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Synthesis, Crystal Structure Analysis, Small Cluster Geometries and Energy Study of (*E*)-Ethyl-4-(2-(thiofen-2-ylmethylene) hydrazinyl)benzoate

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Abstract Derivatives hydrazone are attributed interesting pharmacological properties. The compound under study (E)-ethyl 4-(2-(thiofen-2-ylmethylene) hydrazinyl)benzoate (**1**), crystallized from ethanol as translucent light yellow thin plates. They are monoclinic, space group $P2_1/c$, with unit cell parameters $a = 8.846(6)$, $b = 20.734(14)$, $c = 7.583(5)$ Å, $\beta = 95.743(13)°$, $V = 1383.8(16)$ Å^3. Three hydrogen bonds and two intermolecular π-interaction perpendiculars to the hydrogen bonds patterns are observed in the crystal structure. A detailed description of these interactions will be presented. Also, semiempirical calculations (PM6) show the formation in the gas phase of a supramolecular chain, emulating the C(8) graph set seen in the crystal structure of the compound.

Keywords Hydrazone · Crystal structure · Hydrogen bonds · Semiempirical calculations

Introduction

Hydrazones have shown potential medical applications due to their biological activities as antitumor, anticonvulsants, antimalarial, analgesic, anti-mycobacterial, vasodilators, anti-inflammatory, antivirals agents [1–3]. In recent works, we have studied the interaction of 2,4-dinitro-phenylhydrazones of furan and thiophene with biomolecular targets for cancer treatment such as DNA and tubulin [4, 5]. Additionally, the interaction of these compounds with water and aprotic solvents was also studied, and related with their biological activities [6]. According to these studies the hydrophobic effect, associated with the number of nitro groups on the phenyl ring, is the major driving force involved in the binding of drugs to their receptor targets [4, 5]. The hydrophobic character makes necessary the use of a co-solvent, currently DMSO, which may cause DNA damage at concentrations above 1 % (v/v) [7].

In this respect, our group was prompted to modify the structure of the above mentioned hydrazones with the aim of decreasing hydrophobicity without loss of biological activity. One strategy consists in substitute the nitro groups, responsible for the hydrophobic character, by ester groups. In this sense, we have reported the synthesis, spectroscopic, and crystallographic characterization of the (*E*)-Ethyl-4(2(thiofen-2-ylmethylene)hydrazinyl)benzoate (**1**). Additionally, in order to support the description of the supramolecular structure of crystals, a theoretical study through semiempirical quantum mechanical methods with the second-generation hydrogen-bonding correction (PM6-DH2) was carried out.

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Experimental

General Procedures and Materials

Melting point was determined on a digital IA-9100 ELECTROTHERMAL fusiometer. The IR spectrum was recorded on a Shimadzu model 8300 FTIR spectrophotometer, as KBr pellets.

Synthesis of (*E*)-Ethyl-4-(2-(thiofen-2-ylmethylene)hydrazinyl)benzoate (**1**)

In a 100 mL round bottom flask, 1.24 g (4.62 mmol) of ethyl 4-hydrazinylbenzoate hydrochloride was dissolved in 50 mL of distilled water under magnetic stirring. Then, 0.52 μL (5.54 mmol) of thiophene-2-carbaldehyde were added slowly, stirring for about 20 min after the addition of the aldehyde. The product was collected by filtration, washed with 0.1 M HCl and then with 20 % $NaHSO_3$. The product was recrystallized in EtOH as translucent light-yellow plates with melting point 186–188 °C (Scheme 1).

