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Theoretical crystal structure prediction of aminosalicic acid: charge density topological and electrostatic analyses.

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Highlights

- 31 Crystal packings of aminosalicic acid were predicted
- Predicted structure with lowest energy is close to real structure
- Electrostatic properties and molecular interactions were compared

Abstract

The crystal structure prediction of the possible stable packings of pharmaceutical drug 4-amino-2-hydroxybenzoic acid was initiated through *ab initio* methods. The lattice energy values of the hypothetical conformers of the molecule generated for the global search were minimized, employing the associated distributed multipolar electron density. The crystal packing with minimum global energy corresponds to the experimental crystal. The conformer generated from the valid minimization was subjected to Quantum Theory of Atoms In Molecules (QTAIM) analysis in order to improve insight on the chemical properties of the crystal on which the pharmaceutical activity depends. The electron density and the Laplacian of the electron density were analyzed in detail for the non-covalent interactions in the crystal. While the dimer formed by the COOH/COOH homo-synthon has the strongest energy and is mostly electrostatic, other dimers formed in the crystal are mostly stabilized by dispersive forces. The complementarity of

the inner and exterior electrostatic potential on the Hirshfeld was analyzed in the different crystal packings generated.

Keywords: Aminosalicyclic acid; Crystal Structure Prediction; QTAIM; Interaction energy; Intermolecular Interactions; Electrostatic potential.

1. Introduction

The crystal structures of molecule are the uniform and multidimensional arrangement of the base atoms in the lattice point, generating a least energy thermodynamically stable phase [1,2]. As the pharmaceutical properties and the bioavailability depend on the crystal phase of the molecule, theoretical prediction of possible crystal structures gained importance. The prior aim of the current research is to analyze the predicted crystal lattices of Amino Salicylic Acid (AMSA) molecule and compare them with the experimental reported structure.

The AMSA compound (Fig. 1) is an oral antibiotic pharmaceutical drug used against tuberculosis [3]. It has also been used as a second line agent to sulfasalazine in people with ulcerative colitis and Crohn's disease [4,5]. The crystal structure prediction of the title compound explores the lattice energy surface to identify unknown possible polymorphic crystal structure. The arrangement of molecules in the crystal lattice guides the physical as well as chemical properties and thereby the pharmaceutical performance. As the shape and the size of the solid drugs can influence the dissolution rate, lyophilization and bioavailability, the crystal structure prediction for the stable crystal lattices of pharmaceutical drugs has gained importance.[6]

Figure 1. Chemical structure of AMSA molecule

The prediction of crystal structure of the compound relevant to our study has one experimental crystal packing reported in the CCDC, corresponding to structures with codes AMSALA, AMSALA01 and AMSALA02 [7] successively determined. We have identified some other possible crystal packings from *ab initio* method and thus validate our prediction methodology with respect to the reported X-ray structure.

2. Materials and methods.

2.1 Crystal Structure Prediction

The aim of the research was to identify the lowest energy conformers of AMSA molecule belonging to the possible common space groups listed in the crystal database. The molecular structure of the parent molecule was subjected to an initial gas phase optimization using the DFT [8] approach via B3LYP/6-31g(d) basis set operations using Gaussian 09 package [9]. The initial optimization validated the geometric structure of the parent molecule for the global search. The search for a dense crystal packing was performed in the common space groups P1, P-1, P2, Pm, Pc, P2₁, P2/c, P2₁/m, P2/m, P2₁/c, Cc, C2, C2/c, Pnn2, Pba2, Pnc2, P22₁, Pmn2₁, Pma2, P2₁2₁2₁, P2₁2₁2, Pca2₁, Pna2₁, Pnma and Pbca using the MOLPAK package [10]. The global search for dense crystal structures of AMSA were done by performing step-by-step orientations of the central parent molecule in all common coordination geometries and constructing the appropriate coordination patterns with unit cell volume as a function. The packings of the AMSA molecule within the threshold interactions of the neighboring fragments of the parent molecules were generated from -90° to 90° rotation in 10° steps. The orientation and the repetition of AMSA in the multidimensional grid generated 6859 (19³) hypothetical structures. The lattice energy of these starting structures was optimized by the PMIN [10] operation implementing the repulsion potential field alone as the inner lattice minimization. The hypothetical densest structures of AMSA molecule with minimum cell volume generated in the commonly encountered 31 space groups were subjected to inner lattice minimizations using the DMACRYS algorithm [11] - incorporating a repulsion-dispersion potential field of the form (1)

$$(1) U = \sum_{i \in 1, k \in 2} [(A_{ii}A_{kk})^{1/2}] \exp [-1/2(B_{ii} + B_{kk}) R_{ik}] - (C_{ii}C_{kk})^{1/2} / R_{ik}^6$$

where i and k are the atoms in different types of molecules 1 and 2. The potential field incorporated in the lattice minimization was generated from the FIT potential, parameterized by Williams and Cox [12] with additional terms for the hydrogen atoms bound to nitrogen later fitted by Coombes *et al.* [13]. The discrepancy of the PMIN lattice minimization with repulsion alone potential was rectified in the inner lattice minimization, thereby confirming the accuracy. The electrostatic interactions along with intermolecular binding of the AMSA molecules were analyzed in detail from the set of multipoles generated from the GDMA [14] algorithm via MP2 level [15] charge density scrutiny through MP2/6-31G(d,p) basis set operation. The lattice

minimized AMSA molecules attaining the Born criteria of mechanical stability [16] with valid eigenvalue representations were tabulated [Table 1] on the basis of energy ranking. The thermodynamic stability of the AMSA molecule was verified from the second derivative properties calculated from the C_{ij} elements of the Hessian matrix. In the current research, the invalid hypothetical structures generated with negative eigenvalues were subjected to re-minimization by removing the non-zero representation from the symmetry constraints. The quantitative molecular electrostatic potential map for both experimental and predicted crystal structures was generated and visualized on the three dimensional surface using the program WFA-SAS [17].

2.2 Bader analysis

Topological analysis was carried out for the gas phase molecule lifted from the predicted global minimum structure via Bader Quantum Theory of Atom In Molecules (QTAIM) [18]. This approach tends to analyze the characteristics of chemical bonding (closed and open shell interactions) [19]. Single point calculations were carried out using Hybrid GGA Functional wB97X-D [20] (dispersion corrected) 6-311G ++(d,P) basis set (triple zeta) over the asymmetric unit of AMSA and dimeric pairs in Gamess package [21]. For the QTAIM analysis, the wave function was obtained from the above calculations and analyzed using Multiwfn 3.3.9.[22]

2.2 Electrostatic complementarity in the crystals.

The charge density of the AMSA molecule was modeled using the multipolar atom of Hansen & Coppens [23]. Pseudo-atom multipolar databases offer the possibility to reconstruct the molecular electron density, without the need of performing first principle calculations at each time. The electron density parameters were transferred from the experimental ELMAM2 database of multipolar atoms [24] which is issued from single crystal diffraction studies of peptides and small molecules at ultra-high resolution. After transfer, the number of valence electrons of all atoms was uniformly modified to ensure electroneutrality. The X-H bond lengths were elongated according to standard neutron diffraction distances [25]. The electrostatic potential V was computed with the MoPro software on the Hirshfeld surface [26]. V_{int} was computed from the reference molecule while the external potential V_{ext} was generated from the ensemble of molecular neighbors in contact with the inner molecule. Hirshfeld surfaces and contact enrichment ratios were obtained with MoProViewer [27]. The electrostatic complementarity was assessed by analyzing the V_{int} and V_{ext} values on the Hirshfeld surface.

3. Results

3.1 Predicted crystal structures

Table 1. List of predicted possible stable crystal structures of AMSA molecule. The most stable packing and the experimental one are in bold.

