHB and to compare the effect of symmetrical and asymmetrical substituted amido esters on the crystal packing and noncovalent interactions. We used different theoretical tools such as Hirshfeld surfaces, 2D-fingerprint plots, energy frameworks, and Bader's QTAIM framework to characterize non-covalent interactions. The energetics of different dimers observed in the crystal structures of I and II using the PIXEL method is presented. Among the amido esters I and II, Cole *et. al.* already reported the molecular hyperpolarizabilities, electron delocalization, and intramolecular charge transfer properties of compound I [35].

# 2. Experimental

# 2.1. Synthesis of compounds I and II

Compounds I and II were synthesized using the method reported earlier (Scheme 2) [25,35]. A detailed synthesis procedure for compounds I and II and their spectral data are given in supporting information.

# 2.2. Single-crystal X-ray diffraction

Single crystals of I and II were grown by slow evaporation method at room temperature. Single crystals of I were obtained from DMSO solvent, whereas single crystals of II were obtained in hexane: ethyl acetate mixture (8:2, v/v). The X-ray intensity data were collected at room temperature (296 K) on a Bruker SMART APEX II CCD diffractometer (APEX2, SAINT, and SADABS. Bruker AXS Inc., Madison, Wisconsin, USA) using Mo  $K\alpha$  radiation  $(\lambda = 0.71073 \text{ Å})$ . Both structures were solved by the direct methods using the SHELXS-2014 program [36]. All non-hydrogen atoms in  ${\bf I}$  and  ${\bf II}$  were refined by full-matrix least-squares on  $F^2$  using SHELXL-2018/3 [36]. The positions of amine H atoms were located from a difference Fourier map and refined freely along with their isotropic displacement parameters. All the remaining H atoms were placed at the calculated positions (C-H<sub>aromatic</sub> and C-H<sub>vinvlic</sub> is 0.93 Å; and other C-H=0.96-0.97 Å) using a riding model approach. In the case of methyl H atoms, they were constrained to ride on their parent atoms but were allowed to rotate about the C–C bond. The ORTEP and crystal packing diagrams were generated using the PLATON [37], and Mercury [38], respectively.

# 2.3. Structural optimization

All the quantum chemical calculations were performed using the program Gaussian16 [39]. The gas-phase structural optimization was carried out to study the conformational stability of I and II. The X-ray geometry of I and II was used as an initial model for the optimization calculation with the M06-2X/cc-pVTZ level



Scheme 2. Synthetic route for the compounds I and II.

of theory [40,41] along with the incorporation of Grimme's D3 dispersion correction [42]. Furthermore, the vibrational frequencies were calculated for both optimized molecules to confirm the proper convergence to energy minima on the potential energy surface (PES). There were no imaginary frequencies obtained from optimized molecules which indicates that the energy minima on the PES.

# 2.4. Hirshfeld surface (HS) analysis

The Hirshfeld surface (HS) and the decomposed 2D fingerprint (FP) plots were used to visually analyze the various intermolecular interactions in I and II. The HS and FP plots were generated with the aid of the CrystalExplorer17 program [43]. The energy frameworks were also obtained with the B3LYP/6-31G (d, p) level of theory.

# 2.5. PIXEL energy calculation

Lattice energies for **I** and **II** and the intermolecular interaction energies for molecular pairs in these crystal structures were calculated by the CLP package (version 12.5.2014) with the PIXELC module [44]. For the PIXEL calculation, the electron density for these molecules has been calculated at the MP2/6-31G\*\* level of theory. The percentage contributions of electrostatic and dispersion energies were computed as mentioned in our studies [45-47]. Further, we also calculated dimerization energy for different molecular pairs identified from the PIXEL calculation using single-point energy with M06-2X/cc-pVTZ level of theory along with the incorporation of Grimme's D3 correction [42]. This dimerization energy was further corrected with a basis set superposition error (BSSE) using the counterpoise method [48].

# 2.6. QTAIM analysis

The topological analysis was performed with the AIMALL package [49]. The wave functions were generated at the M06-2X/ccpVTZ level of theory with Grimme's dispersion correction (D3) from normalized isolated molecules (monomer) and molecular pairs (dimer). The selected topological parameters such as electron densities ( $\rho$ ), the Laplacian of the electron density ( $\nabla^2 \rho$ ), local potential energy density (V), kinetic energy density (G), and total electronic energy density (H = V+G) at the bond critical points (BCP's) were used to quantify the strength of intra- and intermolecular interactions. Moreover, the dissociation energy ( $D.E_{int}$ ) for a non-covalent interaction was calculated using an empirical formula proposed by EML [50].