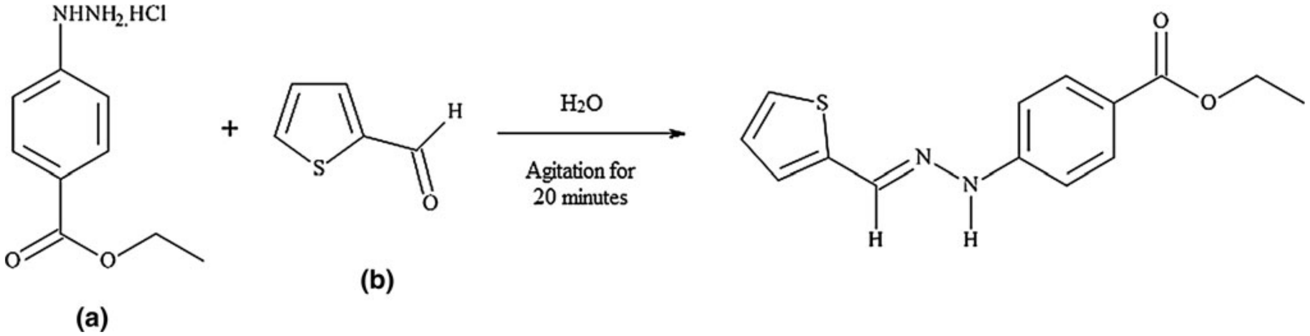
Single Crystal X-Ray Data Collection and Structure Determination

The single crystal X-ray diffraction analysis was carried out on a KAPPA APEX II DUO Diffractometer with graphite monochromator Mo-Kα radiation (λ = 0.71069 Å) operating at 50 kV and 30 mA. A thin plate of (**1**) of approximate dimensions 0.08 mm × 0.14 mm × 0.56 mm was used. A total of 2160 frames were collected with φ and ω scans' every 0.30° for 10 s each [8].

The structure was solved and refined using the Bruker SHELXTL Software Package [9]. The non-hydrogen atoms were refined anisotropically, while the hydrogen atoms bound to C atoms were placed geometrically and refined using a *riding model*, with C–H = 0.93 Å, Uiso(H) = 1.2 Ueq(C) for aryl H; C–H = 0.97 Å for methylene H; and C–H = 0.96 Å Uiso(H) = 1.5 Ueq(C) for methyl H. H atoms bound to the N atom were placed in calculated positions and refined using a *riding model* with N–H = 0.86 Å and Uiso(H) = 1.2 Ueq(N).

Semiempirical Calculations

The geometrical features and packing of molecular clusters are determined in good measure by non-covalent interactions, i.e. van-der-Waals and hydrogen bonds, between the molecules making up the clusters. As a consequence of this fact, a detailed and exact theoretical characterization of molecular clusters as those studied here involves intensive and demanding calculations and require expensive computational tasks. Nevertheless, in general, modeling these kind of complex systems is difficult to perform with such desirable high level of calculations, and frequently, approximated methods have to be employed. Among them, the semiempirical methods have been widely used [10].One of the existing limitations of the semiempirical methods has been the description of many-body interactions, which are important in accounting for the molecular polarization and charge delocalization among the cluster components and play a major role in describing cooperative effects. however, in the last few years, corrections, i. e. those required for including dispersion effects involved in non-covalent interactions, have been introduced into a wide range of semiempirical methods [10]. This fact has broadened substantially the range of applicability of these methods, in particular, making feasible their application to the description of complex systems, such as the supramolecular structures found in the organic crystals of *cis*-4-aminocyclohexanecarboxylic acid that involve head-to-tail interactions. Thus, in this work we have performed semiempirical calculations using a version of the PM6 method [11] that has implemented a second generation correction for the description of hydrogen bonds (DH2) [12]. This correction includes the dispersion effect as a pairwise interatomic force field [12]. Additionally, the energy corrections due to the presence of hydrogen bonds are



Scheme 1 Synthesis of (*E*)-Ethyl-4-(2-(thiofen-2-ylmethylene)hydrazinyl)benzoate (**1**) from ethyl 4-hydrazinylbenzoate hydrochloride (**a**) and thiophene-2-carbaldehyde (**b**) [22]

dependent on the steric donor–acceptor arrangement, defined by six internal coordinates: the H···A distance, the A···H–D and R–A···H angles, and the three torsional angles defining the relative position of the hydrogen bond.

