Self-assembly mechanism based on charge density topological interaction energies

Błażej Dziuk¹ · Christopher G. Gianopoulos^{1,2} · Krzysztof Ejsmont¹ · Bartosz Zarychta¹

Received: 5 October 2017 / Accepted: 16 November 2017 / Published online: 4 December 2017
© The Author(s) 2017. This article is an open access publication

Abstract

The packing interactions have been evaluated in the context of the self-assembly mechanism of crystal growth and also for its impacts on the aromaticity of the trimesate anion. The structure of ethylammonium trimesate hydrate (**1**) measured at 100 K and a charge density model, derived in part from theoretical structures, is reported. Theoretical structure factors were obtained from the geometry-optimized periodic wave function. The trimesic acid portion of **1** is fully deprotonated and participates in a variety hydrogen bonding motifs. Topological analysis of the charge density model reveals the most significant packing interactions and is then compared to a complementary analysis performed by the Hirshfeld surface method. The results presented herein demonstrate that in organic salt crystals the small structural motifs are most stable and once formed as stand-alone structures, may direct the self-assembly process. Moreover, when intermolecular interactions supported by the electrostatic forces are analyzed, the care must be taken with interpretation of the results of Hirshfeld surface analysis for organic salts crystals.

Keywords Supramolecular synthons · Charge density · Intermolecular interactions · Topological analysis

Introduction

Rational design of new materials with tailored properties and predictable structures tends to rely on the formation of hydrogen bonds, and as a consequence of this, certain functional groups serve as supramolecular synthons between molecules and/or ions in the solid state [1]. Crystals composed of salts of carboxylic acids and amines are prototypical examples of the application of such functional groups wherein the resulting crystal structures are stabilized by ionic interactions accompanied by strong hydrogen bonds. Furthermore, organic salts are useful supramolecular synthons owing to several advantageous features, such as strong, charge-assisted hydrogen bonding mediated by proton transfer, clear directionality, and

a wide variety of possible cation-anion combinations [2]. Carboxylic acids, protonated or in the anionic form, often form dimeric structures or in the case of dicarboxylic acids, repeating chains. Hydrogen bonding in these systems is usually strong, and therefore, organic acids are excellent building units for the rational design of supramolecular structures [3, 4]. Strong N-H...O hydrogen bonds are observed in the crystals of carboxylic acid/amine salts and are the primary force directing the resulting solid-state structure [5, 6]. In this context, it is interesting to consider the impact of the solid-state structure on other chemical properties. For example, intermolecular interactions in the solid state may perturb π -electron delocalization (aromaticity) in the case of aromatic carboxylic acids (and/or) amines. The influence of hydrogen bonding on aromaticity is the subject of recent publications devoted to purine and adenine tautomers [7, 8], cytosine [9], supramolecular polymers, and squaramides [10]. These reports suggest that hydrogen bonding may lead to substantial changes in aromaticity, on the basis of variations in calculated aromaticity indices.

The crystal structures of trimesic acid/amine complexes reported in the Cambridge Structural Database (CSD) manifest in several general arrangements [11]. In most crystal structures, trimesic acid takes the form of mono- and tri-anions (about 40 and 39%, respectively), while the di-anion is

Electronic supplementary material The online version of this article (<https://doi.org/10.1007/s11224-017-1060-6>) contains supplementary material, which is available to authorized users.

✉ Bartosz Zarychta
bzarychta@uni.opole.pl

¹ Faculty of Chemistry, University of Opole, Oleska 48,
45-052 Opole, Poland

² Department of Chemistry, University of Toledo, Toledo, OH 43606,
USA

observed in the remaining 21% structures. In the structures of these salts, the carboxylate groups are slightly twisted with respect to the C₆ plane.

Herein, we report experimental and theoretical studies of ethylammonium trimesate hydrate (**1**) and discuss the strength of interactions between the anionic and cationic sublattices, which are representative of supramolecular synthons. Estimated intermolecular interaction energies were derived from topological analysis of the total experimental electron density distribution as determined from the charge density model of the experimental XRD structure, augmented in part from refinement against theoretical structure factors. Calculated descriptors of π -electron delocalization for structures of the trimesate anion in a shrouding of supramolecular synthons (and without) are also discussed. While there are several methods for evaluating aromaticity, we limit our discussions to the Harmonic Oscillator Model of Aromaticity (HOMA), Nucleus Independent Chemical Shift (NICS) indices and *para*-delocalization index (PDI) [12–16].

Experimental

Crystals of **1** were prepared by slow evaporation at room temperature from a mixture of trimesic acid and ethylamine (1:3) in ethanol. Single crystals were selected directly from the mother liquor. The experimental data were obtained on a CCD Xcalibur diffractometer (graphite monochromator, MoK α radiation, $\lambda = 0.71073$ Å) at 100.0(1) K. Corrections to the Lorentz and polarization factors were applied to reflection intensities. Data collection: CrysAlis CCD (2008) cell refinement: CrysAlis RED [17] data reduction: CrysAlis RED [17]. All non-hydrogen atoms were located from difference Fourier synthesis and refined by least squares in the full-matrix anisotropic approximation as implemented in SHELXL14 [18]. Hydrogen atoms were determined geometrically and refined with isotropic temperature factors of 1.2 times the U_{eq} value of the parent atom. The positions of hydrogen atoms have been refined freely in the multipolar model.

Structure drawings were prepared with the SHELXTL program [18].