# 3. Results and discussion

# 3.1. Synthesis, structural description and conformational analysis

Compounds I and II were synthesized as shown in Scheme 2, and these compounds were characterized by IR, NMR, and singlecrystal X-ray diffraction techniques. The <sup>1</sup>H and <sup>13</sup>C–NMR spectra of I and II are provided in the supporting information (SI, Figures S1-S4 and Table S1). It should be mentioned that a broad downfield peak appeared at ~  $\delta$  12 *ppm* for the N–H<sub>aniline</sub> in both compounds. This downfield shift for N–H<sub>aniline</sub> is due to the formation of RAHB (N1–H1<sub>N</sub>···O=C<sub>anilide</sub>, Fig. 1) as observed in symmetrically substituted geminal amido esters [25]. A brief discussion on various characteristic peaks in the <sup>1</sup>H and <sup>13</sup>C–NMR spectra are discussed under the NMR characterization section in the supporting information.

As shown in Fig. 1, the aniline ring (ring 1), anilide ring (ring 2), and ester components are common moieties in compounds I and II, and these moieties are interconnected *via* a central olefinic (C=C) double bond. However, rings 1 and 2 contain different substitutions (asymmetrically substituted) in both compounds. In I, the 4–NO<sub>2</sub> group is substituted in ring-1 whereas as 2, 5–OCH<sub>3</sub> groups in ring-2. In compound II, the phenyl ring in ring-2 is replaced by 1-AAQ moiety. Both compounds crystallize in the monoclinic crystal system with the  $P2_1/c$  space group. The crystal data and crystallographic refinement statistics are summarized in Table S2. The ORTEP diagrams of I and II along with the atom-numbering scheme, and aniline, anilide, and ester components are highlighted with a different colour in Fig. 1.

A slightly twisted molecular conformation is observed for structures I and II. This molecular twist is confirmed using two torsion angles (C7–N1–C1–C2,  $\tau_1$ ; and C9–N2–C10–C15/C11,  $\tau_2$ ) which describe the rotation of rings 1 and 2 (Table 1). In the case of compound, I, the enantiomerically related structure was used to compare the conformation. Compound 1 in Scheme 1, containing unsubstituted phenyl ring on both the sides, *i.e.* ring-1 and ring-2, in the symmetrically unsubstituted geminal amido-ester was taken for comparison and referred to as the parent compound. Both  $\tau_1$ and  $\tau_2$  angles deviated ~20° from each other and a similar trend is



Fig. 1. ORTEP diagrams for the compound I and II are drawn at the 50% probability level. Aniline (blue), anilide (purple), and ester moiety (orange) are highlighted with three different colors, and rings and pseudo rings are also labeled. The intramolecular interactions (N/C-H···O) are shown in dashed lines.



**Fig. 2.** Structural overlay diagrams, (a, b) crystal structure and their optimized molecule of **I** and **II**; (c) crystal structure overlay of compound **I** and parent compound (compound 1 in Scheme 1, containing unsubstituted phenyl ring on both the sides, was taken for comparison and referred to as the parent compound); (d) crystal structure of **II** and parent compound [Colour codes: green: carbon atoms in **I** and **II** crystal structures; purple: carbon atoms in the optimized molecules; gray: carbon atoms in the parent compound].

Table 1

Selected	torsion	angle	$(\theta, \circ)$ .
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Torsion	Ip	II <sup>a</sup>	Parent
C7-N1-C1-C2 (τ <sub>1</sub> )	160.81(19)	179.2(3)	157.93(13)
C9-N2-C10-C15/C11 (τ <sub>2</sub> )	-3.1(3)	19.5(4)	18.3(2)

<sup>a</sup> C9-N2-C10-C11( $t_2$ )

<sup>b</sup> Enantiomerically related molecule

also noticed when compared to the parent compound. The structural overlay diagram shows different combinations of structures including the optimized molecule of I and II (Fig. 2). The RMSD between the X-ray and the optimized molecule of I is 0.02 Å and 0.19 Å for II. These lower RMSD values indicate both experimental and theoretical structures are in good agreement. However, a slight structural deviation is around bulky substituents. 3.2. Resonance and non-resonance assisted intramolecular  $N-H\cdots O$  hydrogen bonds and intramolecular  $C-H\cdots O$  interactions

Intramolecular N1–H1<sub>N</sub>···O1(pseudo ring A), N2–H2<sub>N</sub>···O2 (pseudo ring B), and C15–H15···O1 (pseudo ring C) interactions formed an angularly fused three pseudo S(6), S(6), S(6) ring motif in compound **I**, whereas in compound **II** fused five pseudo S(6), S(6), S(6), S(6), S(5) ring motifs generated *via* intramolecular N1–H1<sub>N</sub>···O1(pseudo ring A), N2–H2<sub>N</sub>···O2 (pseudo ring B), C15–H15···O1 (pseudo ring C) N2–H2<sub>N</sub>···O4(pseudo ring D), and C7–H7···O3 (pseudo ring E) interactions were observed. Among these fused pseudo ring motifs in both the compounds **I** and **II**, ring A with S(6) motif, displayed RAHB due to intramolecular N1– H1<sub>N</sub>···O1 interaction similar to what was observed in our earlier study [25]. The RAHB nature of the pseudo ring motif was assessed by the method proposed by Gilli *et al* [2]. These authors

### Table 2

The selected intranuclear distances in the two fused S(6) motifs in I and II.