Conformers	ID	Space group	U_{lattice} kJ/mol	a (Å)	b (Å)	c (Å)	β (°)	density (g/cm ³)	Z'
exp.		P2 ₁ /c	-121.2	7.1371(3)	3.7278(2)	24.4465(12)	94.386(2)	1.57	1
STR 1 Δ / exp	FC	P2 ₁ /c	-131.7 +8.7%	6.99 -2.0%	3.67 -1.6%	24.82 +3.7%	90.94 +3.6°	1.60 +1.8%	1
STR 2	DC	C2/c	-131.4	13.81	3.59	26.76	103.06	1.58	1
STR 3	AU	Pna2 ₁	-126.5	16.29	3.72	10.95	90.00	1.53	1
STR 4	FA	P2 ₁ /n	-125.6	7.25	26.44	3.61	71.78	1.55	1
STR 5	AQ	P2 ₁ 2 ₁ 2 ₁	-124.5	13.49	13.19	3.64	90.00	1.57	1
STR 6	AY	Pca2 ₁	-124.2	16.59	3.63	11.02	90.00	1.53	1
STR 7	DA	Cc	-123.3	3.58	16.83	11.03	90.82	1.53	1
STR 8	AH	P2 ₁	-123.0	3.57	11.01	8.59	78.23	1.54	1
STR 9	AF	P2 ₁	-122.9	6.96	3.60	16.54	129.60	1.59	1
STR 10	AK	P2 ₁ /c	-122.8	12.82	3.73	14.16	102.68	1.54	1
STR 11	AA	P1	-120.8	3.58	7.00	7.11	84.94	1.55	1
STR 12	AV	Pna2 ₁	-119.1	15.23	12.16	3.69	90.00	1.49	1
STR 13	AM	P2 ₁ /c	-118.4	7.12	7.11	13.37	99.48	1.52	1
STR 14	AZ	P2 ₁ 2 ₁ 2 ₁	-117.6	25.31	3.64	6.99	90.00	1.58	1
STR 15	AB	P-1	-117.2	6.78	7.22	7.74	79.35	1.56	1
STR 16	DB	C2	-114.0	14.62	3.61	12.73	83.47	1.53	1
STR 17	AS	Pna2 ₁	-112.0	11.14	16.84	3.62	90.00	1.50	1
STR 18	CB	Pbca	-111.5	16.47	11.96	6.82	90.00	1.51	1
STR 19	AP	P2 ₁ 2 ₁ 2	-111.2	7.37	25.34	3.66	90.00	1.49	1
STR 20	BA	P2 ₁ 2 ₁ 2	-111.2	25.34	7.35	3.66	90.00	1.49	1
STR 21	BB	P1	-111.1	25.33	7.37	3.66	90.00	1.49	1
STR 22	CD	P2 ₁ /c	-110.4	13.54	6.78	14.68	88.65	1.51	2
STR 23	AI	P2 ₁ /c	-110.0	9.75	5.32	13.96	97.83	1.42	1
STR 24	BH	Pca2 ₁	-108.7	13.11	3.77	13.31	90.00	1.55	1
STR 25	BD	Pna2 ₁	-99.1	16.79	8.97	4.71	90.00	1.43	1
STR 26	DE	C2/c	-97.6	24.08	7.43	13.21	40.21	1.33	1
STR 27	CA	P-1	-96.9	8.02	6.86	6.96	75.05	1.51	1
STR 28	CE	P2 ₁ /b	-94.1	15.52	8.59	11.31	88.82	1.35	2
STR 29	BF	Pm	-93.8	8.42	22.39	3.73	89.32	1.45	2
STR 30	CC	Pbca	-85.7	7.53	7.12	27.26	90.00	1.39	1
STR 31	DD	C2/c	-85.0	13.79	8.01	14.83	62.13	1.40	1

3.2 Global minimum

In the detailed study of the structures from Table 1, the global minimum of the AMSA molecule generated at -131.7 kJ/mol with density of 1.60 g/cm³. As the stability of the crystal structure indirectly depends on the energy associated, studies were carried out to justify the thermodynamic stable nature. The predicted global minimum of AMSA was found to be a monoclinic crystal system with P2₁/c space group. The lattice parameters of the structure were compared with those of the experimental structure and the values were found in good agreement with a maximal deviation of 3.7% [Table 1]. The density of the predicted *STR1* packing is only 1.8% larger than the experimental value. The generated lowest energy structure of AMSA molecule was found to be mechanically stable from the diagonal elements of the Hessian matrix (Table 2) indicating that the Born criteria of stability were satisfied [16].

Table 2. Elements of the mechanical stiffness (GPa) of the predicted most stable crystal of AMSA molecule.

Predicted conformer	C_{11}	C_{22}	C_{33}	C_{44}	C_{55}	C_{66}	Young modulus (GPa)
<i>STR1</i>	74.2	25.8	100.6	23.8	40.8	19.7	51.1

dimer 2

dimer 3

dimer 4

dimer5

dimer 6

Figure 2. Molecular graph of the monomer and of the eight independent dimers of *STR1* crystal structure displaying bond paths (green curves) and critical points (CP). (3,-1) intermolecular bonding CPs are shown as green spheres. Saddle (3,+1) CPs are in blue and cage (3,+3) CPs are in brown.

Table 3 Hydrogen bonds prevailed in the predicted [STR 1] / [EXP] crystal

D-H...A	D-H (Å)	H...A (Å)	D...A (Å)	D-H...A (°)
O1-H6...O3*	0.976	1.970/1.790	2.755/2.611	135.9/149.5
O2-H7...O3#8	1.015	1.738/1.663	2.749/2.640	173.7/174.4
N1-H5...O1#1	1.009	3.133/2.127	4.031/3.137	149.0/173.3
N1-H4...O1#4	1.009	2.211/2.531	2.959/3.337	129.7/136.1
N1-H4...O1#5	1.009	2.757/2.531	3.545/3.337	135.2/136.1
N1-H5...N1#6 ¶	1.009	2.359/3.223	2.834/3.394	107.8/93.3
N1-H5...N1#7	1.009	2.056/3.136	2.834/3.394	132.2/99.1
C4-H1...O1#1	1.083	2.772/3.439	3.811/4.095	160.6 /128.1
C5-H2...O2#2	1.083	2.738/2.660	3.566/3.527	133.1/136.7
C5-H2...O2#3	1.083	2.591/2.757	3.238/3.527	117.6/138.5
C6-H3...O3#5	1.083	2.764/2.840	3.506/3.507	125.5/128.1

* Intramolecular interaction;

Symmetry operators : #1 $-x+\frac{1}{2}, +y-\frac{1}{2}, -z+\frac{1}{2}+1$; #2 $-x, -y-1, -z+2$; #3 $-x, -y, -z+2$;

#4 $+x-1, +y, +z$; #5 $+x-1, +y+1, +z$; #6 $-x-\frac{1}{2}, +y-\frac{1}{2}, -z+\frac{3}{2}$; #7 $-x-\frac{1}{2}, +y+\frac{1}{2}, -z+\frac{3}{2}$;

#8 $-x+1, -y-1, -z+2$

¶ no bond path, nor critical point, there is bond path instead between N1 and H5^{#6}., which is reciprocal of H5...N1^{#7}

3.3 Intermolecular interactions

Thermodynamic stability of the predicted conformer was further analyzed in detail from the possible intermolecular hydrogen bonds prevailed in the system. As the crystallization mechanism of the molecule depends on the ability to achieve strong interactions, the possible short contacts were studied from the PARST [28] analysis (Table 3). The interacting dimers stabilizing the structure are shown in Fig. 2.

The hydrogen bond analysis reveals the stabilized nature of the predicted structure. The investigation to perceive the contribution of the intermolecular short contacts towards the crystal stability was implemented from the two dimensional fingerprint plot of the Hirshfeld surface using the Crystal explorer package [29] (Fig.3).

Figure 3. Two dimensional fingerprint plots in crystal stacking of (a) predicted [STR 1] and (b) experimental AMSA

H...H contacts contribute to 39.8% and 39.5% over the total Hirshfeld Surface (HS) area of the predicted and experiment crystal structures, respectively. The shortest distance $d(\text{H5}, \text{H5}) = 1.913 \text{ \AA}$ is found in dimer 3 of STR1 between two NH_2 groups, while the equivalent distance is $3.206 \text{ \AA}$ in EXP structure. In EXP crystal, $d(\text{H1}, \text{H1}) = 2.305 \text{ \AA}$ in dimer 1 is the shortest H...H contact.

The hydrogen atoms of the NH_2 functional group form a H-bond with the phenol oxygen atom (dimer 1) and interact with the nitrogen atom, perpendicularly to the NH_2 moiety (dimer 6). The $\text{H}\cdots\text{N}$ interactions represent a small proportion of the HS area (pred:2.7%/exp:0.7%).

The shortest $\text{O}\cdots\text{H}$ interaction is found in dimer 7. This corresponds to the double hydrogen atom in the $(\text{COOH})_2$ homo-synthon [30] and is presumably the strongest electrostatic interaction in the crystal. The Hirshfeld surface analysis reveals the dominant nature of the $\text{O}\cdots\text{H}/\text{H}\cdots\text{O}$ interactions via the terminal acid functional groups attached to the aromatic ring. The 2D fingerprint plot of the Hirshfeld surface exhibits the spikes of the $\text{O}\cdots\text{H}/\text{H}\cdots\text{O}$ interaction towards the lowest (d_i, d_e) region. The phenol O-H group is involved as donor in an intramolecular $\text{O}-\text{H}\cdots\text{O}$ hydrogen bond towards the $\text{O}=\text{C}$ oxygen atom.