In this work, we compute the stabilization energy due to the formation of the clusters per participating molecule, this is:

$$\frac{\Delta E}{n} = \frac{E_n - (nE_0)}{n} \tag{1}$$

Here E_n is the total energy for the cluster, E_0 is the energy of the optimized monomer, n is their number of monomers in the cluster. The calculation of ΔE allows evidencing the cooperative enhancement in the formation energy of the clusters [13]. Additionally, this quantity is well suited for extrapolations toward $n \rightarrow \infty$, which is the case of extended chains [14]. This extrapolation is useful for obtaining estimates of the stabilization energies of extended systems, as the ones considered here [15].

Results and Discussion

Spectroscopy IR and Synthesis of (*E*)-Ethyl-4-(2-(thiofen-2-ylmethylene)hydrazinyl)benzoate

This compound was synthetized from ethyl 4-hydrazinobenzoate hydrochloride (*a*) and thiophene-2-carbaldehyde (*b*) according to the procedure 2. Yield 82 %, yellow solid. m.p.186–188 °C. IR (KBr) cm^{-1}: 3273.6 (NH); 1681.8 (N=C), 1600.8 (C=C); 1365.5 (–NO_2) 1272.9 (C–S–C).

Analysis of the Crystal Structure of (*E*)-Ethyl-4-(2-(thiofen-2-ylmethylene)hydrazinyl)benzoate

The details of crystal data and refinement are given in Table 1. A search previous in the Cambridge Structural Database (CSD) [16] no produced any results. Table 2 contain relevant bond lengths and angles for this compound. Figure 1 show the molecular structure with the atom numbering scheme.

The bond distances (Table 2) within the thiophene ring and benzoate ring are consistent with aromatic delocalization. The dihedral angle between the thiophene ring and the adjacent benzoate ring is 7.368(53)°.Table 3 shows the geometrical parameters of the two intermolecular hydrogen bonds observed in the crystal structure, N2–H1···O1 (blue bond) and C5–H6···O1 (purple bond), these interactions are depicted in Fig. 2 as blue and purple dashed lines, respectively. The first one correspond to a classical intermolecular hydrogen bond, the geometric parameters for this interactions mach with the mean values observed for N–H···O interactions between similar moieties (CSD). The interaction C5–H6···O1 corresponds to a non-classical intermolecular hydrogen bond, this type interaction has been observed between similar moieties in eight reports on the CSD, of which may be mentioned,

Table 1 Crystal data and refinement for compound (**1**)

Crystal data	
Formula	$C_{14}H_{14}N_2O_2S$
Formula weight	274.34
Crystal system	Monoclinic
Space group	*P*21/*c* (No. 14)
a, b, c (Å)	8.846(6) 20.734(14) 7.583(5)
alpha, beta, gamma (deg)	90 95.743(13) 90
V (Å^3)	1383.8(16)
Z	4
D(calc) (g/cm^3)	1.317
Mu(MoKα)	0.233
F(000)	576
Crystal size (mm)	0.08 × 0.14 × 0.56
Data collection	
Temperature (K)	296
Radiation (Å)	MoKα 0.71070
Theta min–max (Deg)	2.0, 28.9
Dataset	–11:9; –27:28; –10:10
Tot., uniq. data, R(int)	21936, 3516, 0.032
Observed data [I > 2.0 sigma(I)]	2491
Refinement	
Nref, Npar	3516, 173
R, wR2, S	0.0421, 0.1256, 1.02
Max. and Av. shift/error	0.00, 0.00
Min. and max. resd. dens. [e/Ang^3]	–0.34, 0.32

Table 2 Selected bond distances (Å) and angles (°) for compound (**1**)