	Bond length ir	ı Å							
	d1: C7–N1	d2:C7=C8	d3:C8-C9	d4:C9=01	q1	q2	Q=q1+q2	λ	
N1-H	$1N \cdots 01$ interact	ion							
I II	1.3224 1.3224	1.377 1.377	1.469 1.469	1.238 1.238	0.092 0.079	-0.100 -0.078	-0.008 0.001	0.51 0.50	
N2-H2	2N···O2 interact	ion							
	d1: C9-N2	d2:C8-C9	d3:C8-C16	d4:C16=O2	q1	q2	Q=q1+q2	λ	
I II	1.352 1.369	1.466 1.458	1.467 1.448	1.219 1.219	0.133 0.150	-0.001 0.010	0.132 0.160	0.29 0.25	

q1= d1-d4; q2=d2-d3;  $\lambda = (1-Q/0.320)/2$ 

#### Table 3

Selected topological parameters for intramolecular interactions observed in the asymmetric units of I and II. Rij: Bond path,  $\rho$ : electron density (e Å<sup>-3</sup>),  $\nabla^2 \rho$ : Laplacian electron density (e Å<sup>-5</sup>), V: potential energy density (a.u.); G: kinetic energy density (a.u.). D.E<sub>(int)</sub>: dissociation energy =-V × 0.5 (kcal mol<sup>-1</sup>).

Atoms	Rij	ρ	$ abla^2 ho$	V	G	Н	DE(int)	$\left \frac{-V}{G}\right $
I								
$H1_N \cdots O1$	1.804	0.2844	3.4302	-0.04240	0.03899	-0.00341	13.30	1.09
$H2_N \cdots O2$	1.851	0.2429	3.3413	-0.03465	0.03492	0.06957	10.87	0.99
H15…01	2.228	0.1292	2.03063	-0.01388	0.01747	0.00359	4.36	0.79
II								
$H1_N \cdots O1$	1.847	0.2493	3.3408	-0.03516	0.03316	-0.00200	11.03	1.06
$H2_N \cdots O4$	1.920	0.2174	3.2279	-0.02972	0.03160	0.00188	9.33	0.94
$H2_N \cdots O2$	2.068	0.1674	2.6471	-0.02033	0.02390	0.00357	6.38	0.85
H7…03	2.407	0.1348	2.5258	-0.01790	0.02205	0.00415	5.62	0.81
H11…01	2.217	0.1369	2.1642	-0.01516	0.01881	0.00365	4.76	0.81

use  $\lambda$  value calculated from the bond lengths of the RAHB ring to differentiate between RAHB and non-RAHB. The fully delocalized keto form of enol ring (RAHB) has a  $\lambda$  value of 0.5 and the lower value  $\lambda$  (in the range of 0.25-0.29) indicates the non-RAHB nature (Table 2).

Further, the nature and strength of RAHB and non-RAHB interactions in I and II were explored using Bader's QTAIM calculations. The strength of the RAHB (N1–H1<sub>N</sub>···O1) interaction is stronger compared to non-RAHB (N2-H2<sub>N</sub> $\cdots$ O2, N2-H2<sub>N</sub> $\cdots$ O4), and C-H···O (C15-H15···O1, C7-H7···O3) interactions. The strength of RAHB (N1-H1<sub>N</sub>···O1) interaction falls in the range of 11.03 to 13.30 kcal mol<sup>-1</sup> and these values are comparable with related geminal amido-ester derivatives [25]. The interaction energies (D.E.int) were calculated using an empirical formula as proposed earlier [50]. The positive value of Laplacian ( $\nabla^2 \rho > 0$ ), H < 0, and |-V/G| > 1 suggested that the RAHB, N1-H1<sub>N</sub>···O1 hydrogen bond shows the intermediate bonding character between shared and closed-shell interaction (Table 3). The dissociation energy of non-RAHB interactions particularly, N2–H2<sub>N</sub>···O2, N2–H2<sub>N</sub>···O4 lies between 6.38 and 10.87 kcal mol<sup>-1</sup>. The positive value of Laplacian ( $\nabla^2 \rho > 0$ ), H > 0 H and |-V/G| < 1 suggesting closed-shell nature of non-RAHB's (Table 3). The strength of intramolecular C-H···O interactions are in the range of 4.36 to 5.62 kcal mol<sup>-1</sup>, and these interactions are also closed-shell in nature as observed in the symmetrically substituted amido-ester derivatives [25].