Dimers #2 and #3 show some similarity as molecules have the same relative orientations (rotation) but different translation. Furthermore, the dimer 8 is due to $\text{C}\cdots\text{C}$ interactions which correspond to parallel displaced cycle stacking. The stacking interaction of the aromatic carbon atoms can also be seen in Fig. 4 showing the Hirshfeld surface and some neighbor molecules.

The fingerprint plot also highlights the spikes at short distance of the $\text{N}\cdots\text{H}/\text{H}\cdots\text{N}$ contacts, indicating the strong interaction.

Figure 4 : Hirshfeld surface of the AMSA molecule showing the intermolecular interactions for both (a) Experiment and (b) Predicted structure

The above trend in the interaction energies was further evident from contact enrichment ratio [31] and % contacts listed in Table 4.

Table 4. Nature of intermolecular contacts on the Hirshfeld surface by chemical types and their enrichment. Hc Hydrogen atoms bound to carbon are distinguished from the more polar Hp bound to O and N. The major contacts and most enriched ones are highlighted in bold characters. The last two lines show the surface content and contact enrichment globally in terms of polar (pol) charged atoms and non-polar (np), C and Hc atoms.

	Experimental					Predicted STR1				
chem.	O	Hp	N	Hc	C	O	Hp	N	Hc	C
surf. %	21.1	25.8	4.0	18.3	30.8	21.4	24.0	4.3	20.0	30.3
O	0.3		%	contacts		0.6		%	contacts	
Hp	20.2	8.0				16.4	6.1			
N	0.0	2.5	0.7			0.3	6.2	0.0		
Hc	13.9	9.9	0.0	4.6		15.9	9.7	0.0	5.2	
C	5.9	5.0	3.7	5.2	20.1	8.2	5.9	2.1	4.0	19.4
O	0.07			enrich-		0.15			enrich-	
Hp	1.86	1.11		ment		1.55	0.96		ment	
N	0.00	1.22	4.77			0.14	2.88	0		
Hc	1.78	0.97	0.03	1.26		1.89	0.96	0	1.30	
C	0.49	0.31	1.63	0.45	2.23	0.66	0.4	0.82	0.34	2.24
surf. %	50.9			49.1		49.7			50.3	
enrich.	pol,pol 1.22		np,np 1.24		pol,np 0.77	pol,pol 1.20		np,np 1.13		pol,np 0.84

Globally, the EXP and STR1 crystals show similar contact statistics, the % contacts being 96.2% correlated. The major contacts are of O...Hp (O...H-O and O...H-N hydrogen bonds) and C...C representing aromatic cycle stacking, followed by weak C-H...O hydrogen bonds. Hp..Hp contacts are due to the proximity of NH₂ groups hydrogen-bonded with the phenol oxygen atom. The predicted STR1 structure shows a much stronger occurrence of N-H...N contacts than in the EXP crystal. This interaction is however not in a hydrogen bond as its electrostatic energy (computed after ELMAM2 database transfer is very small) $E_{\text{elec}}(\text{H5},\text{N1}) \approx -10^{-3}$ kJ/mol and the NH₂ nitrogen atom does not show any electron lone pair above or below the sp² plane.

The C...C contact is the most enriched in the EXP structure due to parallel displaced aromatic cycle stacking. Such molecule made of a heterocycle bearing electropositive and electronegative atoms is prone to stacking displaying good electrostatic complementarity.

The non-polar atoms (C and Hc) as well as the charged (O, Hp, N) atoms represent globally approximately half of the Hirshfeld surface. The polar...polar and non-polar...non-polar contact types are both slightly enriched ($E_{\text{exp}} > 1.2$) showing the over-represented occurrence of

electrostatic and of hydrophobic interactions. On the other hand, cross polar...non-polar contacts ($E_{\text{exp}} = 0.77$) are slightly under-represented. The weak C-H...O hydrogen bonds represent however an exception, it is a major contact which is significantly enriched ($E_{\text{exp}}=1.78$)

3.4 Molecular Structure

The STR1 AMSA molecule exhibits a close to co-planar geometry with 30° torsion angle for the carboxylic acid and minimal deviation of 0.07° for the amine and 3.2° for the alcohol groups. This small deviation is not influenced much in the C-C bond lengths [~ 1.395 Å] and internal C-C-C bond angles [$\sim 120^\circ$]. The strong electron withdrawing nature of the amine and carboxylic acid group leads to larger bond distances for C3-N1 [1.410 Å] and C1-C7 [1.457 Å]. The molecular structure of AMSO exhibits the intramolecular H-bond O1-H6...O3, which forms a five membered ring (Fig. 5a). Moreover, this intramolecular interaction dilutes the H-bond donor capabilities of -OH group and makes the carboxylic and amine group having major contribution in intermolecular hydrogen bonding interactions. The structure is indeed stabilized by N-H...O [N1-H4...O1; N1-H5...N1, 2.834 Å] and C-H...O [C4-H1...O1, 3.811 Å; C5-H2...O2, 3.238 Å; C6-H3...O3, 3.505 Å] intermolecular H-bonds. The COOH homo-synthon forms the centrosymmetric dimer 7 through a double hydrogen bond [O2-H7...O3, 2.749 Å] (Fig 5b)]. These dimers are stacked parallel by means of C6...C5 (3.473 Å), C4...C2 (3.473 Å), C1...O3 (3.250 Å) and N1...C3 (3.474 Å) interactions.

(a)

(b)

Figure 5. Energy minimized (a) gas phase conformer and (b) Autostereogram AMSA molecule in STR1 predicted FC crystal (global minimum) showing O-H $\cdots$ O interactions. **a** axis is horizontal.

3.5 Open Shell Interactions

The (3,-1) covalent bond critical point (BCP) [32] were characterized in AMSA molecule for the calculation using *wB97X-D 6-311G++(d,P) basis set*. The complete topological parameters associated with (3,-1) BCP in the theoretical electron density are listed in supplementary Table S1. The topological values at the BCPs after ELMAM2 electron density transfer are also shown. The electron density ρ_{cp} and Laplacian $\nabla^2\rho_{cp}$ values show respectively an 88 and 91 % correlation coefficient, after theoretical calculation and ELMAM2 transfer. The corresponding contour plots of theoretical electron density and Laplacian 2D maps are shown in Figures S1 and S2.

3.6 Closed Shell Interactions

The molecular crystal stability by means of intermolecular interactions was investigated via QTAIM approach. Table 5 shows the topological parameters for the main interactions prevailed in the AMSA crystal. This includes the C $\cdots$ C, C $\cdots$ O, C $\cdots$ N and H $\cdots$ H interactions with distances of 3.473 Å, 3.250 Å, 3.474 Å and 2.332 Å respectively. The existence of these interactions was further observed in QTAIM analysis by locating the bond critical points (BCP) on the bond path between dimers #3, #4 and #8 (Fig. 2). The investigation was extended further by finding CPs of the O-H...O intermolecular [O2-H7...O3^{#8}] and intramolecular hydrogen bond [O1-H6...O3] with the energy values of -44.8 kJ/mol and -26.3 kJ/mol respectively (Table 5). The topological parameters for these interactions [$\rho(\mathbf{r}_{cp})$ and $\nabla^2\rho(\mathbf{r}_{cp})$] at the BCP reveal that these are the strongest non-covalent interactions prevailed in the AMSA crystal structure.

Following to the O-H...O interactions, the two N-H...N hydrogen bonds were found to be strong as their average energy value is about -24.1 kJ/mol.

Unlike N1-H4...O1^{#4} [-13.1 kJ/mol], the energy of N1-H4...O1^{#5} [-3.6 kJ/mol] and N1-H5...O1^{#1} [-1.2 kJ/mol] intermolecular H-bonds are weak and are comparable with those of C-H...O interactions [C4-H1...O1^{#1}, 3.6 kJ/mol, C5-H2...O2^{#2}, -4.5 kJ/mol, C5-H2...O2^{#3}, -6.3 KJ/mol and C6-H3...O3^{#5}, -5.4 kJ/mol. The weak characters of N1-H4...O1^{#5} and N1-H5...O1^{#1}

interactions are attributed to the low values of total energy density, $H(\mathbf{r})$ [1.7 H/ Å³ and 1.2 H/ Å³] at the BCP, whereas for the interaction N1-H4...O1^{#4}, it reaches 4.8 kJ/mol. The energy of the N-H...O hydrogen bonds correlate also with the H...O distances.