Theoretical charge density

The multipolar parameters of the charge density model were derived from theoretical structure factors obtained from periodic wave functions. The procedure has been described in details by Gajda and co-workers [19]. In principal, the strategy consists of four steps: (I) obtain theoretical structure factors from periodic quantum-mechanical calculations; (II) standard multipolar model refinement against theoretical structure factors with molecular geometry obtained in the first step (at this stage atomic coordinates and thermal displacement

parameters were not refined); (III) transfer of the theoretical multipolar parameters to the original spherical model; and (IV) refinement of the atomic coordinates and thermal displacement parameters against experimental structure factors with fixed (i.e., transferred) multipolar parameters (final multipolar refinement). Periodic quantum calculations were performed using CRYSTAL09 [20]. The molecular structure observed experimentally in the crystal was used as a starting geometry; optimization was performed with the density functional theory (DFT) method [21], with the B3LYP hybrid functional and the 6-31G(d,p) basis set [22]. Upon convergence on energy ($\sim 10^{-6}$), the periodic wave function based on the optimized geometry was obtained. The option XFAC was used to generate a unique set of theoretical structure factors (up to 1.2 Å⁻¹) from the computed wave functions. The electron density refinements were performed in the MoPro software suite [23, 24] using the multipolar atom formalism [25]. The multipolar method allows modeling of the non-spherical part of the atomic electron density using atom-centered multipole functions:

$$\rho_{atom}(\mathbf{r}) = P_c \rho_c(r) + P_v \kappa_s^3 \rho_v(\kappa_s r) + \sum_{l=0}^{l_{max}} \kappa_l^3 R_l(\kappa_l r) \sum_{m=0}^l P_{lm\pm} y_{lm\pm}(\theta/\varphi) \quad (1)$$

P_v is the valence population parameter and gives an estimation of the net atomic charge $q = N_v - P_v$, where N_v is the number of valence electrons for the neutral atom. The $y_{lm\pm}$ terms are spherical harmonic functions, the R_l terms are Slater-type radial functions, and the scalars $P_{lm\pm}$ are the multipole populations. The coefficients κ_s and κ_l describe the contraction–expansion for the spherical and multipolar valence densities, respectively. Further refinement details and results are deposited in the supplementary material (Table S1). The positional and isotropic displacement parameters for hydrogen atoms were refined freely.

DFT calculations

Calculations were performed on the trimesate trianion by DFT methods [21] (B3LYP/6–311++G(2d,2p) [22] with no imaginary frequencies using the GAUSSIAN09 program package [26]. Calculations were performed on a system composed of the trimesate trianion, eight ethylammonium cations and two water molecules (taken from the solid-state structure). The calculations were constrained to have frozen donor-acceptor distances, in order to estimate the influence of strong intermolecular N–H...O and O–H...O hydrogen bonds on the aromaticity of the trimesate anion. All calculations were performed using the GAUSSIAN09 program package [26].

Aromaticity indices

The harmonic oscillator model of aromaticity (HOMA) is a popular method for the quantitative determination of π -electron delocalization (aromaticity) in cyclic compounds. In this scheme, aromaticity is estimated based on geometrical criterion, namely that bond lengths in aromatic systems are between the typical distances for canonical single and double bonds. The HOMA index is defined as follows:

$$HOMA = 1 - \frac{\alpha}{n} \sum_{i=1}^n (R_{opt} - R_i)^2 \quad (2)$$

where n is the number of bonds in the cycle; α is a normalization constant (for CC bonds $\alpha = 257.7 \text{ \AA}^{-2}$) chosen such that HOMA = 0 for a model non-aromatic system, e.g., Kekulé structure of benzene and HOMA = 1 for the system with all bonds equal to the optimal value R_{opt} (for CC bonds R_{opt} is 1.388 Å); and R_i is the bond length for bond i [27–31].

The magnetism-based aromaticity index NICS(0) (Nucleus Independent Chemical Shift) [32] and its modifications, NICS(1) and NICS(1)zz [33] are calculated as the negative values of the shielding constant of a ghost atom located at the centroid of a ring system. The NICS(1) values are calculated at a point located 1 Å above the ring and the NICS(1)zz is the zz component of the shielding tensor, where z is the axis perpendicular to the molecular plane. NICS(1)zz is, at present, the recommended [34–36] variant of the original NICS index and was used in this study. Calculations of the NICS indices were performed at the B3LYP/6–311++G(2d,2p) level of theory.

The degree of π -electron delocalization can be also quantified from the perspective of Bader's 'Atoms in Molecules' (AIM) [37, 38] theory by using the delocalization index (DI), denoted as $\delta(A,B)$, which is obtained by double integration of the exchange-correlation density over the basins of atoms A and B (basins are defined by the zero-flux gradient surface in electron density, $\rho(\mathbf{r})$):

$$\begin{aligned} \delta(A,B) &= - \int_A \int_B \Gamma_{XC}(\vec{r}_1, \vec{r}_2) d\vec{r}_1 d\vec{r}_2 - \int_B \int_A \Gamma_{XC}(\vec{r}_1, \vec{r}_2) d\vec{r}_1 d\vec{r}_2 \\ &= -2 \int_A \int_B \Gamma_{XC}(\vec{r}_1, \vec{r}_2) d\vec{r}_1 d\vec{r}_2 \end{aligned} \quad (3)$$

The delocalization index $\delta(A,B)$ provides an estimate of the number of electrons delocalized (or shared) between atoms A and B [39, 40]. Recently, the *para*-delocalization index (PDI) [13] was described as an improved measure of aromaticity based on electron delocalization, where the PDI is the average of all DI for *para*-related carbons in a given six-membered ring. The PDI value has been shown [13] to correlate satisfactorily with the NICS, HOMA, and magnetic susceptibilities methods for estimating aromaticity within a series

of planar hydrocarbons. In this context, it is worth noting that increasing aromaticity is associated with increasing PDI and HOMA indices, while the absolute value of NICS indices also increases.

