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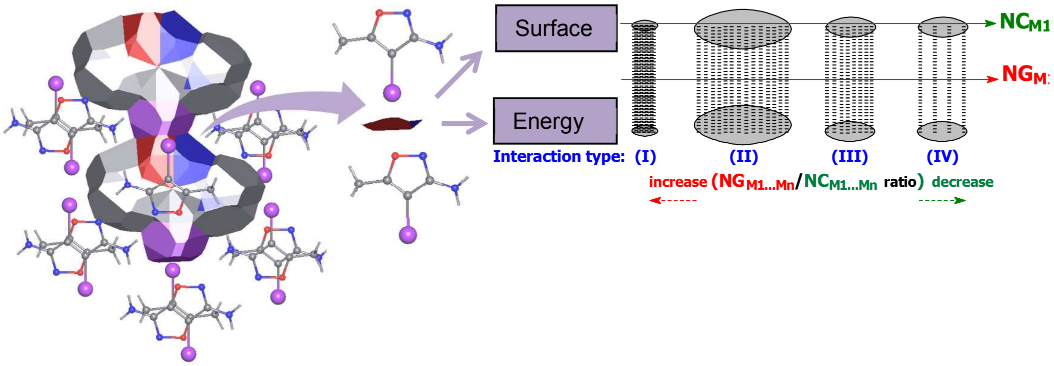
Surface
Energy
NCM1
NGM
Interaction type: (I) (II) (III) (IV)
increase (NGM1...Mn/NCM1...Mn ratio) decrease

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Energetic and Topological Approach for Characterization of Supramolecular Clusters in Organic Crystals

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In this work, an approach is proposed for understanding the crystal arrangements of organic compounds. The crystals are studied, taking into account the stabilization energy and the topological properties like contact surfaces of a molecule (M1) due to the presence of neighboring Mn (cluster). The molecular system models chosen were five heterocycles and one β-enaminone. The cluster of compounds had a Molecular Coordination Number (MCN) of 14, except for one compound that had an MCN of 16. Our study showed that intermolecular interactions can be divided into four main types: type I, with large energy values and a small contact surface; type II, involving a large value for both the energy and the contact surface; type III, with small and medium energy values, and a medium-sized contact surface; and type IV, with small energy values and a relatively large contact surface. Additionally, from this approach we show that only from the supramolecular cluster is it possible to observe the participation of the topological component during the formation of the crystal. This is demonstrated by the fact that the fragility of electrostatic interaction between M1 and one Mn in the same plane is compensated by a strong interaction of M1 with a molecule in another plane.

Introduction

Supramolecular chemistry is an intrinsically dynamic field of chemistry. The crystal design of organic molecules has been discussed as a supramolecular entity and several researchers have focused on predicting them by using theoretical data[1], or basing their results on experimental data from aggregates in solution.[2,3] While experimental results have demonstrated the existence of dimers, trimers, and even aggregates preserved in solution, theoretical results have presented a design trend applicable only to particular crystals. Thus, limited success has been achieved so far.[1]

To better understand how interactions are able to determine crystalline organization, researchers have introduced the "supramolecular synthon" concept.[4-7] Nowadays, this approach may be insufficient to explain weak interactions, since the concept seems to be limited to distances predetermined by the investigator (or software[8]) and based on the van der Waals radii. However, if we pay attention to topological factors associated with these types of interactions, it can be seen that they have a decisive role in the formation of the crystal. Additionally, there is a lack of adequate support from energetic data, and a lack of concern for misaligned molecules, which are both strong limitations of the synthon approach.

Our research group has worked with trihalomethyl heterocycles for more than twenty years and in this time we have cultivated an interest in understanding and controlling the crystallization of these compounds, envisioning the development of new solid material. In recent works,[9-15] we have described supramolecular synthons in the crystal structure of trihalomethyl-substituted heterocycles and their precursors. Remarkably, on these occasions we already observed that the synthon approach was inadequate for responding to a set of questions concerning the crystal arrangement of these heterocycles. Thus, we perceived that it is time to consider a perception based on the energetic and topological data of intermolecular interactions. In order to better understand this, we believe that an approach between chemistry and complexity[16] is required. Taking into consideration that both the parts (the molecules) and the whole (the crystal) have a role in this process, which by the network of interactions gives rise to the emergence of structural design, the best path to understanding this is via the complex approach. Therefore, the aim of this work is to use both viewpoints in the study of self-assembly processes in organic molecules and move towards verifying if crystal design is something that emerges from intermolecular interactions. For this task we will use the supramolecular cluster concept (defined above) and propose a number of useful surface parameters including topological/geometrical and energetics as well as their combinations. To best of our knowledge this is the first attempt to combine Surface (VDP, Hirshfeld) and energetics calculations.

Background

When individual molecules are gathered together, they form what, in the literature, is called a supramolecular system. As some researchers have already pointed out, the lability of interactions connecting molecular components enables supramolecular entities to exchange their constituents, in order to form a different supramolecular structure. In fact, some researchers consider that this process, called self-organization by design, in striving for total control over the initial explicit programming of the molecular or supramolecular entity, reveals itself to be self-organizing by selection.[16] In other words, while operating on the dynamic constitutional diversity responsible for internal and external factors, this process aims to achieve what could be compared to a Darwinian selection.[17] As already noted by some researchers, when we consider a self-organized structure, a startling aspect emerges: the structural and functional properties of molecular associations in the system do not depend on the properties of the individual molecules formed.[2,16,18] Rather, some of these properties, which from now on we will call *emergent*, seem to be best explained as a result of the specific organization of individual molecules. Such properties cannot be predicted a priori from a single component, since they emerge from interactions — they only begin to appear during the process of self-organization, or more precisely, when nucleation aggregates are still in solution. Thus, one can conclude that a supramolecule is constructed and defined as a set of interacting molecules. Such a phenomenon has only recently been dealt with in publications, given its startling characteristics.

The aim of the complex approach is to discover the properties, which emerge from the interactions. As described elsewhere these properties are characterized by their unpredictability and irreducibility[19,20]. In other words, emergent properties cannot be foreseen from a pre-emergent point of view; that is, we cannot describe in advance what they will be like if we are to base our description solely on characteristics from separate structures — the parts (molecules) or the whole (crystal) — or on the laws which govern interactions. Rather, we must turn our attention to the interactions themselves; that is, between the parts and between the parts and the whole. We are talking about a combination of both point of view parts and whole with the aim to achieve a complex view. It is an interaction that will lead to emergence, in a way that the whole presents itself as more (or less) than the sum of all parts. Thus, one of the key features for the proper characterization of an emergent property is its objective unpredictability.

It is well known that self-organized systems characterized as open are able to organize themselves spontaneously when submitted to a given gradient. As the imposed gradient is completely neutral in terms of information, one can conclude that the organization emerges from inside the system. Each single molecule is interacting with all its molecule neighbors, and each molecule neighbor is doing the same with its respective neighbors, and so on. Taking into consideration that both the parts and the whole have a role in this process gives rise to the emergence of structural design.

Also, it is worth noting that, currently, the findings of many researchers point to the fact that the key to understanding crystal design lies in the comprehension of the emergent properties involved during the formation process.[2,3,16,18] However, to achieve such comprehension, a long journey had to be undertaken.

The "supramolecular synthon" concept is the beginning of the journey. A synthon is defined as a molecular fragment attached by intermolecular interactions that contain a reasonable approximation of the organization of the entire crystal.[4-7] The identification of supramolecular synthons arises from distances predetermined by the investigator based on the van der Waals radii. Thus, it was established that non-covalent intermolecular interactions, including strong hydrogen bonds, tend to form robust supramolecular synthons, which, in turn, direct the crystal packing.[4] As aforementioned, this approach may be insufficient to explain interactions weaker than hydrogen bonds. In general, these so-called weak interactions, sometimes referred to as resulting dispersive forces are considered to be of minor importance. Additionally, topological factors are neglected in the synthon approach, thus inducing the researcher to disregard the molecules which, though present in the crystal, are misaligned with the "appropriate direction" indicated by their respective molecular fragment. In other words, this approach focuses only on the molecules that effectively participate in the so-called "robust synthons" to form dimers, chains, layers, or macrocycles.