Among C-H...O intermolecular interactions, C5-H2...O2^{#3} and C6-H3...O3^{#5} have a major contribution in the molecular self-assembly of AMSA. The calculated energies for these interactions were -6.3 kJ/mol and -5.4 kJ/mol respectively. Closed shell and open shell interactions are characterized by $|V(\mathbf{r})|/G(\mathbf{r}) < 1$ for closed shell and > 2 for open shell, respectively, where $V(\mathbf{r})$ and $G(\mathbf{r})$ are the local potential and kinetic energy density as proposed by Espinosa *et al.* [33].

Table 6 shows the interaction energies E_{int} calculated from counterpoise method [34] for the monomer as well as for 8 dimers. Except dimer 7 and dimer 8, the interaction energies E_{int} of all other dimers are of smaller magnitude. The strong binding energies of dimer 7 shows that the molecular self-assembly is, in first instance, governed by the double O-H...O hydrogen bond involving the COOH homo-synthon which yields a centrosymmetric dimer. Dimer 8 has the second strongest E_{tot} energy as it has a large stacking interaction surface and is principally dispersive. Usually, O-H...O interactions have strong to medium hydrogen bond characteristics which are in good agreement with QTAIM study for E_{bond} O2-H7...O3^{#8} [-44.8 kJ/mol].

Dimers 2 and 3 show similar relative orientation of the molecules as their symmetry operators differ by a translation along the short **b** axis. The O2 and H2 atoms display bifurcated O2...H2 hydrogen bonds involving the two dimers (Fig. 2). Dimers 4 and 5 share also some similarity, both having N1-H4...O1 and C6-H3...O3 bifurcated hydrogen bonds.

Table 5. List of the dimer interactions prevailed in the predicted AMSA structure [STR 1] and topological properties at the critical points. G , V and H are the kinetic, potential and total energy density respectively. $E_{\text{Hbond}} = \frac{1}{2} V(\mathbf{r})$ bond is the dissociation energy described in the article Espinosa *et al.* 2001 [33].

Interaction	density ρ (e/Å ³)	Laplacian (e/Å ⁵)	$G(\mathbf{r})$ (a.u.)	$V(\mathbf{r})$ (a.u.)	$H(\mathbf{r})$ (kJ/B ³ /mol)	$ V(\mathbf{r}) /G(\mathbf{r})$	E_{Hbond} (kJ/mol)
O1-H6...O3*	0.0258	0.0945	0.0218	-0.0200	4.73	0.91	-26.3
C4-H1...O1 ^{#1}	0.0047	0.0148	0.0032	-0.0027	1.24	0.85	-3.6
N1-H5...O1 ^{#1}	0.0017	0.0075	0.0014	-0.0010	1.19	0.68	-1.2
C5-H2...O2 ^{#2}	0.0057	0.0177	0.0039	-0.0034	1.35	0.89	-4.5
C5-H2...O2 ^{#3}	0.0078	0.0267	0.0058	-0.0048	2.43	0.84	-6.3
H2...H2 ^{#3}	0.0031	0.0120	0.0023	-0.0017	1.74	0.72	
H3...H6 ^{#4}	0.0095	0.0330	0.0068	-0.0054	3.76	0.79	

N1-H4...O1 ^{#4}	0.0151	0.0544	0.0118	-0.0099	4.79	0.84	-13.1
C6-H3...O3 ^{#5}	0.0068	0.0233	0.0050	-0.0041	2.22	0.83	-5.4
N1-H4...O1 ^{#5}	0.0044	0.0161	0.0034	-0.0027	1.68	0.81	-3.6
N1-H5...N1 ^{#6}	0.0256	0.0938	0.0209	-0.0184	6.68	0.88	-24.1
N1-H5...N1 ^{#7}	0.0256	0.0938	0.0209	-0.0184	6.68	0.88	-24.1
O2-H7...O3 ^{#8}	0.0398	0.1173	0.0317	-0.0341	-6.31	1.087	-44.8
N1...C3 ^{#9}	0.0046	0.0148	0.0030	-0.0023	1.86	0.76	
C6...C5 ^{#9}	0.0053	0.0144	0.0029	-0.0022	1.89	0.75	
C1...O3 ^{#9}	0.0065	0.0223	0.0046	-0.0036	2.64	0.78	
C4...C2 ^{#9}	0.0050	0.0141	0.0028	-0.0021	1.93	0.74	

* Intramolecular interaction; #1 $-x+\frac{1}{2}, +y+\frac{1}{2}, -z+\frac{1}{2}+1$; #2 $-x, -y-1, -z+2$; #3 $-x, -y, -z+2$; #4 $+x-1, +y, +z$; #5 $+x-1, +y+1, +z$; #6 $-x-\frac{1}{2}, +y-\frac{1}{2}, -z+\frac{1}{2}+1$; #7 $-x, -\frac{1}{2}, +y+\frac{1}{2}, -z+\frac{1}{2}+1$; #8 $-x+1, -y-1, -z+2$; #9 $+x, +y+1, +z$

Table 6. Single point energy values $E_{\text{WB97X-D}}$ (in atomic units) for the monomer and the independant dimers of predicted AMSA [STR 1]. Interaction energy, $E_{\text{int}} = E_{\text{dimer}} - 2E_{\text{monomer}}$ (in kJ/mol).

	$E_{\text{WB97X-D}}$ (a.u.)	E_{int} (kJ/mol)
Monomer	-551.4028	-
Dimer 1	-1102.8109	-14.1
Dimer 2	-1102.8093	-9.8
Dimer 3	-1102.8086	-8.0
Dimer 4	-1102.8095	-10.3
Dimer 5	-1102.8111	-14.4
Dimer 6	-1102.8061	-1.4
Dimer 7	-1102.8356	-78.9
Dimer 8	-1102.8178	-32.1

3.7 Energy of molecular dimers

The molecules in the experimental and predicted crystal structure are packed in a ribbon pattern and establish C-H...O, N-H...O, N-H...N and O-H...O types of hydrogen bonds. The dimer with COOH...COOH homo-synthon is highly electrostatic. Moreover, it is, by far, the dimer with strongest total energy.

It appears that most other packings are predominantly stabilized by dispersion energies in both the experimental and predicted crystal structures (Table 7). All the three energy frameworks for the experimental and predicted structures are shown in the Fig. 6.

From the pixel method, the intermolecular energy between 8 molecular pairs (dimers) were calculated and are listed in Table 8 for both predicted and experimental crystal structures. The E_{tot} energy values of predicted packing agree generally with the E_{int} values calculated from counterpoise method. Also, most of the interaction energy values of the dimers found in the experimental and predicted crystal structures are comparable except for dimer 1, framed by C4-H1....O1 and N1-H5....O1 interactions. The corresponding total energy values are -31.6 kJ/mol [experiment] and -13.6 kJ/mol [predicted]. Regarding the O-H...O interaction, the strong interaction energy was calculated for dimer 7, in which the carboxylic group interact with the same of the neighboring molecule yielding E_{tot} values of -71.3 and -61.1 kJ/mol for experiment and predicted crystal structures respectively.

Globally, the $E_{\text{wB97X-D}}$ dimer internal energies (Table 6) are 95.7% correlated with the PIXEL E_{tot} values (Table 7).

Real	Predicted
Coloumb

Dispersion

Figure 6. Dispersion energy frameworks between experimental and predicted crystal structures. The crystal is viewed down the **a** axis. (A cylinder scale of 80 was used for all three energies).

Table 7. PIXEL lattice energies (kJ/mol) for experimental and predicted STR1 crystal structures.

term	Exper.	Predicted
E_{coul}	-88.3	-116.9
E_{pol}	-40.7	-54.2
E_{Disp}	-109.4	-121.7
E_{Rep}	112.3	174.4
E_{total}	-126.0	-118.4

Table 8: PIXEL energies (kJ/mol) for predicted STR1 structure (first line) and experimental (second line) between the molecular pairs. ^p and ^e in last column: predicted or experimental structure only. $E_{\text{int}} = E_{\text{dimer}} - 2E_{\text{monomer}}$. The strong E_{coul} values are highlighted in bold.