Results and discussion

The result of a traditional structure measurement, which is derived from a spherical atom model, can be improved by the use of transferred multipolar charge density parameters (transferred multipolar populations have been deposited in Supplementary Material in Table S2). The transfer of multipole parameters, obtained by refinement against theoretical structure factors, has been proven to enhance the accuracy of the final model beyond simply improving statistical refinement indices [19, 41]. The impact is manifest in improved X-H distances and anisotropic thermal parameters (as well rigid-body behavior of the molecules), which are crucial when hydrogen bonds need to be investigated carefully. In the present case, the residual factor R(F) was dropped from 3.301 to 1.804% indicating ca. 45% improvement. The average B factor was decreased from 2.584 to 2.380 for the multipolar model. Moreover, the rigid-bond test confirms that the anisotropic thermal displacement parameters account only for dynamic and static disorder, and are physically realistic [42]. The general idea of the rigid-bond test is to analyze the differences between the r.m.s. (root mean square) displacements along the bond vectors between neighboring atoms, ΔZ^2 . The discrepancy should be small and ideally less than $10^{-3} \text{ \AA}^2$ [42]. For the present case, the average $|\Delta Z^2|$ value after multipolar refinement improved by 49% (2.184×10^{-3} against 1.112×10^{-3}) and confirms that the result of refinement with transferred multipolar parameters is physically reasonable and that the thermal vibration parameters are properly described.

Ethylammonium trimesate (benzene-1,3,5-tricarboxylate) monohydrate (**1**) (Fig. 1) crystallizes with three ethylammonium cations, a trimesate anion and one water molecule in the asymmetric unit. The total charge density obtained from multipolar refinement against theoretical structure factors has been analyzed within the framework of the AIM quantum theory [37]. The main topological parameters of the intramolecular (covalent) interactions are reported in Table S3 (supplementary material). The properties measured at the bond critical points (BCP's) are consistent and are in typical ranges. Furthermore, the deformation density maps exhibit the expected features (Fig. 2). The deformation maps also reveal polarization of the C–N and C–O bonds in the direction of the N and C atom, respectively. The electron lone pairs (L_p) of the oxygen atoms are clearly visible, with the C–O– L_p angle close to 90°, while the expected value for an idealized sp^2 hybridized atom is 120°. This appears to be due the resonance effect with the neighboring C atom and electrostatic repulsion between

Fig. 1 Diagram depicting the asymmetric unit of **1**. Thermal ellipsoids are drawn at 25% probability. The hydrogen atoms labels are omitted for clarity

lone pairs. While the trimesate trianion is nearly planar, the three carboxylate groups are each twisted slightly out of the plane of the aromatic ring. On average the twist angle is small, with individual twist angles of $3.7(2)^\circ$, $4.4(2)^\circ$, and $6.2(3)^\circ$ respectively for the carboxylate groups of C7, C8, and C9 (Table S4, supplementary material). The twist angle of the carboxylate group(s) may influence the relative amount of conjugation between the aromatic system and the carboxylate groups. This can be noted when the $C_{ar}-COO^-$ bond lengths are taken into account. The difference between $C_{ar}-COO^-$ bond lengths for the least and most twisted carboxylate group amounts to $0.0071(6)$ Å ($1.51054(4)$ Å vs. $1.5083(4)$ Å) (Tables S3 and S4, supplementary material). The difference is rather small; however, the trend is also manifest in both the topological bond order and Laplacian of electron density ($\nabla^2\rho$) at the BCP ($n_{TOPO} = 1.06, 1.05, 1.03$; $\nabla^2\rho = -13.18$ e·Å $^{-5}$, -13.11 e·Å $^{-5}$, -13.06 e·Å $^{-5}$, respectively, for C1-C7, C3-C8, and C5-C9 bonds). While it is tempting to interpret the observed trend in terms of the expected degree of π conjugation, the effect is very subtle and not significant enough to draw general conclusions.

The slight departure from planarity of the trimesic acid trianion is a consequence of the intermolecular interactions between the anionic carboxylate groups and the ethylammonium cations. These fragments are connected to each other by strong N-H...O hydrogen bonding and accompanying electrostatic interactions.

The trimesate carboxylate groups participate in different hydrogen bonding interactions both in quantity and type (Tables 1 and 2). Those formed with the ethylammonium cations are very strong, with N-H...O angles of about 170° and

small donor-acceptor distances. The interaction energy can be estimated from the critical point properties using following the equation and provides reasonable estimates of the dissociation energy (D_e):

$$D_e = \frac{-\alpha_0^3 \cdot V^{CP}}{2} \quad (4)$$

where a_0 is the Bohr radius and V^{CP} is the value of the potential energy at the CP [43]. The two strongest intermolecular interactions ($D_e = 58.9$ and 55.1 kJ mol $^{-1}$) are formed between cations and the C9 carboxylate group (C9O5O6), which is also the most twisted carboxylate group. The C8 carboxylate group (C8O3O4) participates in three strong N-H...O hydrogen bonds ($D_e = 54.4, 40.8,$ and 33.7 kJ mol $^{-1}$) with ethylammonium cations and one strong O-H...O bond with the water molecule. The least twisted carboxylate group (C7O1O2) forms three strong N-H...O bonds ($D_e = 53.0, 45.6,$ and 22.3 kJ mol $^{-1}$) between the ethylammonium cations and one O-H...O interaction with the water molecule.

Self-assembly mechanism

In the structure of **1**, three carboxylate groups as well as the ethylammonium cations and water molecules can participate in the formation of two different types of basic supramolecular synthons (0-D dimers and 1-D chains). In either case, self-assembly is driven by strong O-H...O and N-H...O hydrogen bonds. Geometrical analysis revealed that all of the carboxylate groups in **1** are engaged in hydrogen bonds as acceptors with ethylammonium cations as donors (Table 2), while the water molecules participate as both donors and acceptors. Numerous hydrogen-bonding motifs stabilize the packing of **1** in the solid state and these motifs can be classified in the context of their graph-set representations, which provides a systematic way of describing and categorizing such patterns [44, 45]. In this context, a graph-set representation of some hydrogen-bonding motif is specified as $G_a^d(r)$, where G denotes the basic pattern (e.g., ring, R; chain, C), a and d are the number of acceptors and donors, respectively, and r is the degree of the motif (number of atoms in the case of a ring).