N1–N2	1.365(2)	C8–C9	1.3972
N1–C5	1.281(2)	C9–C10	1.3984
N2–C6	1.380(2)	C10–C11	1.3805
N2–H1	0.8600		
S1–C1	1.7167	N2–N1–C5	116.05(13)
S1–C4	1.7064	N1–N2–C6	120.99(13)
C1–C2	1.3970	C6–N2–H1	120.00
C2–C3	1.4240	N1–N2–H1	119.00
C3–C4	1.3390	N2–C6–C7	118.96(14
C6–C7	1.4010	N1–C5–C1	122.04(15)
C6–C11	1.4037	N2–C6–C11	122.00(14)
C7–C8	1.3787	N2–C6–C7	118.96(14)

Dimethyl 3-(((2,4-dinitrophenyl)hydrazono)methyl)-4-methyl-5-methylenecyclohex-3-ene-1,1-dicarboxylate, refcode EBUVUS [17] and methyl 2-(2-bromo-4,5-dimethoxyphenyl)-4-((2,4-dinitrophenyl) hydrazonomethyl)-7-methoxy-2,3-dihydrobenzofuran-3-carboxylate dichloromethane solvate, refcode QAVXER [18] and have similar geometrical parameters for the interaction C–H···O observed in the crystal structure of compound **1**. As shown in Fig. 2, the intermolecular interactions N–H···O and C–H···O are represented by the graph set symbol C(8) and C(10) respectively and these produce infinite chains along the *a* axes. The intramolecular non-classical hydrogen bond C8–H3···O2 (Table 4), observed in compound **1** can be described by the graph set symbol S(5). Compound **1**, also present two intermolecular π-interaction perpendicular to the hydrogen bonds patterns above described, this interaction involve atoms C4–H11···Cg1 [2.88 Å, 139°] and C12–O1···Cg2 [3.60 Å, 86.24°]. Cg1 and Cg2 correspond to centroid the thiophene ring and benzoate ring respectively.

The π-interaction C4–H11···Cg1 produces as parallel chains growing along the ***c*** axis. Between each chain, we observed the hydrazone molecules alternating with each other, and connected by the interaction C12–O1···Cg2 this interaction occurs between the carbonyl oxygen from a

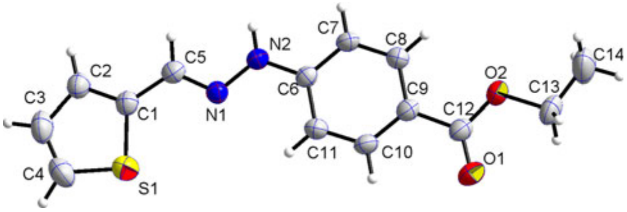


Fig. 1 Molecular structure of (*E*)-Ethyl-4-(2-(thiofen-2-ylmethylene)hydrazinyl)benzoate [21]

Table 3 Hydrogen bonds and short contacts for compound (**1**)

H–Bond	D–H	H···A	D···A	D–H–A	Symmetry	Motif
N2–H1···O1	0.86	2.16	2.986(3)	162	–1 + x,y,z	C(8)
C5–H6···O1	0.93	2.58	3.375(3)	144	–1 + x,y,z	C(10)
C8–H3···O2	0.93	2.45	2.758(3)	100		S(5)
C4–H11···Cg1	0.93	2.88	3.632(3)	139	x,–1/2–y,1/2 + z	
Short Contacts Y–X···Cg	Y–X	X···Cg	Y···Cg	Y–X–Cg	Symmetry	Motif
C12–O1···Cg2	1.3434	3.596	3.7190	86.24	1–x,–y,–z	

Cg1 is the centroid of the thiophene ring and Cg2 is the centroid of the benzoate ring