The way is being paved for the complex approach, since some paradigms of the synthon approach are currently the subject of review. For example, atom-atom distances less than the sum of van der Waals radii do not imply large stabilization energies. Likewise, distances greater than the sum of atomic radii may contain a large amount of stabilization energy.[21a] The attempt to describe interactions in crystals only in terms of short interatomic contacts as the main structural joining component is being recognized as a rather simplistic approach, when, in fact, something far more complex is being dealt with[21].

As an alternative to the synthon approach, we can mention the concept of electrostatic complementarity (already discussed elsewhere),[21b-23] in which the intermolecular interaction in the crystal formation is the result of an exchange reaction in which interactions with solvent in the unbound state are exchanged for intermolecular interactions between partners in the bound complex. In other words, in the crystal, regions of one molecule with high negative charge density on the surface are closer to the regions of another molecule with high positive charge density on the surface. As we insist on searching for a more complete and satisfactory approach to crystals, it seems that, in the literature, a systemic point of view regarding the study of supramolecular interactions is lacking. In response to this, over the last few years we have worked hard in the study of crystalline structures to introduce an approach that is moving towards complexity. From the point of view we propose, the crystal must be considered in terms of all of its parts (the molecules) which present regions with more or less potential energy. One must pay attention not only to the so-called robust synthons (apparently the only regions with strong interactions) but also to other regions. We considered synthons to be parts of the greater structure, parts named by the observer, which contribute, along with others, to the composition of the whole. Precisely because of this, the crystal should be regarded as a complex system, in which regions of different potential energy from a given molecule are part of the harmony of complementary interactions, which, together with the neighboring molecules, results in a stabilizing balance.

Thus, in this article we shall consider two points of view: (i) the parts (the molecules) are components of a complex system which contains regions with different electrostatic densities and topological design that interact with their neighbors in a complementary manner; and (ii) the whole, in which the cluster of the first sphere of coordination of a molecule M1 will constitute the whole of the system. But one may wonder: Why is it important to study the supramolecular cluster? To answer this and, subsequently, to understand the purpose of this work, we must focus on packing rather than interaction, we consider it appropriate to regard the cluster, as formed by the first coordination sphere, as the smallest portion of the crystal — a portion which presents all the necessary information for understanding the intermolecular interactions of the entire crystal system. Although the notion of a cluster formed by the first coordination sphere has not yet been conceptualized at the moment we are preparing this paper, it has been used as a decisive criterion in comparing the molecular packing environment between two or more crystal structures, in reports on the results of a series of blind tests of crystal structure prediction (CSP).[1]

We emphasize that the parts and whole points of view should not be interpreted as separate or non-correlated, but rather as complementary approaches, since they are simultaneously present in the crystal self-assembly. Therefore, the aim of this work is to use both viewpoints in the study of self-assembly processes in organic molecules and move towards verifying if crystal design is something resulting from intermolecular interactions.

Results and discussion

In order to support the proposal of this work, six compounds with differentiated structures were selected (Fig. 1). Compound **1** is a 1,3,5-trisubstituted pyrazole, with a bulky tert-butyl group attached to the N1, and an aryl group attached to the C5. There is perpendicularity between the aryl group and the pyrazole ring (angle of 90.0°). This orthogonality is a consequence of the tert-butyl group's steric effect which entails particularities in the crystal's self-assembly. For example, it is common that two aromatic rings are able to pack via π-stacking; however, the orthogonality of the pyrazole-aryl rings avoids molecular arrangement in a sandwich-type orientation, which is required for this packing. Thus, the topology of compound 1 prevents such an interaction and gives rise to other intermolecular interactions such as C-H···π.

Compound **2** is a fused heterocycle, 2,7-disubstituted pyrazolo[1,5-*a*]pyrimidine with one methyl group attached at C2 and a trichloromethyl group at C7. Pyrimidine and pyrazole rings are almost in the same plane (gap of 3.6°), and one of the Cl atoms from the trichloromethyl group is in the plane of the pyrimidine ring (N8C7C71Cl71, 178.1o). Thus, compound 2 is planar and contains ten π-electrons, and it does not possess any polar group able to participate in classical hydrogen bonds.

Compound **3** is a 3,4,5-trisubstituted isoxazole with polar groups, such as amino and iodine, attached. The planar topology and the small size of this compound, associated with the polar groups attached, characterizes it as an interesting model in which we can visualize the simultaneous topological and electrostatic interactions governing the crystal packing.

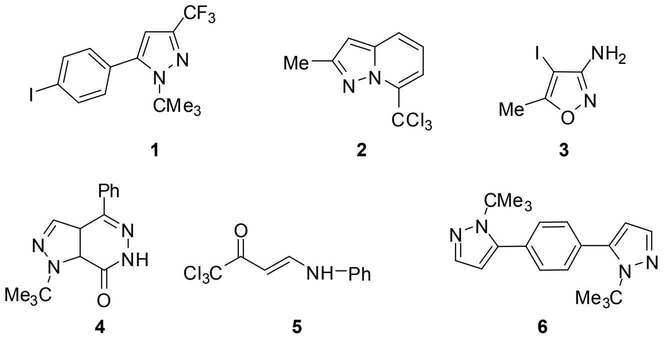

Fig. 1 Structure of compounds 1–6 selected to support this work.

Compound **4** is a 1,4-disubstituted pyrazolo[3,4-*d*]pyridazin-7-one, with a tert-butyl group at N1. This compound unites the topological and electronic properties of compounds 2 and 3. In other words, it has a fused ring and contains polar and bulky groups. Pyridazinone and pyrazole rings are almost on the same plane (gap of 1.7°), and pyridazinone and phenyl plane rings have an angle of 41.4°.

Compound **5** is an enaminone with E-configuration in the C3C4 double bond, containing an aniline group attached to C4 and three chlorine atoms attached to C1. The carbonyl group is 11.8° out-of-plane from the enamine system's (C3C4N4) plane, and presents a chlorine atom in an anti-position in relation to carbonyl oxygen (Cl1C1C2O2, 171.5°). The relationship between the enamine system's (C3C4N4) plane and the phenyl ring's plane is 29.5°. Additionally, compound 5 is not a heterocyclic compound, but rather a longitudinal molecule which contains highly polar groups with the ability to form strong hydrogen bonds.

Compound **6** is made up of two units of 1-tert-butylpyrazoles connected to each other in the 5-position through a phenyl spacer (Fig. 1). The two pyrazole rings are in the same plane, and, with the benzene ring's plane, form angles of 80.3° and 99.7°. Similarly to compound 1, the pyrazole and phenyl rings are almost perpendicular, which is a consequence of the presence of a bulky tert-butyl group attached to N1.

Thus, considering the possible intermolecular interactions, the major difference between compounds **3**,**4**,**5** and **1**,**2**,**6** is the presence of the highly polar N-H functional group which is able to establish a strong hydrogen bond with sp2-nitrogen (**3**) or sp2-oxygen atoms (**4**,**5**).

The Molecular Coordination Number and the Cluster

With our compound model at hand, and considering that our proposal is to understand intermolecular interactions by taking a crystal and designating it as a supramolecular cluster, it is fundamental to first define the coordination spheres and the Molecular Coordination Number (MCN). Kitaigorodskii[24] already proposed the MCN concept for the first coordination sphere as being the number of molecules having at least one contact with a given molecule, which is achieved by applying the principle of close-packing organic crystals. With this in mind, there are basically two calculation methods that may be used to determine contacts: (i) the Voronoi-Dirichlet Polyhedron (VDP) method; and (ii) the Hirshfeld Surface method of analysis.