Two 0-D dimers are found in the structure of **1** and form simple supramolecular aggregates belonging to the R_2^2 (8) and R_4^4 (8) graph sets (S1 and S2, respectively) (Fig. 3). The complete S1 and S2 synthon structures are generated by an inversion center. The S1 ring is perfectly planar (Fig. 3a) while the S2 ring adopts a pseudo-chair conformation (Fig. 3b) and differs from the S1 synthon by the participation of two additional water molecules in S2.

The estimated Cumulative Dissociation Energy (eCDE), derived from the complete topological analysis of the charge density of **1**, can be used to characterize the various synthons.

Fig. 2 Static deformation plots in the main planes of asymmetric part molecules. **a** Trimesic anion. **b** One of the three ethylammonium cation. **c** Water molecule in the plane bisecting H-O-H angle. The contour intervals are at $\pm 0.05 \text{ e} \cdot \text{\AA}^{-1}$. Red dashed lines denote regions of charge depletion, and blue solid lines denote charge concentration

Table 1 Topological characteristics of the electron density at strongest hydrogen bonds ($D_e > 10 \text{ kJ mol}^{-1}$). G^{CP} and V^{CP} ($\text{kJ mol}^{-1} \text{ bohr}^{-3}$) are the kinetic and potential electronic energies [43] at CPs; D_e (kJ mol^{-1}) is the dissociation energy. d ($\text{\AA}$) is the bond length, r_1 and r_2 ($\text{\AA}$) are the

distances from the CP to the atoms defining the hydrogen bond, ρ ($\text{e} \cdot \text{\AA}^{-3}$) and $\nabla^2 \rho$ ($\text{e} \cdot \text{\AA}^{-5}$) denote the total electron density and its Laplacian, D_e is dissociation energy. Separated bottom rows indicate hydrogen bonds associated with water molecule

Interaction	Symmetry code (H atoms)	G^{CP}	V^{CP}	d	r_1	r_2	ρ	$\nabla^2 \rho$	D_e
O6...H2C		115.27	−117.75	1.6811	1.1005	0.5810	0.30	4.1	58.9
O5...H1C		105.44	−110.09	1.7419	1.1234	0.6187	0.28	3.7	55.1
O4...H3A	x-1, y+1, z	106.7	−108.84	1.7331	1.1213	0.613	0.28	3.8	54.4
O1...H3C		106.1	−105.9	1.7194	1.1225	0.5991	0.27	3.9	53.0
O1...H3B	-x+1, -y, -z	91.92	−91.23	1.7907	1.1481	0.6433	0.25	3.4	45.6
O3...H2B	x, y, z+1	85.88	−81.57	1.8041	1.1643	0.6428	0.22	3.3	40.8
O3...H1A	x, y, z+2	72.78	−67.4	1.8776	1.1992	0.6791	0.20	2.9	33.7
O2...H1B	-x, -y+1, -z	50.85	−44.52	2.0018	1.2507	0.7617	0.15	2.1	22.3
O7...H2A		88.03	−84.77	1.8001	1.1639	0.6379	0.23	3.4	42.4
O2...H7A	-x+1, -y, -z	70.72	−60.42	1.8627	1.217	0.6465	0.17	3.0	30.2
O4...H7B	-x, -y+1, -z	64.67	−53.51	1.8793	1.2341	0.6566	0.16	2.8	26.8
O7...H1B	-x, -y+1, -z-1	26.4	−20.32	2.4100	1.3944	1.0386	0.08	1.2	10.2

Table 2 The geometry of hydrogen bonds (Å, °). The N⁺-H...OOC bonds are sorted according to the decreasing value of dissociation energy D_e (see Table 1)

H-bond	D-H	H...A	D...A	$\Delta D-H...A$
N2-H2C...O6	1.0329(8)	1.654(1)	2.6817(3)	172.4(3)
N1-H1C...O5	1.0326(8)	1.701(1)	2.7201(3)	168.2(4)
N3-H3A...O4	1.0327(8)	1.722(1)	2.7247(3)	162.6(5)
N3-H3B...O1 ^{III}	1.0324(8)	1.730(1)	2.7477(3)	167.7(3)
N3-H3C...O1	1.0328(8)	1.722(1)	2.7330(3)	165.0(5)
N2-H2B...O3 ^{II}	1.0330(8)	1.806(1)	2.8038(3)	161.2(6)
N1-H1A...O3 ^{II}	1.0326(8)	1.834(1)	2.8614(3)	173.1(2)
N1-H1B...O2 ^I	1.0329(8)	2.004(2)	2.9393(2)	149.2(9)
O7-H7A...O2 ^{III}	0.9667(8)	1.835(1)	2.7950(3)	171.9(2)
O7-H7B...O4 ^I	0.9672(8)	1.886(1)	2.8264(2)	163.3(3)
N2-H2A...O7	1.0326(8)	1.787(1)	2.8094(3)	170.1(4)
N1-H1B...O7	1.0329(8)	2.406(3)	2.9738(3)	113.6(8)
C2-H2...O2	1.0824(8)	2.506(2)	2.8121(3)	94.8(5)
C2-H2...O3	1.0824(8)	2.473(2)	2.8029(3)	96.1(5)
C4-H4...O4	1.0826(8)	2.560(2)	2.8224(3)	92.5(6)
C4-H4...O5	1.0826(8)	2.440(2)	2.7998(3)	97.8(6)
C6-H6...O1	1.0832(8)	2.462(2)	2.7841(3)	95.5(6)
C6-H6...O6	1.0832(8)	2.468(2)	2.7848(3)	95.2(6)

Symmetry codes: (I) $-x, -y+1, -z$; (II) $x, y, z-1$; (III) $-x+1, -y, -z$

The eCDE as a synthons descriptor has been previously defined and was developed in the context of the comparison between halogen-based synthons (Hal = Cl, Br), and between halogen and hydrogen bonds by Brezgunova and co-workers [46]. The eCDE for S1 amounts to 197.1 kJ mol⁻¹ and represents the highest value among all aggregates observed in **1**. Addition of two molecules of water to the S1 synthon results

Fig. 3 Supramolecular 0D synthons: belonging to R_2^2 (8) graph set: **a** S1 and **b** S2, belonging to R_4^4 (8)

in the formation of synthon S2, resulting in a significantly decreased eCDE (125.3 kJ mol⁻¹; Table 3).