To assess the role of crystal packing on the strength of intramolecular interactions, we performed QTAIM calculation for the optimized structures of **I** and **II**. The selected topological parameters for the intramolecular interactions at the gas-phase optimized molecules are given in Table S3. The molecular graphs showing the intramolecular interactions are illustrated in Fig. S5. It should be noted that the intramolecular C7–H7…O3 is absent in an optimized molecule (Table S3) which is due to the crystal packing effect. From Tables 3 and S6, the topological parameters and the strength of RAHB and non-RAHB interactions are comparable in the crystal structure and optimized molecule. This result suggests that the asymmetric substituents in geminal amido-ester do not alter the strength of the RAHB and there is no effect of crystal packing modulation on the strength of RAHB. However, as reported by us earlier, in the case of the geminal amido-esters with symmetrical substituents, the crystal packing played a significant role in the modulation of the strength of RAHB [25].

# 3.3. Hirshfeld surface (HS) analysis

The HS analysis is a wonderful visualization tool to analyze the intermolecular interactions in the crystal packing [51]. An extensive HS analysis was carried out to qualitatively analyze various intermolecular interactions in **I** and **II**.

The potential short (less than the sum of vdW radii of interacting atoms) intermolecular interactions show red spots on the HS (Fig. 3) and these contacts are also labeled in Table 4. There are five such short inter-contacts observed in I whereas four intercontacts in the case of II. Further, a pattern of convex blue and concave red triangles (highlighted with the circle in SI figure in Fig. 3) is present in II which indicated the existence of  $\pi$ -stacking interaction. No such pattern is observed in I, suggesting the existence of no significant  $\pi$ -stacking interaction.

The fingerprint plots (FP; Fig 4a-b) reveal that the H···H contacts are predominant in both crystal structures with the contribution being in the range of 39.1– 44.4 % to the total HS area. The characteristic sharp spike for H···H contacts located at  $d_i+d_e \approx$ 1.8 Å in **II** and a blunt spike rather than sharp spike is observed for at  $d_i+d_e \approx 2.2$  Å in **I**. A remarkable difference (11.3%) is noticed in the contribution of O···H/H···O contacts in **I** and **II** (Fig. 4c). The variation in the contribution could be due to the presence of



Fig. 3. Two different orientations of HS mapped with  $d_{norm}$  and shape index (SI) for I and II.

#### Table 4

Intermolecular interaction energies (in kcal mol<sup>-1</sup>) are obtained from the PIXEL and DFT methods for various molecular dimers observed in the crystal structure of I and II.

		Geometry (Å/°) <sup>a</sup>				-	-	- b	_	_		HS	
Motif	Possible Interactions	$d(H \cdots A)$	$d(D{\cdots}A)$	$\angle$ D-H···A	Symmetry	CD(A)	E <sub>coul</sub>	Epol	Edisp	Erep	Etot	Δ E <sub>cp</sub> <sup>c</sup>	Label
	Compound I												
M <sub>1</sub>	C2-H2···05-N	2.53	3.327	130	x, y, 1+z	6.983	-5.4	-2.5	-16.3 (67)	10.2	-14.0	-16.9	1
	C6-H601=C9	2.68	3.254	113									
	C20-H20A···O1=C9	2.62	3.640	156									
	C18-H18C…O6	2.72	3.603	138									
$M_2$	C7···C3		3.355(3)		-x, 1-y, -z	7.861	-0.9	-1.2	-13.9 (87)	7.1	-8.9	-11.8	2
	C16…04		3.211										3
M <sub>3</sub>	C6-H6···05-N3	2.69	3.399	123	-x, 1-y,1-z	12.778	-3.8	-1.4	-7.0 (57)	4.8	-7.5	-8.4	
	C5-H5···C5	2.77	3.469	122									
$M_4$	C12-H12…06-C11	2.44	3.476	160	x,1/2-y, -1/2+z	9.225	-2.7	-1.3	-8.8 (69)	6.2	-6.6	-7.6	4
	C19-H19A…O2=C16	2.68	3.726	163									
	C13-H13…Cg2	2.83	3.684 (2)	138									
$M_5$	C20-H20B···O2=C16	2.55	3.532	150	1+x, y,1+z	10.671	-2.2	-0.9	-4.5 (59)	2.4	-5.2	-4.8	5
	C17-H17B···O7	2.66	3.437	128									
M <sub>6</sub>	C3-H3···04-N3	2.78	3.247	106	–1–x,1–y, –z	13.392	-1.7	-0.8	-4.2 (63)	3.1	-3.6	-3.8	
M <sub>7</sub>	C17–H17A···Cg1	2.97	3.860	139	1+x, y, z	9.363	-0.5	-0.4	-4.2 (82)	1.9	-3.2	-3.5	
	Compound II												
M <sub>8</sub>	C2-H2···02=C24	2.68	3.408	124	-x, y+1/2, -z+1/2	5.036	-6.6	-2.4	-26.3 (75)	17.5	-17.9	-25.9	6
	Stacking interactions												
	Cg <sub>RAHB</sub> Cg <sub>RAHB</sub>		3.996										
	Cg1···Cg2		3.704										
	Cg1···Cg4		3.888										
M9	C20-H20····O4=C22	2.59	3.292	1212	-x, 1 –y, -z	8.860	-2.5	-1.5	-10.5 (72)	5.6	-8.9	-9.00	
M <sub>10</sub>	C19-H19…01=C9	2.70	3.482	129	x, 1/2 -y, 1/2+ z	11.423	-2.4	-1.6	-7.3 (65)	5.3	-6.0	-4.7	7
	C3-H302=C24	2.64	3.680	160									
M <sub>11</sub>	C25-H25A···Cg4	2.95	3.907	147	-x, -y, -z	9.101	-1.4	-1.0	-6.4 (73)	4.5	-4.2	-4.4	8
M <sub>12</sub>	C26-H26C···05=C15	2.46	3.525	168	x-1, y, z	13.251	-0.8	-0.5	-3.8 (75)	2.3	-2.8	-2.1	9