S.N o	Symm. code	Centroid distance	E_{coul}	E_{pol}	E_{Disp}	E_{Rep}	E_{total}	Main interactions
#1	-x+½, y+½, -z+½	7.027	-6.5	-1.7	-7.2	2.1	-13.3	C4-H1...O1
		6.733	-21.3	-6.4	-17.8	14.0	-31.6	N1-H5...O1
#2	-x, -y-1, -z+2	6.63	-1.8	-1.1	-10.5	4.4	-9.0	C5-H2...O2
		6.277	-0.2	-2.0	-17.5	8.6	-11.0	C6-H3...O2 ^e
3	-x,-y,-z+2	6.294	-2.7	-3.8	-16.8	14.4	-8.9	C5-H2...O2
		6.927	-0.2	-1.1	-9.8	3.5	-7.5	H2...H2
4	x-1, y, z	7.000	-13.0	-9.0	-18.8	24.9	-15.9	C6-H3...O3 C6-H3...O1
		7.137	-9.1	-2.7	-12.5	6.1	-18.2	N1-H4...O1 H3...H6
5	x-1,y+1,z	7.918	-9.1	-2.2	-8.3	4.7	-14.9	N1-H4...O1
		8.052	-4.2	-1.0	-5.7	1.0	-9.8	C6-H3...O3
6	-x-½, y-½ -z+½+1	8.625	-30.9	-16.1	-21.9	55.9	-13.0	N1-H5...N1
		3.728	2.5	-3.8	-34.3	22.8	-12.7	
7	-x+1,-y-1, -z+2	8.076	-100.5	-47.3	-19.6	106.3	-61.1	O2-H7...O3
		7.965	-113.9	-55.3	-22.4	120.3	-71.3	O2-H7...O2
8	x,y+1,z	3.700	-1.8	-5.0	-34.5	24.1	-17.2	N1...C3;C6...C5 C1...O3; C4...C2
		3.728	2.5	-3.8	-34.3	22.8	-12.7	O3...O2 ^p O3...C7 ^p N1-H5...N1 ^e

3.8 Molecular electrostatic potential

The Molecular ElectroStatic Potential (MESP) calculated *in vacuo* for both experimental and predicted structures is shown in the Fig. 7a and 7b respectively. The MESP reveals the polar

nature of the molecule, which is characterized by $V_{s,max}$, positive and $V_{s,min}$, negative extrema of potentials on the molecular surface [17]. For the predicted structure, it is noted that a strongest positive potential of about +15.52 kcal/mol is found near the phenol hydrogen atom H6. Similar potential is found near the NH_2 group and the $COOH$ hydrogen atom H7 with $V_{s,max}$ values +15.48 and +15.36 kcal/mol respectively. The region between the less polar H-C atoms (H2, H3) has a smaller local maximum at +13.8 kcal/mol

As expected, the oxygen atoms of the carboxylic group (O2, O3) and phenol group (O1) display strong negative potentials ($V_{s,min}$) with values -11.3, -10.2 and -10.2 kcal/mol respectively, which exhibit their high hydrogen bond acceptor capability.

The above discussed potential values are in good agreement with those calculated for the experimental X-ray structure. The hydrogen bond donor capability is exposed from the positive charge accumulation located on the $-NH_2$ and O-H groups and all these characteristics are consistent with the molecular self-assembly.

Fig 7: Molecular electrostatic potential on the AMSA molecule mapped over the electron density isosurface at 0.001 au. (a) Experiment and (b) Predicted structure. The positive ($V_{s,max}$) and negative ($V_{s,min}$) extrema of potentials are indicated by black and blue spheres, respectively. Values are in kcal/mol/e.

3.9 Analysis of the predicted crystal packings.

An illustration of the predicted crystal packings is given in Fig. S6. Among the 31 predicted crystal structures, ten (including the STR1 close to real structure) display the COOH...COOH homo-synthon with double hydrogen bond, which has very favorable electrostatic energy. The CD structure with $Z'=2$ has the two independent molecules forming a (COOH)₂ synthon; this is however not the case for the CD and BF structures with $Z'=2$.

Four other packings display strong hydrogen bonds between COOH groups but with only one H-bond within a dimer (Fig. 8). Each COOH group form then two H-bonds with two different neighbor molecules to forms O=C-O-H...O=C-O-H chains in the crystal.

Table 9. Properties of the different predicted crystal packings. The correlation coefficient is between V_{int} , the inner ESP and V_{out} , the ESP generated by the immediate molecular neighbors. The lattice electrostatic energy E_{elec} is computed after ELMAM2 database transfer.

For packings which display translations along a short unit cell axis ($<3.8\text{\AA}$), the column “Parallel displaced” yields the inter-planar distance d . The relative displacement of the molecule is shown in the next column.

Four packings show stacking of molecules related by 2_1 helical rotation or roto-inversion along a unit cell axis of around $7\text{\AA}$ (underlined); the unit cell parameter, corresponding to two stacking layers is here given.

The last column indicates if the (COOH)₂ synthon is present (Y) or not (/) in the crystal structure; “1HB” refers to O=C-C-O-H...O=C-C-O-H chains.

crystal	ID	Correl. (V_{int} , V_{ext})	E_{elec} kJ/mol	// displaced d (Å)	Displace- ment (Å)	(COOH) ₂ synthon
EXP	EXP	-0.290	-266	3.445	1.42	Y
Str 1	FC	-0.230	-257	3.466	1.20	Y
str 2	DC	-0.123	-245	3.571	0.35	Y
str 3	AU	-0.270	-243	3.489	1.28	/
str 4	FA	0.178	-235	3.598	0.30	Y
str 5	AQ	-0.525	-282	3.515	0.97	1HB
str 6	AY	-0.468	-221	3.531	0.83	/
str 7	DA	-0.447	-200	3.566	0.29	/
str 8	AH	0.008	-208	3.563	0.27	/
str 9	AF	-0.241	-218	3.486	0.90	1HB
str 10	AK	-0.283	-252	3.472	1.36	Y
str 11	AA	-0.185	-139	3.572	0.23	/
str 12	AV	-0.340	-245	3.351	1.55	/
str 13	AM	-0.702	-239	<u>7.10</u>	/	Y
str 14	AZ	-0.070	-225	3.515	0.96	1HB

str 15	AB	-0.565	-217	<u>7.73</u>	/	/
str 16	DB	-0.236	-205	3.408	1.18	/
str 17	AS	-0.449	-181	3.608	0.30	/
str 18	CB	-0.810	-251	/	/	/
str 19	AP	-0.091	-217	3.408	1.32	Y
str 20	BA	-0.080	-219	3.409	1.33	Y
str 21	BB	-0.088	-220	3.410	1.32	Y
<u>str 22</u>	CD	-0.480	-235	/	/	Y
str 23	AI	-0.424	-243	/	/	Y
str 24	BH	-0.179	-170	3.588	1.17	/
str 25	BD	-0.284	-185	/	/	/
str 26	DE	-0.024	-208	/	/	/
str 27	CA	-0.713	-185	<u>6.96</u>	/	/
<u>str 28</u>	CE	-0.777	-217	/	/	/
<u>str 29</u>	BF	0.463	-69	3.507	1.27	/
str 30	CC	0.153	-100	<u>7.12</u>	/	1HB/weak
str 31	DD	-0.244	-174	/	/	/

Figure 8. Auto-stereogram of AQ packing showing the chain of hydrogen bonds between COOH groups. The O...H distance is 1.836 Å. The distance between parallel aromatic planes is 3.514 Å while the unit cell translation vector length is $c=3.6445$ Å.

The two packings with strongest U_{lattice} (STR1=FC* and DC around -131 kJ/mol) belong to the group with (COOH)₂ synthon (Fig. S3, Table 1 and 9). In the group of packings which have the (COOH)₂ synthon, the U_{lattice} value is always stronger than -110 kJ/mol.

The three packings (AQ, AF, AZ) with strong chains of O=C-O-H...O=C-O-H hydrogen bond chains all take U_{lattice} values in the [-124.5,-117.6] kJ/mol range.

The eight packings with weakest U_{lattice} values belong all to the “none” group having no hydrogen bond between COOH moieties. Several packings with no H-bond between COOH group have however strong U_{lattice} values reaching -125 kJ/mol for AU.

As the molecule is nearly planar and is formed by an aromatic ring bearing hetero-atoms, it is likely to form stacking interactions [31,35,36]. Among the 31 predicted crystal structure, twenty are involved in parallel displaced stacking via a translation of short unit cell axis, whose length is in the 3.573-3.733 Å range. The inter-planar distance is in the 3.351-3.608 Å range and parallel displacements are between 0.230 and 1.552 Å. The real crystal packing belongs to this subgroup and shows one of the largest displacement at 1.42 Å.