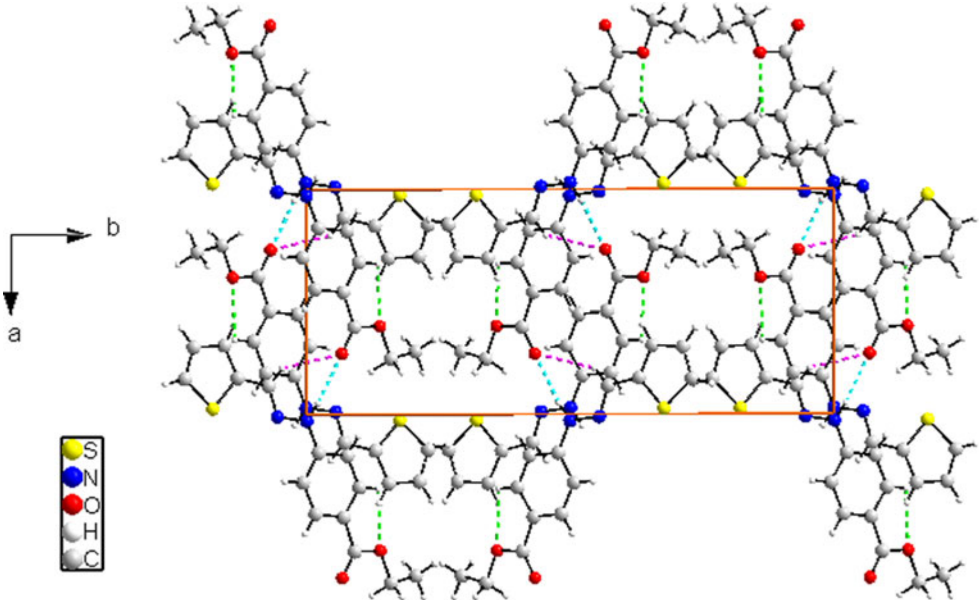


Fig. 2 View of the structure of (*E*)-Ethyl-4-(2-(thiofen-2-ylmethylene)hydrazinyl)benzoate along the *b* axes

Table 4 Average value on selected geometrical details of ethyl-4-(2-(thiofen-2-ylmethylene)hydrazinyl)benzoate clusters

Cluster	H···O (Å)	N···O (Å)	N–H···O (°)	Dihedral angle between interacting molecules (°)
2	1.892	2.874	155.9	58.1
3	1.776	2.823	151.0	46.1
4	1.861	2.847	156.3	28.3
5	2.032	2.988	150.5	2.07

molecule and the benzoate ring from a symmetry-related molecule. Between the thiophene ring and benzoate ring it's observed a π–π interaction. All this no-covalent interactions generate a packing arrangement as a parallel layers in zigzag pattern with a packing index of 67.0 % without solvent accessible voids in the structure.

A single π–π interaction between thiophene ring and benzoate ring links the molecules into pairs. The reference molecule is related by inversion to the adjacent molecules lying across the axes along (–x, –y, 1 – z). The ring centroid separations between the thiophene ring and benzoate ring from an adjacent molecule is 3.788(2) Å. Propagation of this interaction by inversion thus generates a dimers of π-stacked molecules along the [100] direction.

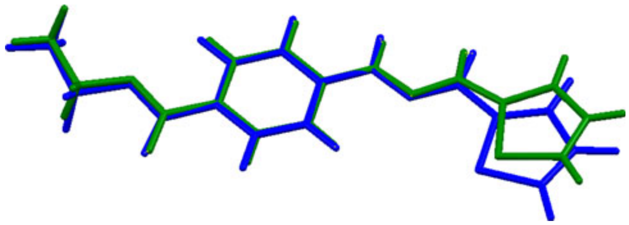


Fig. 3 Comparison of the crystal structure of (*E*)-Ethyl-4-(2-(thiofen-2-ylmethylene)hydrazinyl)benzoate (*green*) with the structure obtained from the PM6-DH2 calculations (*blue*)

Small Cluster Geometries and Energy

The geometry of the optimized monomer (blue) compared with the crystal structure (green) is exhibited in Fig. 3. The largest differences of the optimized monomer are in the thiophene and ester moieties, these differences are due to a higher planarity of the molecule in the gas phase. The calculated value for E_0 is –69451.171 kcal/mol. The optimized geometry of the dimer is found starting from optimized monomers at several intermolecular relative orientations. Once this structure was obtained, a monomer is randomly placed close to it, and optimization of the trimer is carried out. This procedure is repeated many times and the result reported corresponds to the obtained minimum having the smallest energy.