CD: distance is the centroid-centroid of the molecules in Å;  $Cg_{RAHB}$ : the center of gravity for the resonance-assisted hydrogen-bonded ring (N1-H1<sub>N</sub>···O1/C9/C8/C7); Cg1-C2, and Cg4: the center of gravity for the phenyl rings C1-C6 (ring-1); C10-C15(ring-2) for I, and C10 – C14, and C23(ring -2) for II; and C16 – C21 (ring -4) for II, respectively. <sup>a</sup> Neutron values are given for all D-H···A interactions. <sup>b</sup> Values in parenthesis represent % dispersion energy contribution (%E<sub>disp</sub> = ((E<sub>disp</sub>/ E<sub>elec</sub>)\*100) towards the total stabilization

a greater number of O atoms in I. We also note that the short  $O \cdots H/H \cdots O$  contacts appeared at  $d_i+d_e \approx 2.4$  Å in I whereas the corresponding contacts located beyond 2.5 Å in II. The intermolecular  $C \cdots H/H \cdots C$  contacts are third significant in I-II with  $\sim 16 - 19$  %. The C-H··· $\pi$  interactions show as wings like arrangement in FP and these interactions are located around 2.6-2.7 Å in these structures. The relative contribution of  $C \cdots H/H \cdots C$  contacts is also comparable in I and II. Another difference in the relative contribution is noted for  $C \cdots C$  contacts and these contacts are higher in II compared to I. It indicates that  $\pi$ -stacking interaction exists in II.

# 3.4. PIXEL energy analysis

3.4.1. Molecular dimers in the Crystal structure of I

The PIXEL program was used to extract all possible dimers or molecular pairs from the crystal structures and these dimers are held together by different intermolecular interactions. Since the strong donating units are actively engaged in intramolecular hydrogen bonds, the weak intermolecular C-H···O, C-H···C ( $\pi$ ), and  $\pi \cdots \pi$  interactions play a key role in the stabilization of crystal structures of I and II as observed in symmetrically substituted



Fig. 4. (a-b). Decomposed two-dimensional fingerprint plots for I and II. (c) The relative contribution of various contacts in I and II.

amido esters [25]. The energetically significant dimers  $(M_1-M_7)$  in I were identified from PIXEL energy analysis and the intermolecular interaction energies for these dimers are ranging from -14.0 to -3.2 kcal mol<sup>-1</sup> (Table 4). These dimers are also depicted in Fig. S7. A most stabilized dimer,  $M_1$  is formed by three C-H···O interactions. The interaction energy  $(E_{tot})$  for this dimer is -14.0 kcal mol<sup>-1</sup>. Briefly, the O5 atom in  $-NO_2$  moiety and O1 atom in  $-C{=}O_{\text{amide}}$  group act as acceptors, and the H2, H6, and H20A atoms act as a donor for the above three  $C-H\cdots O$  interactions in  $M_1$ . Among these interactions, the C2-H2...O5 interaction links neighbouring molecules into a C(6) chain which runs parallel to the c axis (Fig. 5a). Further, this molecular chain stabilized by another two C-H···O interactions in  $M_1$  and these interactions, C6-H6···O1; and C20–H20A···O1, independently generate C(8) and C(9) motifs, respectively. At the same time, the  $R_2^2$  (14) closed-loop formed by the combination of C2-H2···O5 and C6-H6···O1 interactions, and a  $R_2^2(17)$  closed-loop formed from C6–H6···O1, and C20-H20A···O1 interactions. These closed-loops are highlighted in Fig. 5a. In addition to the above-mentioned interactions, the C18-H18C····O6 (the H···O distance is 0.01 Å longer than the sum of vWd radii) interactions provide additional support to the stabilization of dimer  $M_1$ . It is interesting to note that the strong dimer,  $M_1$ in I is totally different from other strong dimers observed in the symmetrically substituted geminal amido-esters [25]. The stacking interactions (Cg<sub>RAHB</sub>···Cg<sub>RAHB</sub>) between two RAHB's rings were observed and it was observed as the strongest dimer in the symmetrically substituted geminal amido-esters [25]. However, no such Cg<sub>RAHB</sub>...Cg<sub>RAHB</sub> stacking interaction is observed in **I**. The absence of  $Cg_{RAHB} \cdots Cg_{RAHB}$  stacking interaction in I might be due to the

arrangement of the molecules in the crystal packing and the steric hindrances of –OMe in the *ortho* position.