The second type of synthon prominent in the packing of **1** is 1D chain, and form five-membered pseudo rings. Both of these synthons, denoted as S3 and S4, belong to the R_2^3 (10) graph set (Fig. 4). The geometries of S3 and S4 are almost identical (Fig. 5) with the exception of substitution of an ethylammonium cation in S3 with a water molecule in S4.

Here again, the inclusion of water in the S4 structure produces a decrease in the eCDE relative to S3 ($\Delta eCDE = 24.1$ kJ mol⁻¹). From this vantage point, it is clear that electrostatic interactions strongly modulate the eCDE (stability) of the supramolecular motifs observed in **1** and suggests that such considerations are of crucial importance to the rational design of supramolecular architectures.

As noted previously for halogen-based synthons [46], it becomes apparent that the eCDE values may be of use to categorize the packing motifs of importance to self-assembly. For example, synthons may be considered as primary units (secondary, tertiary, etc.) with respect to the assembly process. In other words, motifs with a higher eCDE should be most robust and favored in the solid state. Indeed, the CSD (Cambridge Structural Database, ver. 1.19, 5.38 Nov 2016 + updates) [11] has revealed that the number of synthon occurrences for motifs S1–S4 follows the same trend as the eCDEs. The S1 synthon (highest eCDE value) occurs in 851 structures, while S2 (lowest eCDE) appears in only 8 unique entries (18 entries in the hit list). Occurrences of an S2 like synthon increase to 21 unique records (41 records in the hit list) upon replacement of the water molecule with a hydroxyl (-OH) group. The comparison of the eCDEs and CSD occurrences (Fig. 6) shows clearly the correlation between these data.

The most stable and abundant units will then link together in more complex, but less energetically stable supramolecular units. From a structural point of view, 0D ought to be more preferential than 1D or 2D or structures; however, the energetic impact cannot be neglected. Of the motifs present in **1**, the eCDE values suggest that the S1 synthon should be privileged in the self-assembly mechanism and, once formed, should be the most stable structure. The second 0D synthon, S2, has the lowest eCDE and is most likely assembled following growth of the more stable S1, S3, and S4 supramolecular structures.

The non-covalent interactions can be further characterized in terms of the estimated electronic kinetic and potential energies at the bond critical point, as demonstrated previously [46]. The ratio of these energies $\langle |V|/G \rangle$ provides an indicator for the flavor of the interaction; closed-shell ($|V|/G < 1$), pure shared-shell ($|V|/G > 2$), and intermediate interactions between electronic states ($1 < |V|/G < 2$) [47]. In this context, we note that the intermolecular interactions in the

Table 3 Topological characteristics of the synthons in each of the linear and dimeric motives. The parameters ρ_{Σ} ($\text{e}\cdot\text{\AA}^{-3}$), $\nabla^2\rho_{\Sigma}$ ($\text{e}\cdot\text{\AA}^{-5}$), G_{Σ} , V_{Σ} ($\text{kJ mol}^{-1} \text{ bohr}^{-3}$), and eCDE (kJ mol^{-1}) are calculated as the sum over the

pairwise interactions building the synthon, while $|V|/G$ is taken as an average of the corresponding parameters at CP

Graph set	Synthon	ρ_{Σ}	$\nabla^2\rho_{\Sigma}$	G_{Σ}	V_{Σ}	$\langle V /G\rangle$	eCDE
R_2^2 (8)	S1	1.04	14.60	396.04	−394.26	0.995	197.14
R_4^4 (8)	S2	0.80	12.52	295.94	−250.52	0.833	125.26
R_2^3 (10)	S3	1.00	14.02	379.37	−376.81	0.985	188.42
	S4	0.88	13.49	348.19	−328.67	0.925	164.34

structure of **1** are closed-shell interactions $|V|/G < 1$, as expected. Analysis of the topological properties calculated at the BCP's reveals a clear trend across all important topological parameters, namely that the magnitude of the summed density, summed Laplacian and derived properties decrease in the order of $S1 > S3 > S4 > S2$.

Hirshfeld surface vs. dissociation energy analysis

As a complement to the topological (AIM) analyses that have been described above and summarized in the supporting information (see Table S5), we have also analyzed all interactions in the crystal by the Hirshfeld surfaces method [48]. Calculated Hirshfeld surfaces are depicted in Fig. 7a–d (for synthons arrangements S1 through S4) and a graphical representation of the AIM analysis (BCP's and bond paths) is depicted in Fig. 7e, including hydrogen bonds and short contacts (i.e., contacts shorter than vdW distances). In general, the

Hirshfeld surfaces and the positions of the AIM critical points exhibit comparable features; there is, however, disagreement between the methods with respect to the lowest energy interactions.

With this in mind, a comparison of the relative importance of the packing interactions as determined by the Hirshfeld surfaces method and the AIM based method (estimated cumulative dissociation energy) is presented in Fig. 8. Both methods agree that the most important packing interactions involve hydrogen atoms; over 90% of the Hirshfeld surface area and eCDEs are due to O...H, H...H or C...H contacts. Surprisingly, the relative importance of these interactions is quite different depending on the chosen method. For example, the two methods disagree on the relative importance of C...H interactions. The Hirshfeld surface method estimates that C...H interactions are responsible for ~15% of the total interaction energy while the same interactions represent only ~2% of the total eCDE produced by the AIM based method.