The VDP molecular concept was introduced by Fischer and Koch[25] to find the number of neighboring molecules that make contact with a given central molecule. From this, it was established that the area of a VDP face corresponds to the contact area between two molecules and reflects the strength of this intermolecular interaction in the crystal. By utilizing this concept, a Russian research group have shown that the vast majority of supramolecular clusters of organic molecules provide a first coordination sphere that is predominantly composed of 14 molecules (> 50%), and, secondly, by either 12 or 16 molecule.[26] Based on these results, Blatov[26a] justified the "rule of 14 neighbors", which establishes that soft spherical or quasi-spherical groups tend to form the closest packing, in accordance with the principle of maximum occupancy of space.

Considering the second method mentioned above, we notice that the Hirshfeld surface is becoming a valuable tool for analyzing intermolecular interactions, while maintaining a whole-of-molecule approach. This method allows the determination of the MCN and the contact area between the molecules of the cluster from the first coordination sphere. Spackman et al. [22] have already determined the first coordination sphere (14 molecules) surrounding a fluorobenzene molecule in the crystal. Shishkin et al.[6] showed the MCN and determined the energy for the dimers of the first coordination sphere of a phenanthroline. Additionally, for the determination of a supramolecular cluster and, consequently, its MCN, it is important to keep in mind that: (i) the self-organization of molecules in a crystal includes electrostatic and topological factors; (ii) the first coordination sphere around M1 is formed by all molecules that touch M1, considering the set of interactions of all molecules near this molecule; (iii) a systemic approach is needed in relation to the whole, and a linear approach is needed to understand the parts; and (iv) a crystal possesses supramolecular self-assembly, in other words, a complex system. Thus, in the crystal of **1–6**, if we consider any M1 molecule in the crystal, the supramolecular cluster will be formed by all neighboring molecules (M2, M3, M4, …, and Mn), thus forming the first coordination sphere of M1 (Fig. 2). The contact surfaces between the M1 molecule and the Mn molecule (PM1•••Mn) were determined for compounds **1-6** using Hirshfeld surface analysis and VDP.[27] Fig. 3 shows the VDP[28] and Hirshfeld surface for compound 3. Both VDP and Hirshfeld surface analysis lead us to the definition of the first coordination sphere of the supramolecular cluster with an MCN of 14 molecules for compound **3**, for instance. From the data obtained using the methods described, the MCN was determined for compounds **1–6** (Table 1).

The Contact Surface

Furthermore, in the process of determining the contact surfaces, we calculated the contact surface of the central molecule M1 alone (S_{M1}), as well as the contact surface of M1 and any Mn molecule ($S_{M1\cdots Mn}$). Thus, the contact surface between M1 and the Mn molecules ($C_{M1\cdots Mn}$) can be expressed as: $S_{M1\cdots Mn}$ subtracted from two times SM1 and then dividing this difference by two, since the contact surface between M1 and Mn is considered twice. We expressed this relationship in Equation (1); $C_{M1\cdots Mn}$ % is expressed in Equation (2), and the total contact surface of the cluster ($C_{cluster}$) is presented in Equation (3).

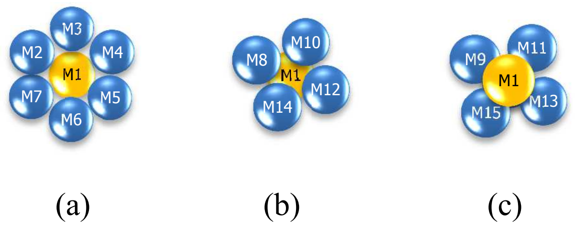

Fig. 2 Cluster of first coordination sphere around M1 is formed by Mn molecules for a compound with MCN = 14: (a) M1 and six in-plane molecules; (b) M1 and four above-plane molecules; and (c) M1 and four below-plane molecules.

$$C_{M1\cdots Mn} = \frac{(2\cdot S_{M1} - S_{M1\cdots Mn})}{2} \qquad (1)$$

$$C_{M1\cdots Mn}\% = \frac{C_{M1\cdots Mn}}{\sum_n (C_{M1\cdots Mn})}\cdot 100 \qquad (2)$$

$$C_{cluster} = \sum_n (G_{M1\cdots Mn}) \qquad (3)$$

Data from the contact surfaces ($C_{M1\cdots Mn}$) — which were obtained using the methods described — for the supramolecular cluster formed by the first coordination sphere of compounds 1–6, is presented in Table 1. Although the contact surfaces obtained from VDP and Hirshfeld surface ($C_{M1\cdots Mn}$) calculations are obtained from the same X-ray diffraction data, it is important to examine the correlation between these data to confirm the structure of the cluster.

In our analysis, the correlation between VDP contact surfaces and $C_{M1\cdots Mn}$ showed good linearity, ($VDP_{M1\cdots Mn}$ % = 1.013 × CM1•••Mn % – 0.091; r = 0.980; N = 86). This result confirms that both methods are valuable for understanding supramolecular clusters.

Interaction Energy versus Contact Surface

Now that we have established the contact surface for all the supramolecular clusters, we shall turn our attention to the interaction energy between M1 and its molecule neighbours. According to our proposal, the crystal is formed when molecules in solution aggregate around a central molecule and such a process occurs in harmony with the forces responsible for crystal stability. Thus, the concept of crystal stability necessarily passes through the determination of the amount of energy for M1 and each Mn molecule from the first coordination sphere of the cluster.

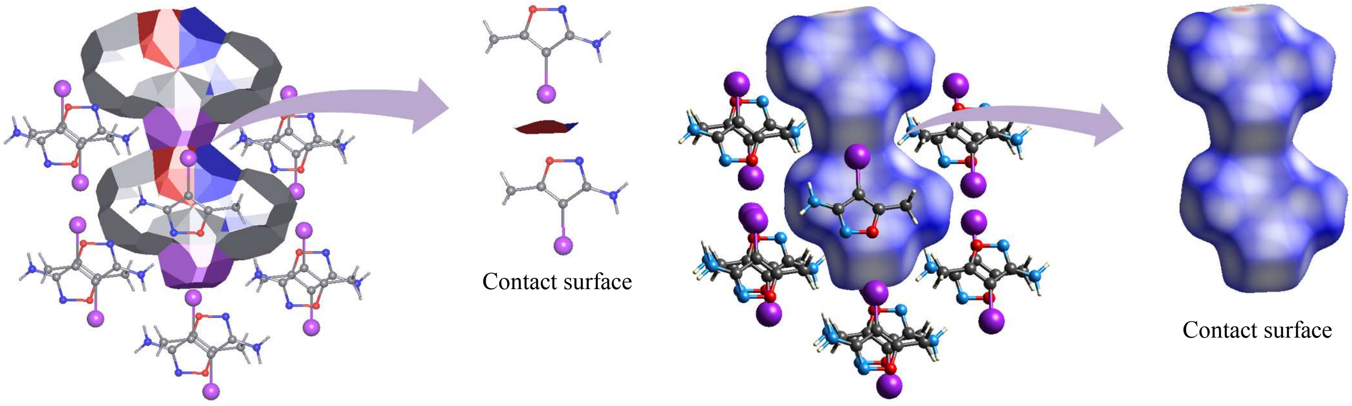

Fig. 3 (a) Voronoi-Dirichlet Polyhedron (VDP) for 3 (MCN = 14); and (b) the Hirshfeld surface of M1•••Mn (i.e., of the supramolecular cluster).