Extensive stacking occurs in four additional crystal structures at distance ~3.5 Å where the molecules are related by 2-fold helical axis or roto-inversion (AM, AB, CA, CC, Table 9). Application of the symmetry operation twice leads to a translation of unit cell vector of about 7 Å.

E_{elec} , the electrostatic contribution to the lattice energy, computed from the electron density multipolar model transferred from ELMAM2 database, is shown in Table 9. The E_{elec} and U_{lattice} values are 63% correlated. The real crystal structure comes in second position as strongest E_{elec} lattice value, while the predicted close to real STR1 structure is in third position.

The crystal AQ has the strongest E_{elec} value, it has indeed strong hydrogen bonds, chains of O=C-O-H...O=C-O-H hydrogen bonds along the c unit cell axis (Fig. 8). One hydrogen atom of the NH₂ group forms two bifurcated hydrogen bond towards two C=O carbonyl groups while the other H atoms is H-bonded to two hydroxyl groups. The NH₂ group has therefore one more H-

bond partner in AQ packing than in the real crystal where one strong ($d_{\text{OH}}=2.246$) and two longer ($d_{\text{OH}}=2.634$ and 3.045 Å) N-H...O interactions occur.

4. Complementarity of electrostatic potential in the packings.

Electrostatic potentials mapped on Hirshfeld surfaces provide direct insight into intermolecular interactions in crystals [37]. The experimental crystal shows a correlation C_{vv} of -29% between the interior and exterior potential (Fig. 9). The regions of highest inner potential correspond to the polar hydrogen atom Ho and Hn while oxygen atoms are at the origin of the most electronegative areas. A high anti-correlation is related to a good complementarity of inner and outer potentials. Some predicted packings such as CE reach much stronger anti-correlations ($c=-0.777$); CE has two molecules per asymmetric unit.

Three crystals have a positive (unfavorable) C_{vv} correlation between V_{int} and V_{ext} . The worst is crystal BF (with $Z'=2$) where NH_2 interacts with two other NH_2 groups and with the hydroxyl hydrogen atom (Fig. S4). Crystal FA has a positive C_{vv} correlation +0.178 which may be explained by a parallel stacking with low // displacement (0.30 Å) which results in atoms being in contact with themselves (unfavorable electrostatic contacts) and moreover the electropositive NH_2 interacts with two other NH_2 groups.

While the $(V_{\text{int}}, V_{\text{ext}})$ correlation indicator does not discriminate the real crystal among the best predicted packings, it evidences some unrealistic features in some of them.

Figure 9. Scatterplot of inner and outer electrostatic potential V on the Hirshfeld surface for the experimental crystal structure. The contacts donated by oxygen and by the polar hydrogen atom Ho/n from the inner molecule are highlighted in red and blue color, respectively.

The electrostatic potential was computed from the multipolar model derived from ELMAM2 database transfer [24]. The outer potential V_{ext} was computed from the 14 neighbor molecules in contact with the central one.

Figure 10. Average percentage C_{xy} of actual contacts on the Hirshfeld surface in the predicted crystal packings (in blue). The values for the real packing are shown in black. The errors bars represent the standard deviation in the sample of predicted structures. Hc and Hp (polar) represent hydrogen atoms bound to C and N/O respectively.

In terms of contact types, the difference between the real crystal and predicted ones can be seen in Fig. 10 and S5. The real crystal is more involved in C...C stacking and weak hydrogen bonds of O...Hc type, compared to the average in the predicted structures. On average, the amount of strong hydrogen bonds O...Hp (O...H-N and O...H-O) contacts in the predicted packings is very close to the real crystal (19.5 ± 3.3 vs. 20.2%) while the non-polar contacts Hc...Hc and Hc...C (C-H... π interactions) are very slightly less represented.

5 Conclusion

The *ab initio* prediction of the possible crystal packings of AMSA molecule, commenced by a gas phase optimization using the DFT level approach, was found to be valid. The global search for the hypothetical conformers of the AMSA compound successfully generated possible dense packings within the repulsion alone potential field. The inner lattice minimization was carried out with repulsion-dispersion field. The predicted crystal structure with lowest lattice energy, generated in $P2_1/c$ space group, was found to be close to the experimental thermodynamically stable one. The experimental crystal is notably stabilized by a double hydrogen bond forming a $(\text{COOH})_2$ synthon and parallel displaced cycle stacking. These two dimers have the highest interaction energy. The Hirshfeld surface reveals the contribution of the prior interactions towards crystal stability. The chemical bonding characteristics of closed shell interactions were

thoroughly investigated by QTAIM approach and the reactive nature of the global minimum was exploited from the electrostatic potential analysis. The 31 predicted crystal structures were analyzed and compared through several descriptors. The EXP crystal structure has the second strongest lattice electrostatic energy. Concerning the V_{int} and V_{ext} electrostatic potentials on the Hirshfeld surface, about one third of the predicted structures displayed a better complementarity than the EXP crystal, but this indicator can pinpoint some awkward packings.

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Compliance with ethical standards

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

Ethical statement: All ethical guidelines have been adhered.

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Supplementary Materials.

Table S1. Topological parameters at the bond critical points of predicted aminosalicyclic acid crystal structure [STR 1]: Electron density ρ , Laplacian $\nabla^2\rho$, Hessian eigenvalues, Ellipticity ε , Potential, Kinetic and Total energy density.

Bonds	$\rho(\mathbf{r}_{\text{cp}})$ $\text{e}/\text{\AA}^3$	$\nabla^2\rho(\mathbf{r}_{\text{cp}})$ $\text{e}/\text{\AA}^5$	λ_1	λ_2	λ_3	ε	$V(\mathbf{r}_{\text{cp}})$ $\text{kJ} / (\text{mol.B}^3)$	$G(\mathbf{r}_{\text{cp}})$	$H(\mathbf{r}_{\text{cp}})$
O1-C2	2.00	-15.6	-15.4	-15.2	15	0.02	-4.99	1.95	-3.04
O2-C7	2.02	-16.9	-16.2	-16.0	15.3	0.01	-5.00	1.91	-3.09
O3-C7	2.74	-16.0	-26.0	-23.2	33.2	0.12	-8.53	3.70	-4.83
O1-H6	2.34	-58.0	-41.3	-40.6	23.8	0.02	-4.94	0.44	-4.50
O2-H7	2.13	-46.7	-33.6	-33.0	19.9	0.02	-4.05	0.39	-3.66
N1-C3	1.95	-20.7	-14.9	-13.4	7.6	0.11	-3.21	0.88	-2.33
N1-H4	2.26	-37.6	-30.5	-28.7	21.5	0.06	-3.39	0.38	-3.01
N1-H5	2.26	-37.6	-30.5	-28.7	21.5	0.06	-3.39	0.38	-3.01
C1-C2	2.12	-22.1	-16.9	-13.8	8.5	0.23	-2.87	0.66	-2.21
C1-C5	2.09	-21.3	-16.2	-13.6	8.4	0.19	-2.82	0.66	-2.15
C1-C7	1.91	-18.1	-14.6	-12.8	9.2	0.14	-2.26	0.5	-1.77
C2-C4	2.11	-21.9	-16.8	-13.5	8.4	0.25	-2.89	0.68	-2.21
C3-C4	2.11	-21.7	-16.5	-13.6	8.4	0.22	-2.86	0.67	-2.19
C3-C6	2.11	-22.2	-16.6	-13.9	8.4	0.20	-2.87	0.66	-2.21
C4-H1	1.90	-23.3	-18.4	-17.9	12.9	0.03	-2.15	0.26	-1.89
C5-C6	2.09	-21.1	-16.2	-13.3	8.5	0.22	-2.84	0.68	-2.16
C5-H2	1.93	-24.4	-19.1	-18.9	13.5	0.01	-2.16	0.23	-1.94
C6-H3	1.90	-23.4	-18.3	-17.8	12.8	0.03	-2.17	0.26	-1.90