In the dimer the N···O distance is 2.874 and 0.1 Å shorter respect to distance observed in the crystal (Table 5). The molecules in the gas phase dimer displays a dihedral angle, between the two mean molecular planes, of 58.1°, while in the crystal structure, the molecular planes between two interacting molecules are almost parallel. In the trimer and the tetramer the average N···O distance are 2.823 and 2.847 Å respectively, being these about 0.14 Å shorter than in the crystal, the dihedral angles of the molecular planes between two interacting molecules are 46.1° and 28.3°. In the pentamer the N···O distance is larger than the others clusters with a value of 2.988 Å and only differs on 0.002 Å with the distance observed in the crystal, for this cluster the dihedral angle between two interacting molecules decreases to 2.07°, this decrease implies a nearing of the hydrogen atoms. These H···H contacts in the pentamer induce short repulsive interaction between molecules [19].

For the fully optimized clusters, the variation of the stabilization energy per participating molecule (ΔE) is displayed in Fig. 4a. From there, it is possible to see that, due to the creation of a HB, a sharp stabilization accompanies the formation of the dimer. Moreover, it is also observed that the bonding of new monomers increases gradually the stabilization energy per molecule. From

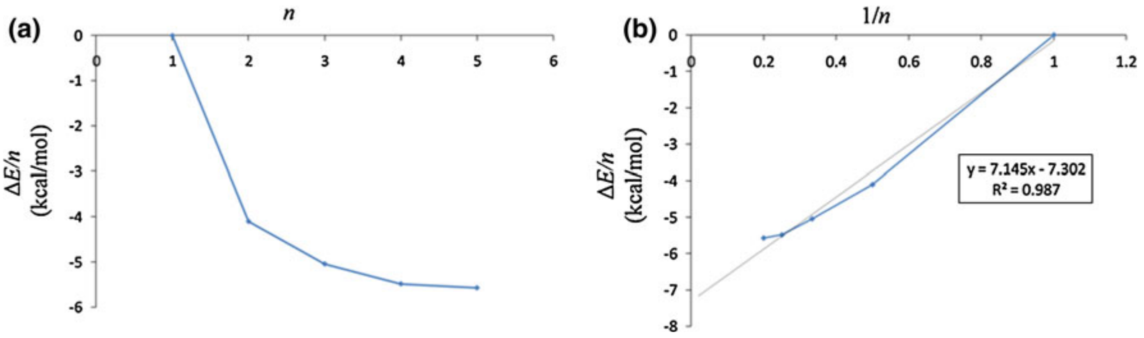


Fig. 4 **a** Variation of the stabilization energy per molecule with the number of monomers in the cluster. **b** Variation of the stabilization energy per molecule in function of the inverse of the number of monomers, 1/*n* in compound **1** clusters

Fig. 4a we can also conclude that the stabilization rate decreases with the cluster size, which should lead to an asymptotic value for the stabilization energy per molecule. At this point it is convenient to recall that simple electrostatic models predict that the stabilization energy per molecule should be constant; therefore, the additional stabilization is the result of the presence of cooperative effects, consequence of the formation of consecutives HB of the type N–H···O between the interacting molecules[20]. If the dependence of ΔE with the cluster size is considered in terms of the inverse of n, a nearly perfect linear behavior is obtained (Fig. 4b). This fact, allows us to perform an extrapolation to the asymptotic limit of an infinite chain, $n \rightarrow \infty$, which leads to an estimate of –7.30 kcal/mol for the maximum stabilization energy for the clusters. This value represents an increment of approximately 44 % in the stabilization energy respect to that of the dimer.

Supplementary material

X-ray crystallographic data for this structure has been deposited at the Cambridge Crystallographic Data Center under code CCDC 908021.

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