The determination of the intermolecular interaction energies of M1•••Mn dimers was done using the difference between twice the M1 (alone) energy and the total energy of each of the M1•••Mn dimers (i.e., M1•••M2, M1•••M3, …, M1•••Mn). In Equation (4), $G_{M1\cdots Mn}$ is the energy resulting from the interaction between M1 and the Mn molecule; E_{M1} is the energy of M1 in the absence of any neighboring molecule; and $E_{M1\cdots Mn}$ is the total energy of the dimer formed by M1 and Mn. $G_{M1\cdots Mn}$ % is expressed in Equation (5), and the total energy of the cluster ($G_{cluster}$) is presented in Equation (6). The data presented in Table 1 is for the interaction energy $G_{M1\cdots Mn}$ of the supramolecular cluster formed by the first coordination sphere of compounds **1–6**. As mentioned earlier, a systemic approach is needed to reach the whole. Thus, when calculating the intermolecular interaction energies, it is desirable to consider the energetic contribution that each Mn molecule provides for M1 stabilization — always having all cluster molecules. However, this kind of calculation, depending on the number of atoms in each molecule at a calculation level of *ab initio* MP2, results in an almost unjustifiable computational cost. There is (also) the risk of estimating intermolecular interaction energies from dimers that are separated from the rest of the cluster: obviously, the energy to be found from neighboring molecules will not be computed. In order to find a solution to this impasse, by using a calculus approximation at DFT level (wB97X-d/cc-pVTZ-PP), the stabilization energies of all cluster molecules (14 molecules) on M1 were determined for compound **3**. Results were compared with those obtained from the sum of energies of each dimer considered separately from the rest of the cluster. The difference between these two parameters was less than 5%. Keeping such data in mind, and understanding that the idea of a systemic view of the cluster would not be compromised, we chose to perform a more robust calculation (MP2), by considering each dimer without the presence of the other cluster molecules.

It is reasonable to imagine that the magnitude of the stabilization energy of each neighboring molecule on the central molecule M1 ($G_{M1\cdots Mn}$) should be proportional to the contact surface ($C_{M1\cdots Mn}$) of each dimer M1•••Mn.[20a] In attempting to apply this statement to our experiment, we made a correlation between $G_{M1\cdots Mn}$ % and $C_{M1\cdots Mn}$ % for the compounds **1–6** (Fig. 4). As a result, from the data of 86 dimers we achieved a poor correlation coefficient (r = 0.760). We observed that there are some outliers which can emerge from dimers that present: (i) energies much greater than expected when confronted with the contact surface existing between the molecules considered; or (ii) contact surfaces larger than expected when considering the detected energy.

$$G_{M1\cdots Mn} = (2 \cdot E_{M1} - E_{M1\cdots Mn}) \tag{4}$$

$$G_{M1\cdots Mn}\% = \frac{G_{M1\cdots Mn}}{\sum_n (G_{M1\cdots Mn})} \cdot 100 \tag{5}$$

$$G_{cluster} = \sum_n (G_{M1\cdots Mn}) \tag{6}$$

Our initial impression is that, in the first case, this refers to dimers with strong interactions (e.g., hydrogen bonds); and in the second case, we can relate this to dimers containing interactions with *dispersive forces*. Having reached this point in our examination, it is time to consider why these outliers are organized in such a way. In other words: Why do we not observe a proper correlation between $G_{M1\cdots Mn}$ % and $C_{M1\cdots Mn}$ %? The outlier dots seem to be imperfections we see when considering only the parts, and not the greater whole or the part-part and part-whole relationships. Thus, the answers we are trying to achieve depend on a new kind of consideration, as mentioned above.

Table 1. Hirshfeld contact surface[a] and energy interaction[b] for dimers of compounds **1-6**.

Compound	**1**		**2**		**3**	
Dimer	$G_{M1\cdots Mn}$	$C_{M1\cdots Mn}$	$G_{M1\cdots Mn}$	$C_{M1\cdots Mn}$	$G_{M1\cdots Mn}$	$C_{M1\cdots Mn}$
M1···M2	-2.16	30.65	-0.47	9.00	-8.00	8.93
M1···M3	-1.24	17.05	-1.71	12.63	-1.48	7.94
M1···M4	-1.25	17.05	-2.00	8.73	-0.56	4.52
M1···M5	-2.16	30.65	-0.49	9.00	-0.79	15.23
M1···M6	-2.46	21.50	-2.00	8.73	-1.45	7.94
M1···M7	-2.46	21.50	-1.71	12.63	-0.38	14.04
M1···M8	-0.98	11.28	-2.45	19.82	-0.93	6.99
M1···M9	-0.98	11.28	-2.45	19.82	-0.90	6.99
M1···M10	-1.02	10.86	-0.61	3.35	-1.49	10.33
M1···M11	-1.02	10.86	-0.61	3.35	-1.49	10.33
M1···M12	-0.98	11.29	-2.27	20.03	-0.32	3.41
M1···M13	-0.98	11.29	-2.27	20.03	-0.63	6.29
M1···M14	-8.47	56.13	-6.14	39.73	-3.33	26.23
M1···M15	-8.47	56.13	-6.14	39.73	-3.31	28.76
M1···M16	0.00	4.13	—	—	—	—
M1···M17	0.00	4.13	—	—	—	—
Compound	**4**		**5**		**6**	
Dimer	$G_{M1\cdots Mn}$	$C_{M1\cdots Mn}$	$G_{M1\cdots Mn}$	$C_{M1\cdots Mn}$	$G_{M1\cdots Mn}$	$C_{M1\cdots Mn}$
M1···M2	-4.04	29.80	-2.22	12.94	-0.43	9.20
M1···M3	-2.07	14.64	-0.80	7.05	-4.36	48.13
M1···M4	-2.80	32.57	-10.76	30.13	-1.26	9.64
M1···M5	-7.55	11.28	-2.22	12.94	-0.43	9.20
M1···M6	-2.07	14.64	-0.79	7.05	-4.31	48.13
M1···M7	-0.77	14.70	-10.76	30.13	-1.15	9.64
M1···M8	-5.07	37.35	-8.50	36.47	-5.46	29.24
M1···M9	-5.07	37.35	-7.38	33.46	-5.45	29.24
M1···M10	-3.14	20.59	0.16	0.21	-2.22	18.30
M1···M11	-0.90	11.36	-0.59	11.03	-2.27	19.00
M1···M12	-3.05	24.88	-4.90	29.74	-8.65	52.08
M1···M13	-3.05	24.88	-4.90	29.73	-8.65	52.08
M1···M14	-3.31	21.73	0.02	11.74	-0.52	4.62
M1···M15	-0.51	0.89	0.02	11.74	-0.51	4.62

[a] CM1•••Mn, Å^2, Hirshfeld contact surface, Equation (1). [b] GM1•••Mn, Kcal•mol^{-1}, energy interaction, Equation (4).

The total energy ($G_{cluster}$) and the total contact surface ($C_{cluster}$) for **1–6** are listed in Table 2. The $G_{cluster}/C_{cluster}$ ratio shows average stabilization energy distributed over the molecule in a homogeneous manner, which shows how the M1 molecule would appear if it had its interaction energy homogeneously distributed on its surface. For example, compound **1** would need to have stabilization energy distributed over the molecule in the proportion of -0.109 Kcal•mol^{-1}/Å^2 (Table 2).