Topological parameters derived from ELMAM2 database transfer

bond	$\rho_{\text{bcp}}(\mathbf{r})$ e/Å ³	$\nabla^2 \rho_{\text{bcp}}(\mathbf{r})$ e/Å ⁵	λ_1	λ_2	λ_3	ε
O1-C2	2.06	-16.7	-16.1	-14.8	14.2	0.09
O2-C7	2.37	-19.3	-20.1	-17.4	18.2	0.16
O3-C7	2.76	-29.3	-26.4	-24.6	21.6	0.08
O1-H6	2.44	-52.2	-41.4	-40.7	29.8	0.02
O2-H7	2.47	-55.6	-42.8	-42.7	29.9	0.00
N1-C3	1.92	-12.7	-14.7	-11.9	13.9	0.23
N1-H4	2.26	-38.1	-32.1	-30.5	24.5	0.05
N1-H5	2.26	-38.1	-32.1	-30.5	24.5	0.05
C1-C2	2.13	-18.8	-16.4	-13.2	10.8	0.24
C1-C5	2.07	-17.6	-15.6	-12.9	10.9	0.21
C1-C7	1.92	-15.4	-14.3	-12.2	11.1	0.18
C2-C4	2.19	-20.0	-17.0	-13.7	10.7	0.24
C3-C4	2.11	-18.2	-16.1	-12.9	10.8	0.25
C3-C6	2.11	-18.2	-16.1	-12.9	10.8	0.25
C4-H1	1.88	-19.8	-18.0	-17.0	15.2	0.06
C5-C6	2.13	-18.8	-16.1	-13.4	10.7	0.21
C5-H2	1.87	-19.8	-18.0	-17.0	15.2	0.06
C6-H3	1.87	-19.8	-18.0	-17.0	15.2	0.06

Figure S1. Deformation density of predicted AMSA [STR1], obtained with software Wfn2plot and Denprop

Figure S2. Laplacian of electron density of predicted AMSA [str 1] in the aromatic cycle and in the COO group planes.

Figure S3. Analysis of U_{lattice} with respect to the presence of (COOH)₂ synthons (orange color) or of O=C-O-H...O=C-O-H chains (in blue) and absence (in black). The U_{lattice} data are the same as those in Table 1.

Figure S4. Scatterplot of lattice energy (Table 1) and electrostatic energy (Table 9) derived from transferred multipolar atom model. #: predicted close to real FC, structure. *: real crystal structure.

Figure S5. Percentage of actual contacts in the real and predicted crystal packings.

Table S2. Coordinates of the predicted crystal structures.

Predicted Crystal Structures of the AMSA molecule, in SHELX format.

```
TITLR = AA
CELL 1.0  3.5794  7.0005  7.1132  75.2797  84.9393  71.7453
ZERR  1 0.0 0.0 0.0 0.0 0.0 0.0
LATT -1
SFAC O N C H
O1      1  0.19309083  0.68476660  0.87088053
O2      1  0.23822319  0.72442953  1.43181542
O3      1  0.04786735  0.53893518  1.25933968
N1      2 -0.13642067  1.42635828  0.65941241
C1      3  0.04488319  0.88651636  1.10972309
C2      3  0.09000373  0.87238265  0.91641917
C3      3 -0.07552305  1.24507283  0.81060923
C4      3  0.02976946  1.05167041  0.76687311
C5      3 -0.06041176  1.07992403  1.15342932
C6      3 -0.12065201  1.25919098  1.00389484
C7      3  0.10604986  0.70116672  1.26793969
H1      4  0.06531895  1.03974686  0.61709295
H2      4 -0.10133970  1.09606699  1.30192128
H3      4 -0.20312810  1.40850085  1.03964605
H4      4 -0.21238753  1.56630255  0.69095015
H5      4 -0.10368591  1.41624044  0.51958309
H6      4  0.24033907  0.57262376  0.98846617
H7      4  0.28000788  0.59457932  1.54122859
END
```

```
TITLR = AB
CELL 1.0  6.7803  7.2237  7.7386  62.0637  79.3515  77.1553
ZERR  2 0.0 0.0 0.0 0.0 0.0 0.0
LATT  1
SFAC O N C H
O1      1  0.66626204  1.01983050  0.85198186
O2      1  0.75651469  1.54697760  0.87837533
O3      1  0.52492123  1.43337118  0.78696876
N1      2  1.38034091  0.87793533  0.66916097
C1      3  0.87557472  1.28074728  0.77586672
C2      3  0.85193404  1.08405585  0.79683576
C3      3  1.21083332  1.01318510  0.70499842
C4      3  1.01955981  0.95029602  0.76138466
C5      3  1.06683440  1.34362105  0.71947266
C6      3  1.23446017  1.20986121  0.68402157
C7      3  0.70240234  1.42279129  0.81199854
```

H1 4 1.00030615 0.79776856 0.77794873
H2 4 1.08969701 1.49612427 0.70013212
H3 4 1.38211201 1.26062715 0.63991580
H4 4 1.51875791 0.92328416 0.62846541
H5 4 1.36337347 0.73562572 0.68436955
H6 4 0.56449871 1.12424964 0.87911535
H7 4 0.63494985 1.64537972 0.90315501
END

TITLR = AF
CELL 1.0 6.9631 3.6011 16.5399 90.0000 129.6038 90.0000
ZERR 2 0.0 0.0 0.0 0.0 0.0 0.0
LATT -1
SYMM -X, +Y +1/2, -Z
SFAC O N C H
O1 1 0.61112150 -0.12494153 0.83454052
O2 1 0.25368911 0.01383482 0.52228612
O3 1 0.24593157 -0.35913065 0.63104913
N1 2 1.38608782 0.20714427 0.91572316
C1 3 0.62601140 -0.06084762 0.69426686
C2 3 0.74173389 -0.04984454 0.80082499
C3 3 1.13086952 0.11714889 0.84137062
C4 3 0.99417099 0.03913363 0.87437298
C5 3 0.76274030 0.01715933 0.66127694
C6 3 1.01514611 0.10612521 0.73481787
C7 3 0.36271449 -0.15354509 0.61625872
H1 4 1.08296163 0.04733238 0.95697854
H2 4 0.67880279 0.00740761 0.57923940
H3 4 1.11947437 0.16540204 0.70826626
H4 4 1.48506431 0.26380017 0.89189989
H5 4 1.46987866 0.21529193 0.99279632
H6 4 0.43566448 -0.16874493 0.77511413
H7 4 0.07032962 -0.05228617 0.46844235
END

TITLR = AH
CELL 1.0 3.5734 11.0139 8.5886 90.0000 78.2309 90.0000
ZERR 2 0.0 0.0 0.0 0.0 0.0 0.0
LATT -1
SYMM -X, +Y +1/2, -Z
SFAC O N C H
O1 1 1.16310898 0.22792466 0.27138876
O2 1 0.89627719 -0.06372155 0.56805853
O3 1 1.21915154 0.11515476 0.55212373
N1 2 1.30114434 -0.03932086 -0.17933014
C1 3 1.15020201 0.01260311 0.31404759

C2	3	1.18132566	0.11265527	0.21259282
C3	3	1.25044992	-0.02187499	-0.01365684
C4	3	1.23147229	0.09540823	0.04874324
C5	3	1.16919835	-0.10467058	0.25163725
C6	3	1.21934498	-0.12191762	0.08778768
C7	3	1.09813858	0.02869607	0.48545571
H1	4	1.25534151	0.17341757	-0.02942946
H2	4	1.14965574	-0.18412494	0.32715606
H3	4	1.23445885	-0.21341007	0.04071578
H4	4	1.31468802	-0.12413853	-0.22453338
H5	4	1.32353148	0.03300408	-0.25275899
H6	4	1.11325243	0.22698372	0.38742251
H7	4	0.86140295	-0.05174405	0.68733084

END

TITLR = AI
CELL 1.0 9.7479 5.3195 13.9583 90.0000 97.8287 90.0000
ZERR 4 0.0 0.0 0.0 0.0 0.0 0.0
LATT 1
SYMM -X, +Y +1/2, -Z +1/2
SFAC O N C H

O1	1	0.75003590	0.80761795	0.97536660
O2	1	0.99933207	1.34683757	0.88128057
O3	1	0.87011256	1.27573665	1.00237194
N1	2	0.57323015	0.61409890	0.64512151
C1	3	0.80968419	1.07518160	0.84902157
C2	3	0.74126940	0.86571943	0.87962607
C3	3	0.65262501	0.76891439	0.71360520
C4	3	0.66273543	0.71260989	0.81191051
C5	3	0.79956325	1.13147869	0.75071422
C6	3	0.72102928	0.97836915	0.68299865
C7	3	0.89207975	1.23754820	0.91860364
H1	4	0.60988398	0.55021544	0.83608430
H2	4	0.85035740	1.29405833	0.72478829
H3	4	0.71371536	1.02429371	0.60688403
H4	4	0.56592886	0.65464426	0.57399197
H5	4	0.52376402	0.46252158	0.66719690
H6	4	0.81203163	0.92376308	1.01428294
H7	4	1.05614494	1.45955206	0.93024594