Fig. 4 Supramolecular 1D synthons; belonging to R_2^3 (10) graph set. **a** S3. **b** S4

Fig. 5 Overlay diagram of S3 (in blue) and S4 (in red) synthons

Similarly, the H...H contacts appear to be more significant from the viewpoint of the Hirshfeld surface method (~20% for Hirshfeld surface vs. ~5% of eCDE). On the other hand, the O...H interactions appear to be less significant when analyzed by the Hirshfeld surface area method (56% for Hirshfeld surface vs. 91% of eCDE). Surprisingly, the Hirshfeld surface analysis of **1** suggests that weak contacts (C...H and H...H, ~35% of total Hirshfeld surface area) have more significant contribution to the crystal packing than expected as compared to the strong N-H...O and O-H...O interactions (~55% of total Hirshfeld surface area). This discrepancy is systematic and from the treatment of the promolecule in the Hirshfeld surface method, which is based on neutral atom electron densities. On the other hand, electrostatic ($\delta^+ \dots \delta^-$) contributions to the interactions are properly accounted for in the AIM approach. Such deficiency in the Hirshfeld method has been discussed previously in the case of the ionic salt NaCl. In this light, we further recommend caution when interpreting the results of Hirshfeld surface analysis in organic crystals where electrostatic interactions are significant.

The remaining weak interactions have a relatively small influence on crystal packing and do not merit detailed discussion other than to note that their relative importance is also estimated to be more significant by the Hirshfeld surface method.

Aromaticity

The hydrogen-bonding network around the trimesate anion is complex and it is worth considering what, if any, is the influence on the aromaticity of the C₆ ring. The aromaticity in the trimesate anion ought to be primarily influenced by two competing phenomena. One of these is connected with the relative twisting of the π -electron-withdrawing carboxylate groups, which is of course a consequence of the packing environment, and should increase delocalization in the system. The second effect is the presence of Resonance-Assisted Hydrogen Bonds (RAHBs), which are known to decrease the aromaticity of the adjusted phenyl ring, due to strong interrelation between the π -electron delocalization and the strength of the hydrogen bonds which form the RAHB rings. These phenomena are well known and have been described extensively elsewhere [31, 49, 50]. At first glance, it seems reasonable that the rather small twist angle of the carboxylate groups is stabilized due to intramolecular C-H...O interactions, forming a five-membered ring. The geometry criterion for H-bonds suggests that each carboxylate group could participate in (up to) two of these interactions, which are classified as RAHBs [49]. Surprisingly, the presence of these H-bonding interactions could not be confirmed from the total charge density following topological analysis. Moreover, the presence of such interactions (i.e., a bond critical point) could not be confirmed in the case of the purely theoretical dataset either. On this basis, it is unlikely that there is any significant intramolecular hydrogen bonding for the trimesate anion in **1** as a BCP ought to be present in the total charge density were there any interaction present [51]. For these reasons, the presence of RAHBs and its influence on aromaticity will not be considered further.

In our study, we have employed five aromaticity indices, i.e., geometry-based HOMA model, the magnetism-based NICS, NICS(1), NICS(1)zz, and the PDI, which is based on electron delocalization. Evaluating the relative aromatic character requires a reference compound, and for this reason, the HOMA value of benzene is defined to be 0.996. The HOMA

Fig. 6 Comparison of eCDE of S1–S4 synthons (in blue) and the synthon occurrences (Cambridge Structural Database) (in red)

Fig. 7 Hirshfeld surfaces plotted against d_{norm} (**a–d**; synthons's arrangement S1 through S4) and **e** BCP environment. Gray labels indicating interactions mates

value for the C_6 ring in **1** amounts to 0.993 for the experimental structure, reflecting slightly decreased aromaticity relative to benzene. In order to probe the impact of twist angle and local environment, we have carried out theoretical calculations at various geometries and the results of which will be described shortly.

The aromaticity indices were used for four theoretical models (Table 4): as mentioned before for benzene ring

(C_6H_6); for isolated trimesate anion with planar conformation (model I), for isolated trimesate anion with frozen torsion angles around the carboxylate groups as observed in the crystal structure (model II), and for the trimesate anion [geometry (II)] participating in N-H...O and O-H...O type hydrogen bonds (model III). All three models were geometry optimized and frequency analysis was done to confirm minimum.

Fig. 8 Hydrogen bonds and short contacts distribution as determined by Hirshfeld surfaces and estimated cumulative dissociation energies at BCPs

Table 4 Aromaticity indices for calculated geometries (DFT)

Structure	Point group symmetry	HOMA	NICS(0)	NICS(1)	NICS(1)zz	PDI
Exp.	C ₁	0.993				
C ₆ H ₆	D _{6h}	0.996	−7.58	−9.92	−29.80	0.1034
I	C _{3h}	0.952	−7.27	−9.46	−26.00	0.0920
II	C ₁	0.952	−7.30	−9.49	−26.17	0.0931
III	C ₁	0.969	−7.48	−9.81	−23.84	0.0878

Results of these calculations (Table 4) indicate that aromaticity is not affected by the small twist angle of the carboxylate groups (comparing models I and II). Meaningful changes in the aromaticity indices [HOMA, NICS(0), NICS(1), NICS(1)zz, and PDI] are observed when the carboxylate groups participate in intermolecular hydrogen bonding (model III). This effect has been previously observed in the structure of 4,4'-(diazenediyl)dibenzoate [52] wherein the carbonyl oxygen atom of an ester group participates in hydrogen bonding to surrounding molecules. In the present case, hydrogen bonding to the carboxylate oxygen atoms slightly reduces the electron withdrawing ability of the carboxylate group and therefore reduces conjugation with the aromatic ring. Accordingly, the HOMA, NICS(0), and NICS(1) indices reflect increased aromaticity in model III relative to models I or II (Table 4); however, the opposite is observed for the PDI and NICS(1)zz indices. As previously noted, the intramolecular C–H...O hydrogen bonds are, at most, very weak, therefore their influence on aromaticity ought to be negligible. The geometry-based HOMA model shows variations across the models resulting from slight bond length asymmetries across the models and should reflect π -electron perturbations caused by substituent effects. Undoubtedly, the NICS index, and its variants, is more sensitive than the HOMA model. The NICS(0) and NICS(1) indices both indicate increased aromaticity (more negative value) for model III relative to models I or II. However, the value of NICS(1)zz and PDI for model III demonstrates an opposite effect, a decrease of aromaticity in the presence of strong intermolecular N–H...O and O–H...O hydrogen bonds. Therefore, it appears that these different indices are conveying information about quite different physical phenomena [53] and should be taken with caution [54]. The HOMA index when compared to other aromaticity indices occasionally disclose discrepancies attributed to the problems (parameterization or arbitrary choice of the reference system), which should not be ignored [55]. The NICS(0) and NICS(1) indices better reflect changes in both s- and p-electron structures, while the NICS(1)zz index and PDI reflect p- delocalization.