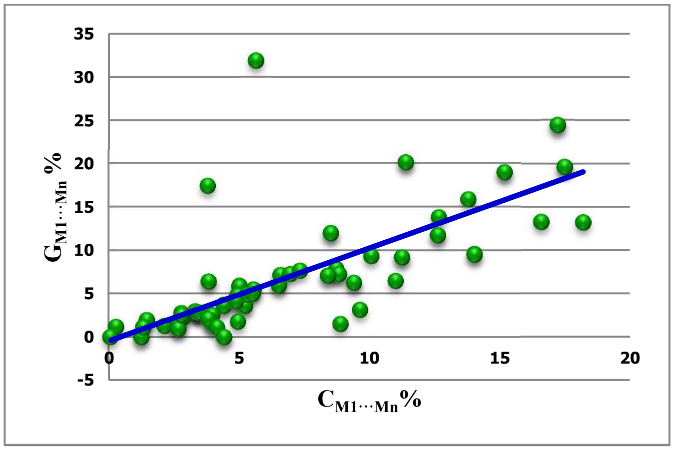

Fig. 4 Correlation between calculated energy interaction ($G_{M1\cdots Mn}$ %) and contact surface ($C_{M1\cdots Mn}$ %) in the supramolecular cluster formed by the first coordination sphere for compounds **1–6** ($G_{M1\cdots Mn}$ % = 1.073 × $C_{M1\cdots Mn}$ % – 0.506; r = 0.760; N = 84).

Polar organic molecules do not show a homogeneous distribution of stabilization energy over the molecule surface. In Fig. 5, we take a closer look at inhomogeneous distribution. It shows part of the supramolecular cluster of compound **3**, as well as the molecules M1 to M7 in the isoxazole ring plane. When we examine the molecular arrangement, considering the data inside the sum of the van der Waals radii (using Mercury® software), we observe that there are only contacts between M1•••M2, M1•••M3, M1•••M6, and M1•••M7 — see Fig. 5(a). For contacts between M1•••M4 and M1•••M5, it appears that an increase of 0.4 Å in the sum of the van der Waals radii is required. These results are confirmed by Fig. 5(b) which shows the Hirshfeld surface (d_{norm}, using Crystal Explorer® 3.1) of molecules M2 to M7, where the close contacts between M1•••M2, M1•••M3, M1•••M6, and M1•••M7 (red regions) and the distant contacts between M1•••M4 and M1•••M5 (light blue regions) can be seen. The electronegativity differences and size disparities between atoms produce polarized bonds which, along with n- and π-electron resonances and steric hindrances in polar molecules, lead to an unequal distribution of charge density[21b] creating a positive electrostatic potential zone or a negative electrostatic potential zone on the molecular surface. While interacting with its neighboring molecules, the molecule M1, which already presents inequality in charge density distribution, has its inequality increased or decreased, in accordance with the induction by its molecular partners, especially those at the first coordination sphere. Such distribution of charge densities in the molecule may be that is able to quantify the robustness of intermolecular interactions. These parameters will give us an estimate of how each interaction of M1 with a particular Mn molecule deviates observed with the aid of Molecular Electrostatic Potential (MEP) calculations, which are determined through ab initio calculations (obtained using Gaussian® 09 [29,30]).

In Fig. 5(c), regarding the supramolecular cluster of compound 3, the MEP of M1 and molecules M2 to M7 is presented in the isoxazole ring plane. The molecular arrangement between M1•••M2, M1•••M3, M1•••M6, and M1•••M7 can be understood if we recall the electrostatic complementarity concept.[14b-16] Considering Fig. 5(a) and (b), we verify that M4 and M5 do not develop close contacts in relation to M1.

Looking at the greater context, all dimers (M1•••Mn) in the cluster have some amount of interaction energy and so it is reasonable to assume that this energy is due primarily to the greater or lesser force of attraction between molecules, which in turn is a consequence of the difference in electrostatic potential between the contact regions of the molecules involved in the interaction. On the other hand, it is no less true to consider that molecules have regions with nearly neutral electrostatic potential. These regions generate small forces of attraction between neighboring molecules, which is the reason why little interaction energy is detected. Fig. 5 presents this situation for the molecular arrangement between M1•••M4 and M1•••M5. In this case, it may be proposed that molecules M4 and M5 are like puzzle pieces in relation to M1: they fit at a supramolecular level, part of a wholeness controlled by topological complementarity.[26a] However, a question remains: Which dimers exhibit the most important intermolecular interaction in the cluster? To answer this question, we must consider the magnitude of the interaction energies of each dimer. Considering the total interaction energy of the cluster ($G_{cluster}$) to be 1.0, and imagining the interaction energy to be homogeneous for the whole surface, the interaction energy between M1 and any of the neighboring molecules would be the same. In other words, each molecule in the first coordination sphere would contribute with a 1/MCN fraction of the total stabilization energy ($G_{cluster}$). For example, the contribution will be 0.0714 for MCN = 14, and 0.0625 for MCN = 16. Using the same line of thought, if the molecules were perfectly spherical, one also might expect that each would contribute with 1/MCN of the total contact surface of the cluster. But we are well aware that almost all organic molecules do not have the same contact surface with every neighboring molecule and do not interact with the same energy with all of them. Therefore, in order to determine which molecules have the most important interactions for the stabilization of the cluster, we search for a set of parameters from the ideal contribution of 1/MCN of the energy and 1/MCN of the contact surface.

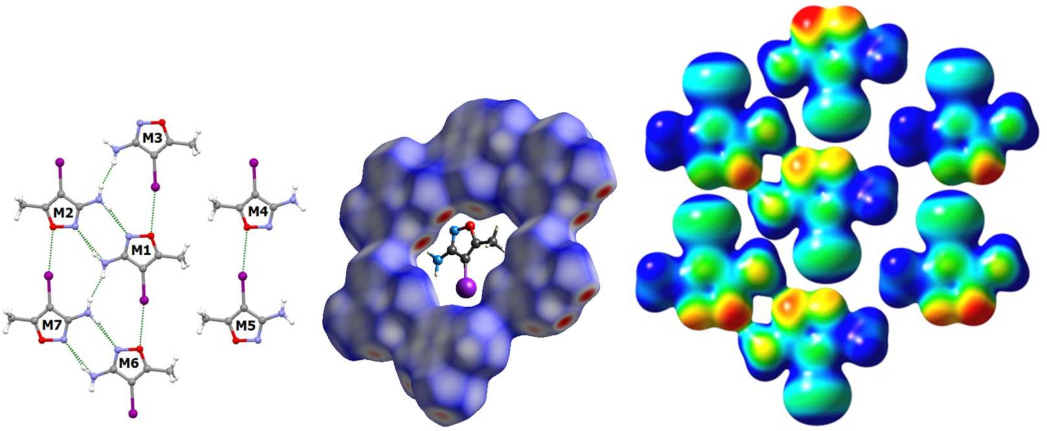

Fig. 5 M1 and M2 to M7 in the isoxazole ring plane of the supramolecular cluster of compound **3**: (a) the molecular close contacts inside the sum of van der Waals radii; (b) the Hirshfeld surface (d_{norm}) of molecules M2 to M7; and (c) MEP of molecules M1 to M7 (red = -0.08 au, green = 0, and blue = 0.08 au) of compound **3**. Performed by GaussView (Gaussian 09) program and calculated with an isosurface value of 0.01; MEP were generated from wave functions obtained from single point calculations using X-ray data and the ωB97X-D/cc-pVDZ level of theory.

Table 2. Total energy ($G_{cluster}$) and total contact surface ($C_{cluster}$) for the supramolecular clusters.

Cpd	MCN[a]	$G_{cluster}$[b] (Kcal·mol^{-1})	$C_{cluster}$[c] (Å^2)	$G_{cluster}$ /$C_{cluster}$ (Kcal·mol^{-1}/Å^2)
1	16	-34.63	317.52	-0.109
2	14	-31.32	226.58	-0.138
3	14	-25.06	157.93	-0.159
4	14	-43.40	296.66	-0.146
5	14	-53.62	264.36	-0.203
6	14	-45.67	343.12	-0.133

[a] The MCN is the number of molecules in the supramolecular cluster formed by the first coordination sphere. [b] Equation (6). [c] Equation (3).