It is well known that the weak  $C-H\cdots O$  interactions play an important role in crystal packing of (-NO<sub>2</sub>) nitro group substituted benzene and aniline derivatives, [52] and the nitro substituted malonic acid half-ester [53]. Similar to previous studies, the oxygen atoms, O4 and O5 of the nitro group are participating in weak C-H···O interactions (dimer  $M_3$  and  $M_6$ ) in I. Briefly, one of the oxygen atoms in the nitro group act as an acceptor for the C6-H6 $\cdots$ O5 interactions in  $M_3$  and it forms a centrosymmetric  $R_2^2$  (12) closed-loop with  $E_{tot}$ : -7.5 kcal mol<sup>-1</sup>. This **M**<sub>3</sub> motif is further stabilized by C5-H5...C5 interaction. The interactions in M<sub>3</sub> motif help to connect two neighbouring molecules with tail to tail (ring-1 to ring-1, Fig. 5b) fashion. The O4 atom in -NO2 group is involved in the C3–H3···O4 interaction ( $M_6$ , the H···O distance is 0.08 Å longer than the sum of vWd radii), forms a centrosymmetric dimer with  $E_{tot}$ : -3.6 kcal mol<sup>-1</sup>. The dimer **M**<sub>3</sub> is stronger than dimer  $M_6$  and the difference in strength due to the presence of additional C-H···O/C interactions present in dimer  $M_3$ .

The O2 and O6 atoms belong to ester carbonyl (C=O<sub>amide</sub>) and methoxy (-OCH<sub>3</sub>) groups act as acceptors for the C-H···O interactions (C19–H19A···O2 and C12–H12···O6) in **M**<sub>4</sub> with  $E_{tot}$ : -6.6 kcal mol<sup>-1</sup>. These two C-H···O interactions collectively to form a  $R_2^2$ (14) closed-loop and these interactions contact neighbouring molecules with head to head (ring-2 to ring-2, Fig. S7) fashion. This head to head arrangement in **M**<sub>4</sub> is further stabilized by the C13– H13···Cg2 interaction. The ester carbonyl oxygen atom, O2, and O7 atom belongs to one of the methoxy groups act as acceptors for C20–H20B···O2 and C17–H17B···O7 interactions in **M**<sub>5</sub> with



Fig. 5. Part of the crystal packing of I (a) three C-H···O interactions (in  $M_1$ ) forms a molecular array; (b) the C6-H6···O5 (in  $M_3$ ), C20-H20B···O2 and C17-H17B···O7 (in  $M_5$ ) interactions form another molecular array. Different closed loops, 1D molecular chains, and the respective dimers are labeled and highlighted with colors.

 $E_{tot}$ : -5.2 kcal mol<sup>-1</sup>. Both C–H···O interactions in **M**<sub>5</sub> combined to form a  $R_2^2(8)$  closed-loop and these interactions link neighbouring molecules into the molecular layer which runs parallel to the crystallographic *a* axis. The two parallel **M**<sub>5</sub> molecular layers are further interconnected by the C6–H6···O5 interaction (**M**<sub>3</sub>) and form a molecular array along *ab* plane (Fig. 5b). It should be mentioned that all the dimers in **I** are predominantly dispersive in nature with >57 % of contribution towards the stabilization of these dimers. Among them, the **M**<sub>2</sub> (87 %) and **M**<sub>7</sub> (82 %) dimers have the highest dispersion energy contribution could be due to the presence of C···C and C···H contacts existing in these dimers.

As shown in Fig. 6, the molecules of I form the zigzag double layers in head to head (ring-2 to ring-2) and tail to tail (ring-1 to ring-1). The head to head (ring-1 to ring-1) groups are interconnected by the interactions in  $M_4$ , and tail to tail (ring-1 to ring-1) groups are in contact by interactions in  $M_2-M_3$  and  $M_6$  dimers. The C20-H20B···O2 and C17-H17B···O7 in  $M_5$  and C17-H17A···Cg1 ( $M_5$ ;  $E_{tot}$ : -3.2 kcal mol<sup>-1</sup>) interactions link two neighbouring zigzag double layers. The up and down double layers are connected by the C-H···O interactions in  $M_1$ . Overall, the molecules of I are packed as typical herringbone architecture along the crystallographic ab plane (Fig. 6)

# 3.4.2. Molecular dimers in the crystal structure of II

Five energetically significant molecular pairs ( $M_8-M_{12}$ ) were extracted from the crystal packing of II using PIXEL energy analysis (Table 4, Fig. S8). Among them, the most stabilized dimer in II is formed by the molecular stacking interaction (Cg1...Cg2 and Cg1...Cg4) and further supported by the C2–H2...O2 interactions with  $E_{tot}$ : -17.9 kcal mol<sup>-1</sup>. In this dimer, the Cg<sub>RAHB</sub>...Cg<sub>RAHB</sub> interaction is also formed between two pseudo-RAHB *S*(6) ring motifs. The strength of this dimer is comparable to that of similar dimers observed in symmetrically substituted geminal amidoesters [25]. One of the oxygen atoms, O4 of C=O<sub>AAQ</sub> group acts as an acceptor for the C20–H20...O4 interaction in  $M_9$ . This interaction links two neighbouring AAQ moiety using inversion symmetry and forms a centrosymmetric  $R_2^2$  (10) closed-loop with  $E_{tot}$ : -8.9 kcal mol<sup>-1</sup>, see Fig. S8. Another O5 atom of C=O<sub>AAQ</sub> group involved



Fig. 6. The crystal structure of I viewed down the *c* axis.