Conclusion

A traditional structure refinement of ethylammonium trimesate hydrate (**1**), based on a spherical atom model, was improved by

the use of transferred multipolar charge density parameters derived from refinement against theoretical structure factors. The residual factor, $R(F)$, was improved by ca. 45%, the average B factor was decreased from 2.584 to 2.380, and the rigid-bond test showed improvement by 49% for the final model. In the crystal structure, the carboxylate groups in **1** participate in a variety of hydrogen-bonding motifs and are representative of basic supramolecular synthons, belonging to the R_2^2 (8), R_4^4 (8), and R_2^3 (10) graph sets. Interactions in the solid state have also been characterized and classified by means of their estimated cumulative dissociation energy (eCDE), derived from topological analysis of the total charge density. The eCDE values indicate that the small S1 (R_2^2 (8) graph) motif is most stable and once formed as a stand-alone structure, may direct the self-assembly process. Further characterization of the interactions in this system by means of gas-phase reaction coordinate mapping and solution studies ought to prove useful in terms of judging the proposed hypothesis and the usefulness of self-assembly mechanisms deduced by the estimated cumulative dissociation energies of packing motifs.

Quantitative and qualitative analysis of the intermolecular interactions based on Hirshfeld surface analysis and the AIM derived dissociation energies has also been reported. It is interesting to note that qualitative picture is quite similar for either method but that the Hirshfeld surface method underestimates the importance of the strongest interactions, namely $N^+H...O^-$ and $O-H...O^-$ hydrogen bonds. This discrepancy results from the use of neutral atom electron densities to build the promolecule in the Hirshfeld surface analysis and neglects to properly account for interactions between charged groups/atoms. These effects are, however, properly accounted for in the topological analysis of the total charge density.

We have also sought to address the impact of geometry and packing on the aromaticity of the C₆ ring in **1**. In this regard, interpretation of our results is less clear, as opposite trends were observed across the aromaticity indices employed in this work. This may be due in part to the fact that these various indices depend on different phenomenon (e.g., geometry and magnetic susceptibility) and may actually reflect different aspects of what is commonly referred to as aromaticity [54].

Acknowledgements The authors are thankful for calculation facilities and software. Calculations have been carried out in Wroclaw Centre for Networking and Supercomputing (<http://www.wcss.pl>), grant no. 311.

Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

Open Access This article is distributed under the terms of the Creative Commons Attribution 4.0 International License (<http://creativecommons.org/licenses/by/4.0/>), which permits unrestricted use, distribution, and reproduction in any medium, provided you give appropriate credit to the original author(s) and the source, provide a link to the Creative Commons license, and indicate if changes were made.