Given that $NG_{M1\cdots Mn}$ and $NC_{M1\cdots Mn}$ are the normalized energy and normalized surface — Equation (8) and Equation (9), respectively — in a supramolecular cluster with MCN molecules, the robustness of the interaction between M1 and any Mn molecule can be estimated from the contributions of these normalized parameters.

$$NG_{M1\cdots Mn} = MCN \cdot \frac{G_{M1\cdots Mn}}{G_{cluster}} \tag{8}$$

$$NC_{M1\cdots Mn} = MCN \cdot \frac{C_{M1\cdots Mn}}{C_{cluster}} \tag{9}$$

Considering an initial overview of the energy parameter, it could be seen that: the amount of energy involved in the interaction of M1•••M14 and M1•••M15 of **1** was three times higher than the energy reference (1/MCN); and interaction M1•••M2 of **3** was four times larger than 1/MCN. On the other hand, the contact surface M1•••M14 and M1•••M15 of **1** is twice that of the 1/MCN surface, while for M1•••M2 of **3**, the contact surface is smaller than 1/MCN.

The robustness criterion was anchored in the data for $NG_{M1\cdots Mn}$ dimers of the compounds that have hydrogen bonds: **3**, **4**, and **5**. From these data we believe that a robust amount of interaction could be considered to take place when $NG_{M1\cdots Mn} > 2.0$. The parameter NCM1•••Mn can be small, such as for dimers M1•••M2 (**3**), M1•••M5 (**4**), and M1•••M4 and M1•••M7 (**5**); or large, such as for M1•••M14 and M1•••M15 (**1**,**2**) and M1•••M12 and M1•••M13 (**6**) — see Fig. 6. In the compounds **3**,**4**, and **6**, some dimers have a somewhat lower $NG_{M1\cdots Mn}$; however, considering that $NG_{M1\cdots Mn} > 1.5$, they can be considered to be robust. Based on these parameters, it is reasonable to affirm that dimers with $NG_{M1\cdots Mn} > 2.5$ may possibly be observed still in solution, before forming the crystal; and, in some cases, they will govern crystal growth. [2,3] However, to understand the crystal design of compounds **1–6**, a closer examination of the energy and surface parameters of each dimer is necessary. Initially, we need to define the main types of interactions that are truly present, according to $NG_{M1\cdots Mn}$ and $NC_{M1\cdots Mn}$ data (Table 3 and Fig S27 — Supporting Information). Thus, we define a type I interaction as one having large $NG_{M1\cdots Mn}$ values and small $NC_{M1\cdots Mn}$ values; that is, a molecular dimer with a high interaction energy in a small surface contact. This feature appears in compounds **3** and **4**, in which strong hydrogen bonds (N-H•••N and N-H•••O) are present. A type II interaction is one involving a large amount of both $NG_{M1\cdots Mn}$ and $NC_{M1\cdots Mn}$; that is, a molecular dimer with high interaction energy in a large surface contact. This feature is present in all the compounds studied (**1–6**) and appears in interactions with an important contribution of π•••π and C-H•••π contacts. Meanwhile, the type III interaction is the one present in the largest quantity, and it has small values of $NG_{M1\cdots Mn}$ and $NC_{M1\cdots Mn}$, with a maximum difference of ±0.5 between the two parameters. Finally, the type IV interaction has a small $NG_{M1\cdots Mn}$ parameter and a relatively higher $NC_{M1\cdots Mn}$ parameter. This is a type of interaction that appears less frequently. However, it is an interesting kind, as in it the topological factor has a more influential contribution over the electrostatic component. These last dimers, along with, which both present low parameters, confirm what we have said above: their fitting is analogous to that of puzzle pieces and is mainly driven by topological complementarity.

Table 3. Type of interaction in accordance with the normalized energy ($NG_{M1\cdots Mn}$) and contact surface ($NC_{M1\cdots Mn}$) for the main dimers of compounds **1-6**.

Cpd.	Dimer	$NG_{M1\cdots Mn}$	$NC_{M1\cdots Mn}$	Inter. Type
1	M1···M14; M1···M15	> 3.5	>2.5	II
2	M1···M14; M1···M15	>2.5	>2.0	II
3	M1···M2; M1···M14	> 4.0	< 1.0	I
	M1···M15; M1···M5	> 1.5	> 2.0	II
	M1···M7; M1···M4	< 0.5	> 1.2	IV
4	M1···M5	> 2.0	< 0.5	I
	M1···M8; M1···M9	> 1.5	> 1.5	II
	M1···M4	< 1.0	> 1.5	IV
5	M1···M4; M1···M7	> 2.8	> 1.6	II
	M1···M8; M1···M9	> 1.9	> 1.7	III
6	M1···M12; M1···M13	> 2.6	> 2.1	II
	M1···M8; M1···M9	> 1.6	> 1.2	III
	M1···M3; M1···M6	> 1.3	> 2.0	II

Energetic and Topological Complementarity

As mentioned earlier, compound **3** shows that the dimers M1•••M4 and M1•••M5 have low interaction energy, suggesting that the correlation between M1 and M4 and M5 is due to topological complementarity.[26a] The subject raises some doubts: How do two molecules, with low interaction energy, maintain themselves as cluster components? What prevents them from tearing apart? Is topological fitting sufficient to justify the permanence of these molecules in their positions? In order to answer these questions we need to leave the perception of parts for a moment and go towards a systemic perception of the cluster, noting that (as mentioned above) the cluster, as formed by the first coordination sphere, should be regarded "as the smallest portion of the crystal — a portion which presents all the necessary information for understanding intermolecular interactions of the entire crystal system".

Thus, in Fig. 6 we schematically represent the interaction types described here for organic crystal, where the grey circles represents the contact surface of the molecules and the dashed lines represent the energy between them. Fig. 6 helps us to broaden our point of view from parts to system. It shows the supramolecular cluster of compounds **2** and **3**, which can be seen in perspective at the M1 layer and the upper and lower layers. The regions of weak interactions and strong interactions are positioned. It is possible to answer the questions initially posed by looking at the cluster of **3** shown in Fig. 6 (left). It is easy to understand why M4 and M5 are placed at the locations shown if you rationalize that their low stabilization energies in relation to M1 are compensated by the high stabilization energy present in the dimers at the upper and lower layers. In the same figure, a similar rationalization is shown for compound **2** (right). In conclusion, the fragile bond between the molecules in some dimers at a given cluster layer is compensated by the strong bond between other molecules in dimers at the corresponding upper and lower cluster layers. This perception must be extended to all clusters. It is clear that, if there is a heterogeneous distribution of electrostatic potential in the molecule, there will always be dimers with high stabilization energy and, therefore, dimers with low stabilization energy at the studied cluster. Thus, the arrangement of molecules in the cluster necessarily shows that, for dimers with low stabilization energy in a given layer, there will be co-existent dimers with high stabilization energy in a layer immediately thereafter. But some doubts still remain: How does the crystal formation begin? Which intermolecular interactions govern crystal growth? And, at the convergent process of pre-crystal formation, which component was more important — the electrostatic one or the topological one?

Examining compounds **1–6** in light of what has been determined in this work it is possible to infer that dimers possessing intermolecular interactions with large energetic content (e.g., dimers M1•••M2 [**3**], and M1•••M5 [**4**], or the polymeric fragments of M8•••M1•••M9 [**5**]) already exist in concentrate solutions of these compounds as non-protic solvents with low polarity. Regarding the energetic content of the interactions, we can conclude that polymeric fragments from molecules M14•••M1•••M15 (**1**, **2**, and **3**), M8•••M1•••M9 (**4**), and M12•••M1•••M13 (**6**) also exist in concentrate solutions of these compounds. Thus, keeping in mind the studies of solutions already published in the literature,[4,5] which demonstrate that the aggregates observed in solution will generally persist in future crystal, we verify that the formation of crystals from compounds **1–6** took place in a Darwinian fashion, in which the originated crystals preserved pre-existing aggregates — those which we mentioned as "polymeric fragments". Remarkably, polymeric fragments possess important components of interactions such as C-H•••π (**1** and **6**), π•••π (**2**, **3**, and **4**), and N-H•••O hydrogen bonds (**5**).