**Fig. 7.** Part of the crystal packing of **II** (a) the C26-H26C····O5 interaction (**M**<sub>13</sub>) links neighbouring molecules into a molecular chain; (b) Two C-H···O interactions in **M**<sub>10</sub> link the neighbouring molecules into molecular arrays which run parallel to crystallographically *c* axis.

Table 5 Lattice energy (in kcal  $mol^{-1}$ ) for compounds I and II.

Compound	Ecoul	E <sub>pol</sub>	E <sub>Disp</sub>	Erep	Etot	% E <sub>Disp</sub>
I	-8.50	-14.44	-50.26	19.89	-53.32	69
II	-5.31	-12.28	-54.37	22.01	-49.95	76

as an acceptor for the C26–H26C···O5 interaction ( $M_{12}$ ) with  $E_{tot}$ : -2.8 kcal mol<sup>-1</sup>. This interaction links the neighbouring molecules into a molecular chain that runs parallel to *a* axis (Fig. 7a).

The oxygen atoms, O1 and O2, of C=O<sub>amide</sub> and C=O<sub>ester</sub> groups, respectively act as acceptors for the C19-H19····O1=C9 and C3-H3····O2=C24 interactions ( $M_{10}$ ). These two interactions collectively generate a  $R_2^2$  (21) closed-loop with  $E_{tot}$ : -6.0 kcal mol<sup>-1</sup>, and it links the neighbouring molecules into molecular arrays which run parallel to the crystallographically c axis (Fig. 7b). In addition to C-H···O interactions, the C-H··· $\pi$  interaction (C25-H25A····Cg4;  $M_{11}$ ,  $E_{tot}$ : -4.2 kcal mol<sup>-1</sup>) also make a dimer. The dispersion energy component contributes 52-75% towards the stabilization of dimers observed in II. Overall, the molecules of II are arranged as columnar architecture and it extended along the crystallographic b axis. This arrangement is favored by the C26-H26C···O5  $(M_{12})$  interaction. Further, the C19-H19···O1=C9 and C3-H3…O2=C24  $\left(M_{10}\right)$  interactions and stacking interactions in M<sub>9</sub> link the neighbouring columns into herringbone architecture which is extended parallel to the crystallographic bc plane (Fig. 8)

# 3.5. Lattice energy and topology of energy frameworks

The lattice energies for crystals **I** and **II** were calculated using the PIXEL method and the results are summarized in Table 5. The results suggest that crystal **I** is 3.4 kcal mol<sup>-1</sup> more stable than crystal **II**. In the latter crystal, there is a 7% increase in the contribution of dispersion energy component towards stabilization of crystal structure. This increasing contribution of the dispersion energy component in **II** is due to the presence of stacking interactions *i.e.* Cg<sub>1</sub>...Cg<sub>2</sub>; Cg<sub>1</sub>...Cg<sub>4</sub>; and Cg<sub>RAHB</sub>...Cg<sub>RAHB</sub> in **M**<sub>8</sub>.

We performed energy framework analysis for I and II to get further insights into interaction topology and mechanical behaviour at a molecular level [54,55]. The 3D topology of the energy framework for both structures is shown in Fig. 9. The distinct 3Dtopology was observed for compounds I and II. In I, the larger cylinders are arranged in vertical layers, while smaller cylinders are arranged in a horizontal layer. Both vertical and horizontal layers are orchestrated into a ladder-like arrangement that runs parallel to the crystallographic *b* axis. As mentioned earlier, the crystal packing of I is predominantly driven by the dispersion energy component (see Table 4). The magnitude of cylinders in the Coulomb energy component is smaller than the dispersion, and total interaction energy component. The larger cylinders in the vertical layers are representing the different interactions in  $M_2$ - $M_3$  and  $M_6$ dimers, and the smaller cylinders in the vertical layers are representing the different interactions in  $M_4$  dimers. The small and large cylinders are arranged alternately in vertical layers. Further, the smaller cylinders in the horizontal layers are representing the different interactions in M<sub>5</sub> and M<sub>7</sub> dimers. In II, the zig-zag large green and blue cylinders correspond to molecular stacking in M<sub>8</sub> dimer. The adjacent zig-zag large cylinders are interconnected by small horizontal and diagonal cylinders correspond to the different interactions in  $M_{10}$ - $M_{12}$ . These zig-zag patterns run parallel to the crystallographic b axis. Due to different substitutions in I and II, they show distinct 3D- energy topology which in turn suggesting different mechanical properties of these crystals.