References

- Desiraju GR (2002). *Acc Chem Res* 35(7):565–573
- Yuge T, Sakai T, Kai N, Hisaki I, Miyata M, Tohrai N (2008). *Chemistry* 14(10):2984–2993
- Rodriguez-Cuamatzi P, Arillo-Flores OI, Bernal-Uruchurtu MI, Hopfl H (2005). *Cryst Growth Des* 5(1):167–175
- Biradha K, Dennis D, MacKinnon VA, Sharma CVK, Zaworotko MJ (1998). *J Am Chem Soc* 120(46):11894–11903
- Szatyłowicz H (2008). *J Phys Org Chem* 21(10):897–914
- Ejsmont K, Zaleski J (2006). *Acta Cryst E* 62:3386–3388
- Stasyuk OA, Szatyłowicz H, Krygowski TM (2012). *J Org Chem* 77(8):4035–4045
- Stasyuk OA, Szatyłowicz H, Krygowski TM (2014a). *Org Biomol Chem* 12(3):456–466
- Stasyuk OA, Szatyłowicz H, Krygowski TM (2014b). *Croat Chem Acta* 87(4):335–342
- Talens VS, Englebienne P, Trinh TT, Noteborn WEM, Voets IK, Kiełtyka RE (2015). *Angew Chem Int Ed* 54(36):10502–10506
- Groom CR, Bruno IJ, Lightfoot MP, Ward SC (2016). *Acta Cryst B* 72:171–179
- Chesnut DB, Bartolotti LJ (2000). *Chem Phys* 257(2–3):175–181
- Poater J, Fradera X, Duran M, Solà M (2003). *Chem Eur J* A9(2):400–406
- Poater J, Fradera X, Duran M, Solà M (2003). *Chem Eur J* A9(5):1113–1122
- Poater J, García-Cruz I, Illas F, Solà M (2004). *Phys Chem Chem Phys* 6(2):314–318
- Poater J, Solà M, Duran M, Fradera X (2001). *J Phys Chem A* 105(25):6249–6257
- CrysAlis CCD, CrysAlis RED 1.171.32.29 Oxford diffraction. Oxford Diffraction Ltd, Abingdon
- Sheldrick GM (2008). *Acta Cryst A* 64:112–122
- Gajda K, Daszkiewicz Z, Kozubek E, Ejsmont K, Zarychta B (2014a). *Cryst Growth Des* 14(11):5737–5748
- Dovesi R, Orlando R, Erba A, Zicovich-Wilson CM, Civalieri B, Casassa S, Maschio L, Ferrabone M, De La Pierre M, D'Arco P, Noël Y, Causà M, Rérat M, Kirtman B (2014). *Int J Quantum Chem* 114(19):1287–1317
- Becke AD (1988a). *Phys Rev A* 38(6):3098–3100
- Lee C, Yang W, Parr RG (1988). *Phys Rev B* 37(2):785–789
- Guillot B, Viry L, Guillot R, Lecomte C, Jelsch C (2001). *J Appl Cryst* 34(2):214–223
- Jelsch C, Guillot B, Lagoutte A, Lecomte C (2005). *J Appl Cryst* 38(1):38–54
- Hansen NK, Coppens P (1978). *Acta Cryst A* 34:909–921
- Frisch MJ, Trucks GW, Schlegel HB, Scuseria GE, Robb MA, Cheeseman JR, Scalmani G, Barone V, Mennucci B, Petersson GA, Nakatsuji H, Caricato M, Li X, Hratchian HP, Izmaylov AF, Bloino J, Zheng G, Sonnenberg JL, Hada M, Ehara M, Toyota K, Fukuda R, Hasegawa J, Ishida M, Nakajima T, Honda Y, Kitao O, Nakai H, Vreven T, Montgomery JA Jr, Peralta JE, Ogliaro F, Bearpark M, Heyd JJ, Brothers E, Kudin KN, Staroverov VN, Kobayashi R, Normand J, Raghavachari K, Rendell A, Burant JC, Iyengar SS, Tomasi J, Cossi M, Rega N, Millam JM, Klene M, Knox JE, Cross JB, Bakken V, Adamo C, Jaramillo J, Gomperts R, Stratmann RE, Yazyev O, Austin AJ, Cammi R, Pomelli C, Ochterski JW, Martin RL, Morokuma K, Zakrzewski VG, Voth GA, Salvador P, Dannenberg JJ, Dapprich S, Daniels AD, Farkas Ö, Foresman JB, Ortiz JV, Cioslowski J, Fox DJ (2009) *Gaussian, Inc., Wallingford CT*
- Kruszewski J, Krygowski TM (1972). *Tetrahedron Lett* 13(36):3839–3842
- Krygowski TM (1993). *J Chem Inf Comput Sci* 33(1):70–78
- Krygowski TM, Cyrański MK (1996). *Tetrahedron* 52(30):10255–10264
- Krygowski TM, Cyrański MK (2001). *Chem Rev* 101(5):1385–1419
- Krygowski TM, Zachara-Horeglad JE, Palusiak M, Pelloni S, Lazzeretti P (2008). *J Org Chem* 73(6):2138–2145
- Schleyer PVR, Maerker C, Dransfeld A, Jiao H, Van Eikema Hommes NJR (1996). *J Am Chem Soc* 118(26):6317–6318
- Cyrański MK, Krygowski TM, Wisiorowski M, Hommes N, Schleyer PV (1998). *Angew Chem Int Ed* 37(1–2):177–180
- Schleyer PV, Manoharan M, Wang ZX, Kiran B, Jiao HJ, Puchta R, Hommes N (2001). *Org Lett* 3(16):2465–2468
- Corminboeuf C, Heine T, Seifert G, Von Ragué Schleyer P, Weber J (2004). *Phys Chem Chem Phys* 6(2):273–276
- Fallah-Bagher-Shaidaei H, Wannere CS, Corminboeuf C, Puchta R, Schleyer PV (2006). *Org Lett* 8(5):863–866
- Bader RFW (1990). *Atoms in Molecules: a Quantum Theory*. The International Series: Monographs in Chemistry. Clarendon Press, Oxford
- Bader RFW (1991). *Chem Rev* 91(5):893–928
- Bader RFW, Stephens ME (1975). *J Am Chem Soc* 97(26):7391–7399
- Fradera X, Austen MA, Bader RFW (1999). *J Phys Chem A* 103(2):304–314
- Zarychta B, Zaleski J, Kyzioł J, Daszkiewicz Z, Jelsch C (2011). *Acta Cryst B* 67:250–262
- Hirshfeld FL (1976). *Acta Cryst A* 32:239–244
- Espinosa E, Molins E (2000). *J Chem Phys* 113(14):5686–5694
- Kuleshova LN, Zorky PM (1980). *Acta Cryst B* 36(9):2113–2115
- Zorkii PM, Kuleshova LN (1981). *J Struct Chem* 22(6):921–923
- Brezgunova ME, Aubert E, Dahaoui S, Fertey P, Lebegue S, Jelsch C, Ángyán JG, Espinosa E (2012). *Cryst Growth Des* 12(11):5373–5386
- Espinosa E, Alkorta I, Elguero J, Molins E (2002). *J Chem Phys* 117(12):5529–5542
- Spackman MA, McKinnon JJ (2002). *CrystEngComm* 4(66):378–392
- Palusiak M, Simon S, Solà M (2006). *J Org Chem* 71(14):5241–5248
- Zych T, Misiaszek T, Szostak MM (2007). *Chem Phys* 340(1–3):260–272
- Koch U, Popelier PLA (1995). *J Phys Chem* 99(24):9747–9754
- Gajda K, Zarychta B, Daszkiewicz Z, Domański AA, Ejsmont K (2014b). *Acta Cryst C* 70:575–579
- Cyrański MK, Krygowski TM, Katritzky AR, Schleyer PVR (2002). *J Org Chem* 67(4):1333–1338
- Bultinck P, Rafat M, Ponc R, Van Gheluwe B, Carbó-Dorca R, Popelier P (2006). *J Phys Chem A* 110:7642–7648
- Szczepanik DW, Solà M, Andrzejak M, Pawelek B, Dominikowska J, Kukułka M, Dyduch K, Krygowski TM, Szatyłowicz H (2017). *J Comput Chem* 38:1640–1654