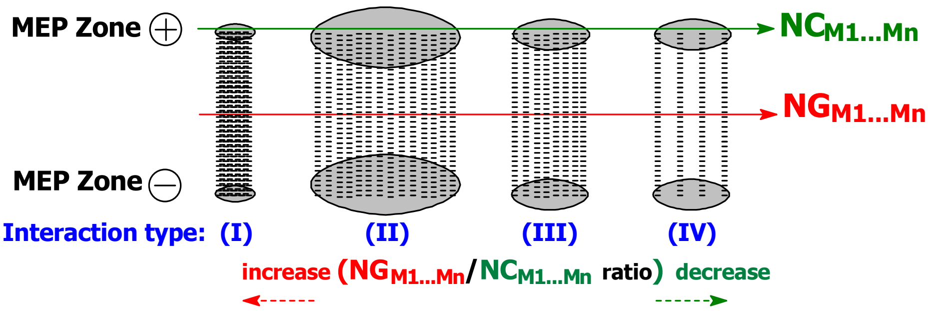

Fig. 6 Type of interaction in accordance with the normalized energy ($NG_{M1\cdots Mn}$) and contact surface ($NC_{M1\cdots Mn}$).

Experimental

Synthesis

The synthesis and complete ^{1}H and ^{13}C NMR data, mass spectrometric data, and elemental analysis of compounds **1**,**2**,**4**,**5**, and **6** is available in the literature.[31-35] 3-Amino-4-iodo-5-methylisoxazole (**3**) was synthesized from the iodination, with N-iodosuccinimide (NIS), of the commercial reagent 3-amino-5-methylisoxazole. To a solution of 3 (1.0 mmol) in acetic acid (5 mL), NIS (1.0 mmol) was added and stirred for 30 min at room temperature. After the reaction time, the solution was extracted with chloroform. The solvent was removed in a rotary evaporator and the product 3 was purified by recrystallization from hexane. Physical and spectrometric data of **3**: Mp. 97°C–99°C; ^{1}H NMR, δ 2.37 (s, 3H, Me), 4.08 (br s, 2H, NH2); ^{13}C NMR, δ 12.7 (Me), 51.2 (C4), 163.2 (C3), 169.6 (C5); MS, 224 (M^+, 100), 97 (7), 66 (11), 55 (33). The crystals of **1** were obtained by solubilization in 6 mL of a mixture of ethanol and dichloromethane at a ratio of 1:1, followed by slow evaporation at 12°C. The crystals of **2** were obtained by solubilization in 5 mL of a mixture of ethanol and DMSO at a ratio of 6:4, followed by slow evaporation at 25°C. The crystals of **3** were obtained by solubilization of 5 ml of heat hexane followed by slow evaporation at 25°C. The crystals of **4** were obtained by solubilization in 5 mL of chloroform followed by slow evaporation at 25°C. The crystals of 5 were obtained by solubilization in 6 mL of ethanol followed by slow evaporation at 25°C. The crystals of **1** were obtained by solubilization in 6 mL of a mixture of ethanol and chloroform at a ratio of 1:1, followed by slow evaporation at 25°C.

X-ray diffraction data

The diffraction measurements were performed using graphite monochromatized Mo Ka radiation with k = 0.71073 Å, on a Bruker SMART CCD diffractometer.[36] The structures were solved with direct methods using the SHELXS program, and refined on F2 by full-matrix least-squares with the SHELXL package.[37]Absorption correction was performed by the Gaussian method.[38] Anisotropic displacement parameters for non-hydrogen atoms were applied. The hydrogen atoms were placed at calculated positions with 0.96 Å (methyl CH_3), 0.97 Å (methylene CH_2), 0.98 Å (methyne CH), 0.93 Å (aromatic CH), and 0.82 Å (OH), using a riding model. Hydrogen isotropic thermal parameters were kept equal to Uiso(H) = xUeq (carrier C atom), with x = 1.5 for methyl groups and x = 1.2 for all others. The valence angles C–C–H and H–C–H of the methyl groups were set to 109.5°, and H atoms were allowed to rotate around the C–C bond. Molecular graphs were prepared using ORTEP for Windows.[39] Data collection and structure refinement for the structures of **1–6** are given in Table 4.

Voronoi-Dirichlet Polyhedron (VDP)

The molecular Voronoi-Dirichlet Polyhedron (VDP) concept was introduced to find the number of neighboring molecules that have contact with a given central molecule.[25]It introduced the idea of the face of the molecular VDP as a set of atomic VDP faces corresponding to the adjacent contacts between the atoms of two molecules. From this it was established that the area of the face of a VDP corresponds to a molecular M1•••Mn, and its contact area is determined by the strength of molecular interaction. Such a concept was proposed by Blatov et al. [26]

Hirshfeld Surface (HS)

The supramolecular cluster was constructed considering the central molecule M1 and the Mn molecules of the first molecular coordination sphere. The clusters were built using Crystal Explorer® 3.0 software. [27]

Computational Calculations

The energies of intermolecular interactions in supramolecular clusters of compounds **1–6** were determined by single point calculations (without optimization of molecular geometry) performed with geometries obtained from X-ray diffraction. All quantum mechanical calculations were performed with the aid of the Gaussian® 09 software package.[29] To obtain the interaction energy between each M1•••Mn dimer, second-order Moller-Plesset (MP2) perturbation theory was used with a level of theory of MP2/cc-pVDZ for compounds **2**,**4**,**5**, and **6**; and cc-pVDZ-PP for compounds **1** and **3**. The use of the cc-pVDZ-PP basis was necessary in order to correct the relativistic effects of the iodine atom. The counterpoise method of Boys and Bernardi[30] was employed to minimize the error of overlapping bases (BSSE). The MP2 perturbation theory is the method for wave function theories that is most frequently used in the study of intermolecular interactions, due to the relationship between computational cost and good performance.[30]

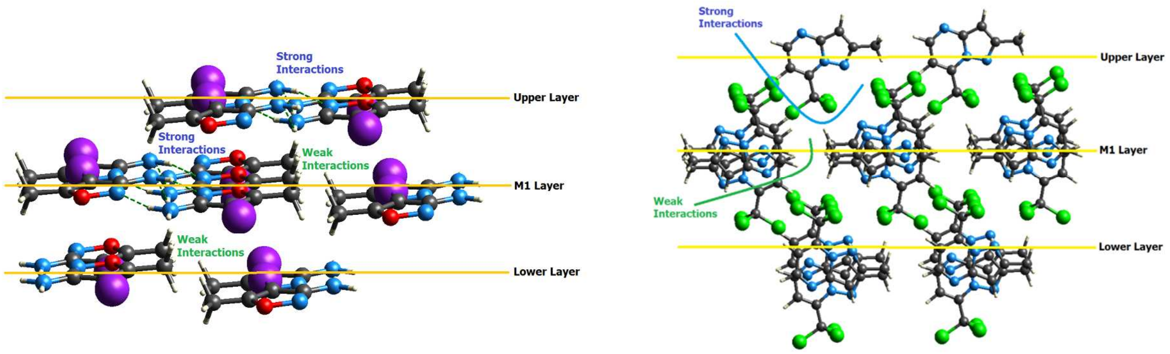

Fig. 7 Clusters of **3** and **2**: an overview of strong and weak interactions.