# 3.6. Topological analysis of non-covalent interactions in compound ${\bf I}$ and ${\bf II}$

To evaluate the strength of various intermolecular interactions, the topological parameters at their bond critical points (BCPs) for these interactions were calculated and quantitatively analyzed. These parameters are summarized in Tables S4-S5, and the molecular graphs of various dimers are illustrated in Figs. S9-S10. There are ten weak C-H···O interactions observed in **I**. The  $\rho$ , and  $\nabla^2 \rho$  values for these C-H···O interactions are observed in the range of 0.036 – 0.068 e Å<sup>-3</sup>, and 0.46 – 0.92 e Å<sup>-5</sup>, respectively. The



Fig. 8. Crystal packing of II viewed two different orientations. All the H atoms have been omitted for clarity.



**Fig. 9.** Energy frameworks for the compound **I-II.** (a) molecular packing diagram of **I** showing the double layer arrangement (viewed down the *c* axis); (b) molecular packing diagram of **II** showing the herringbone arrangement (viewed down the *a* axis). The red, green, and blue cylinders are representing Coulomb, dispersion, and total interaction energies. The same cylinder scale of 80 used for all diagrams and the energies with magnitude <15 kJ mol<sup>-1</sup> have been omitted for clarity.

electron density value for all C-H···O interactions observed in I satisfies the Koch and Popelier limit (0.013 <  $\rho$  e Å<sup>-3</sup> > 0.236) suggested for hydrogen bonds [56]. The dissociation energies (D.E. (int)) for these interactions fall in the range of 0.90 - 1.96 kcal mol  $^{-1}$ , and the bond path distances (R<sub>ii</sub>) vary from 2.453 – 3.091 Å. The positive value of Laplacian ( $\nabla^2 \rho > 0$ ), H > 0, and |-V/G| <1 suggests that all the C-H···O interactions in I are closed-shell in nature. In II, there are six weak C–H $\cdots$ O interactions observed in different dimers. The positive electron density value, and other three parameters ( $\nabla^2 \rho > 0$ , H > 0, and |-V/G| < 1) satisfy the C–  $H \cdots O$  interactions in **II** are closed-shell bonding type. There are five C-H···C interactions observed in I-II. These C-H···C type interactions also satisfy the above conditions, and these interactions are in a closed-shell nature. The topology analysis suggested that not only C-H···O interactions, and the C-H···C type interactions also play an important role in the stabilization of these crystal structures.

# 4. Conclusions

Two asymmetrically substituted geminal amido-esters, (2E)-2-[(2,5-dimethoxyphenyl) carbamoyl]-3-[(4-nitrophenyl)amino] prop-2-enoate (I) and ethyl (2E)-2-[(9,10-dioxo-9,10dihydroanthracen-1-yl)carbamoyl]-3-(phenylamino) prop-2-enoate (II) were synthesized and intramolecular RAHB and non-RAHB and other weak non-covalent interactions observed in them were characterized. Angularly fused pseudo tricyclic ring motifs generated by intramolecular N-H···O hydrogen bonds and an intramolecular C-H···O interaction were similar in compound  ${\bf I}$  and symmetrically substituted amido-ester derivatives reported earlier. In contrast, fused pseudo pentacyclic ring motifs constructed by intramolecular N-H···O, and C-H···O interactions in compound II. The central structural motif in symmetrically substituted amidoester derivatives was derived from adjacent resonance assisted pseudoring stacking. A similar pseudoring stacking interaction was formed only in compound II. This study also demonstrated that the crystal packing did not play a larger role in the modulation of the strength of RAHB in asymmetrically substituted compounds I and II, in contrast, to symmetrically substituted counterparts. The PIXEL energy analysis suggested that compound I had slightly higher stabilization energy than compound II. The contribution of dispersion energy component towards stabilization of crystal structure in II was 7 % higher than that of compound I, arising out of stacking interactions including pseudoring stacking in II whereas no stacking interactions found in I. The theoretical charge density analysis reveals that C–H···O, and C–H···C( $\pi$ ) interactions are closed-shell in nature. The crystal packing of I and II analyzed based on the energy frameworks shows that these compounds have a different 3D topology, suggesting these compounds may have different mechanical behavior.

# Authorship contribution statement

**Perumal Venkatesan:** Conceptualization, Chemical synthesis, Investigation, Writing – review & editing. **Subbiah Thamotharan**: Conceptualization, Supervision, Investigation, Writing – review & editing. **M. Judith Percino**: Resources, Data curation, Writing- review & editing. **Andivelu Ilangovan**: Conceptualization, Chemical synthesis, Investigation, Supervision.

# **Declaration of Competing Interest**

The authors declare no potential conflict of interest.

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# Supplementary materials

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