Some authors have demonstrated that the MP2 method is highly dependent on the set of basis used.[30] Considering the number of atoms in the molecules of compounds 1–6, the complexity of the calculations required, the computational cost, and the quality of results in some preliminary tests, we found that the level of calculation used in this study was satisfactory. Density functional theory (DFT) calculations were performed using the Gaussian® 09 software package[29] with a ωB97X-d/cc-pVTZ level of theory for compounds 2,4,5, and 6; and ωB97X-d/cc-pVTZ-PP for compounds **1** and **3**.

Table 4. Data collection and structure refinement for the structures of **1–6**.

Compound	**1**	**2**	**3**	**4**	**5**	**6**
Empirical formula	$C_{14}H_{14}F_3IN_2$	$C_8H_6Cl_3N_3$	$C_4H_5IN_2O$	$C_{15}H_{16}N_4O$	$C_{10}H_8Cl_3NO$	$C_{20}H_{26}N_4$
Molecular weight	394.17	250.52	224.00	268.32	264.54	322.46
Temperature (K)	293(2)	293(2)	293(2)	293(2)	293(2)	293(2)
Wavelength (Å)	0.71073	0.71073	0.71073	0.71073	0.71073	0.71073
Crystal system	Orthorhombic	Orthorhombic	Triclinic	Triclinic	Monoclinic	Triclinic
Space group	Pnma	$Pca2_1$	P-1	P-1	P 2_1/n	P-1
a (Å)	9.3152(7)	15.307(2)	6.5261(3)	6.2936(4)	11.3649(3)	6.90930(10)
b (Å)	9.5241(7)	9.4510(14)	7.3488(3)	8.6404(5)	6.0949(2)	7.91880(10)
c (Å)	17.5001(11)	6.9446(10)	7.6401(3)	13.6969(7)	16.6562(5)	10.0033(2)
α (deg)	90	90	96.998(3)	104.214(3)	90	67.3110(10)
β (deg)	90	90	100.396(3)	95.590(3)	100.811(2)	89.2900(10)
γ (deg)	90	90	113.411(3)	105.184(3)	90	65.6060(10)
Volume ($Å^3$)	1552.59(19)	1004.65	323.04(2)	686.328	1133.26	452.795(13)
Z/density (calcd.)(Mg/m^3)	4, 1.686	4, 1.656	2, 2.303	2, 1.298	4, 1.550	2, 1.183
Abs.coef.(mm^{-1})	2.085	0.871	4.861	0.085	0.779	0.072
F(000) (e)	768	504	208	284	536	174
Crystal size (mm^3)	0.632 x 0.442 x 0.385	0.35 x 0.25 x 0.13	0.23 x 0.16 x 0.15	0.48 x 0.29 x 0.25	0.27 x 0.18 x 0.08	0.582 x 0.474 x 0.204
θ range for data collection (deg)	2.43 to 27.50	2.15 to 28.33	2.78 to 27.13	2.55 to 27.18	3.57 to 24.84	2.24 to 27.94
Reflections collected/unique	12700 / 1875 [R(int) = 0.0203]	9557 / 2091 [R(int)= 0.0396]	9332 / 1432 [R(int) = 0.0275]	17893 / 3015 [R(int) = 0.0205]	9428 / 1926 [R(int) = 0.0449]	8313 / 2173 [R(int) = 0.0199]
Completeness to θ (%)	(27.50) 99.1 %	(28.33) 99.9 %	(27.13) 99.9 %	(27.18) 99.2 %	(24.84) 98.4 %	(27.94) 100.0%
Max. and min. transmission	0.6895 and 0.5117	0.8951 and 0.7502	0.5292 and 0.4011	0.9789 and 0.9601	1.000000 and 0.854664	0.9978 and 0.9495
Data/restraints/ parameters	1875 / 0 / 106	2091 / 1 / 127	1432 / 0 / 73	3015 / 0 / 182	1926 / 0 / 136	2173 / 0 / 117
Goodness-of-fit on F^2	1.062	1.052	1.077	1.041	1.042	1.086
Final R indices [$I \geq 2\sigma(I)$][a]	R_1 = 0.0417, wR_2 = 0.1143	R_1 = 0.0459, wR_2 = 0.1196	R_1 = 0.0219, wR_2 = 0.0511	R_1 = 0.0369, wR_2 = 0.0948	R_1 = 0.0809, wR_2 = 0.1558	R_1 = 0.0456, wR_2 = 0.1268
R (all data)[a]	R_1 = 0.0538, wR_2 = 0.1234	R_1 = 0.0682, wR_2 = 0.1342	R_1 = 0.0256, wR_2 = 0.0531	R_1 = 0.0485, wR_2 = 0.1030	R_1 = 0.1024, wR_2 = 0.1683	R_1 = 0.0543, wR_2 = 0.1426
Largest diff. peak and hole (e A^{-3})	0.838 and -0.494	0.466 and -0.291	0.358 and -0.719	0.216 and -0.154	1.267 and -0.671	0.158 and -0.261

[a] $R_1 = \Sigma||F_o| - |F_c||/\Sigma|F_o|$, $wR_2 = \{\Sigma w(F_o^2 - F_c^2)^2/\Sigma[w(F_o^2)^2]\}^{1/2}$.

Conclusions

Continuing with the relentless pursuit of researchers to determine a priori the design of a crystal structure through the use of experimental and theoretical tools, in this article we gave our contribution, which proposes considering the crystal as a complex system. Our experimental and theoretical interpretation takes into account both a linear interpretation of parts (molecules), as well as a systemic interpretation of the whole cluster (represented by the first coordination sphere of supramolecular cluster).

Crystal design is an emergent property featuring irreducibility and unpredictability. The unpredictability of crystal design has already been shown in the literature, and here we also contribute to the evidence of this property by showing that if one is able to estimate the interaction energies between molecules, one only acquires data about the already-formed crystal. This information does not guarantee the ability to predict the structure of the future crystal. The energies obtained are capable of informing one about the stability of the crystal to a greater or lesser degree, whereas the distances between molecules are able to determine which is closer or further — *synthons* can inform us about the possibility of interactions originating at the *synthons* and which might be repeated in other similar systems. In our study we showed that molecules with classical *synthons* are capable of forming hydrogen bonds (**3**,**4**, and **5**), but, despite having the highest interaction energies, they are unable to be appointed as responsible for the design of the crystal, as shown with the possible formation of dimers (**3**,**4** and **5**). On the other hand, for the irreducibility of crystal design, it seems quite clear: there is no way to determine the crystal design from a molecule, because an emergent property cannot be deduced from a part. The molecule is able to determine the molecular surface regions with higher or lower electron density, with a greater or lesser possibility of electrostatic attraction; however, this is not enough for the understanding of crystal design. Thus, our study showed that, only from the supramolecular cluster is it possible to observe the participation of the topological component during the formation of the crystal. This is demonstrated by the fact that the fragility of electrostatic interaction in a particular layer of molecules is compensated by a strong interaction of molecules in the layers above and below that given layer. Thus, we may conclude that our approach is a challenging yet necessary contribution to further research on the beautiful universe posed by crystal design.

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Notes and references

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Electronic Supplementary Information (ESI)

Supplementary data associated with this article is available in the online version at http://dx.doi.org/10.1016/j.molstruc.2014. Crystallographic data for the structural analysis of the compounds have been deposited at the Cambridge Crystallographic Data Center with the deposition numbers CCDC 993665 (**1**), CCDC 734995 (**2**), CCDC 993666 (**3**), CCDC 914132 (**4**), CCDC 680898 (**5**), and CCDC 993672 (**6**). Copies of the data can be obtained free of charge upon application to CCDC at 12 Union Road, Cambridge CB21EZ, United Kingdom; Fax: +44 1223 336033 or e-mail: deposit@ccdc.cam.ac.uk.available: [details of any supplementary information available should be included here]. See DOI: 10.1039/b000000x/

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GRAPHICAL ABSTRACT