END

TITLR = AK
CELL 1.0 12.8194 3.7284 14.1640 90.0000 102.6804 90.0000
ZERR 4 0.0 0.0 0.0 0.0 0.0 0.0
LATT 1
SYMM -X, +Y +1/2, -Z +1/2

SFAC O N C H

O1	1	0.82703265	1.13322204	0.58473149
O2	1	0.51588044	1.19676422	0.61020336
O3	1	0.63377676	1.48694006	0.53834017
N1	2	0.92924499	0.74515634	0.91590571
C1	3	0.69775372	1.15437991	0.68400007
C2	3	0.80040569	1.07752373	0.67159330
C3	3	0.85151677	0.88254986	0.83803964
C4	3	0.87728695	0.94164019	0.74861473
C5	3	0.67199028	1.09531024	0.77341260
C6	3	0.74887153	0.95942671	0.85043402
C7	3	0.61638049	1.29678057	0.60450149
H1	4	0.95683733	0.88240338	0.73855012
H2	4	0.59333511	1.15551502	0.78556409
H3	4	0.72797582	0.91539997	0.91957409
H4	4	0.91064227	0.70218100	0.98059799
H5	4	1.00349324	0.68937825	0.90697307
H6	4	0.76512797	1.21542717	0.53648707
H7	4	0.45974672	1.29713592	0.55454913

END

TITLR = AM

CELL 1.0 7.1174 7.1082 13.3682 90.0000 99.4777 90.0000

ZERR 4 0.0 0.0 0.0 0.0 0.0 0.0

LATT 1

SYMM -X, +Y +1/2, -Z +1/2

SFAC O N C H

O1	1	0.94611578	0.11716341	0.40385583
O2	1	1.48369727	-0.00787801	0.35360414
O3	1	1.33365720	0.15146809	0.46504190
N1	2	0.74014742	0.17426959	0.04414042
C1	3	1.17952440	0.11158221	0.29332845
C2	3	0.99074278	0.12462780	0.30861815
C3	3	0.88767926	0.15321676	0.12782333
C4	3	0.84482692	0.14546695	0.22586048
C5	3	1.22235781	0.11934244	0.19528054
C6	3	1.07645090	0.14017180	0.11253364
C7	3	1.33393211	0.08997847	0.37874421
H1	4	0.69853874	0.15546784	0.23819841
H2	4	1.36759963	0.11141739	0.18103572
H3	4	1.11152724	0.14640750	0.03678740
H4	4	0.77104177	0.17979487	-0.02680567
H5	4	0.60356892	0.18365346	0.05513899
H6	4	1.06002361	0.09531177	0.45405541
H7	4	1.59053985	-0.02223716	0.41355192

END

TITLR = AP
 CELL 1.0 7.3657 25.3385 3.6551 90.0000 90.0000 90.0000
 ZERR 4 0.0 0.0 0.0 0.0 0.0 0.0
 LATT -1
 SYMM +X +1/2, -Y +1/2, -Z
 SYMM -X, +Y +1/2, -Z
 SYMM -X +1/2, -Y, +Z
 SFAC O N C H
 O1 1 0.14122601 0.83364647 0.99554074
 O2 1 -0.00248893 0.98896069 1.09006208
 O3 1 0.23850825 0.93482643 1.19031278
 N1 2 -0.46083644 0.78320607 1.36421679
 C1 3 -0.06326358 0.90010018 1.21605088
 C2 3 -0.02466554 0.84767633 1.12911096
 C3 3 -0.32732589 0.82245389 1.31444529
 C4 3 -0.15669139 0.80885251 1.17834450
 C5 3 -0.23387846 0.91370141 1.35215989
 C6 3 -0.36589465 0.87487776 1.40138383
 C7 3 0.07282864 0.94120437 1.16696975
 H1 4 -0.12597846 0.76822282 1.11029984
 H2 4 -0.26735570 0.95395593 1.42542517
 H3 4 -0.49773677 0.88590482 1.50797041
 H4 4 -0.58431500 0.79302470 1.46247819
 H5 4 -0.43303932 0.74528559 1.30126989
 H6 4 0.21783265 0.86469343 0.96167811
 H7 4 0.09329169 1.01734577 1.05631629
 END

TITLR = AQ
 CELL 1.0 13.4859 13.1875 3.6445 90.0000 90.0000 90.0000
 ZERR 4 0.0 0.0 0.0 0.0 0.0 0.0
 LATT -1
 SYMM +X +1/2, -Y +1/2, -Z
 SYMM -X, +Y +1/2, -Z +1/2
 SYMM -X +1/2, -Y, +Z +1/2
 SFAC O N C H
 O1 1 0.09429204 0.77656319 0.87029633
 O2 1 0.11180528 0.48330160 1.22970465
 O3 1 0.20270204 0.59991643 0.91689127
 N1 2 -0.25192980 0.72796711 0.60946380
 C1 3 0.02555274 0.60912939 0.90789192
 C2 3 0.01521882 0.71272354 0.84043749
 C3 3 -0.15875398 0.68807290 0.70968747
 C4 3 -0.07692933 0.75219856 0.74131538
 C5 3 -0.05627007 0.54502186 0.87624365

C6	3	-0.14841036	0.58447642	0.77711709
C7	3	0.12115539	0.56643056	1.01134208
H1	4	-0.08452034	0.83268379	0.68937353
H2	4	-0.05039677	0.46416115	0.92337545
H3	4	-0.21133995	0.53390721	0.75268067
H4	4	-0.31114916	0.68162972	0.58672779
H5	4	-0.25946675	0.80289080	0.56077315
H6	4	0.15293299	0.73994982	0.95443912
H7	4	0.17876225	0.45408099	1.30039422

END

TITLR = AS

CELL 1.0 11.1404 16.8373 3.6205 90.0000 90.0000 90.0000

ZERR 4 0.0 0.0 0.0 0.0 0.0 0.0

LATT -1

SYMM -X , -Y , +Z +1/2

SYMM +X +1/2, -Y +1/2, +Z

SYMM -X +1/2, +Y +1/2, +Z +1/2

SFAC O N C H

O1	1	-0.00563737	0.13826692	-0.01225853
O2	1	0.27884185	0.28907480	0.12174444
O3	1	0.10414717	0.27928945	-0.19938617
N1	2	0.26259161	-0.08436146	0.08922286
C1	3	0.20679732	0.16146233	-0.00802282
C2	3	0.10882224	0.10993401	0.00544405
C3	3	0.24384739	-0.00181852	0.05658391
C4	3	0.12735781	0.02829551	0.03772388
C5	3	0.32327717	0.13134215	0.01080894
C6	3	0.34180232	0.04971100	0.04308146
C7	3	0.18933391	0.24688512	-0.04207631
H1	4	0.05096235	-0.01141853	0.04816729
H2	4	0.40113975	0.16974713	-0.00253090
H3	4	0.43266211	0.02702654	0.05669094
H4	4	0.34682772	-0.10617834	0.10304342
H5	4	0.19177999	-0.12166394	0.09914283
H6	4	-0.00585244	0.19620821	-0.02019997
H7	4	0.26593428	0.34850629	0.09670451

END

TITLR = AU

CELL 1.0 16.2944 3.7171 10.9463 90.0000 90.0000 90.0000

ZERR 4 0.0 0.0 0.0 0.0 0.0 0.0

LATT -1

SYMM -X , -Y , +Z +1/2

SYMM -X +1/2, +Y +1/2, +Z +1/2

SYMM +X +1/2, -Y +1/2, +Z

SFAC O N C H

O1	1	0.89596552	0.79046265	0.78641483
O2	1	1.05205373	0.78744563	1.07902152
O3	1	1.02503586	0.46781872	0.90660707
N1	2	0.67770436	1.19213943	1.04860732
C1	3	0.91776911	0.80305993	1.00309264
C2	3	0.86786009	0.85962924	0.90131610
C3	3	0.75831191	1.06149964	1.03331213
C4	3	0.78813342	0.98882527	0.91644230
C5	3	0.88794074	0.87572790	1.11995295
C6	3	0.80821699	1.00490627	1.13506699
C7	3	1.00116342	0.66795819	0.98922985
H1	4	0.74968327	1.03232748	0.83710436
H2	4	0.92490771	0.83130408	1.20078007
H3	4	0.78568737	1.05960778	1.22627510
H4	4	0.65611393	1.24494733	1.13311895
H5	4	0.64158281	1.23324751	0.97505019
H6	4	0.95331832	0.71500600	0.78858391
H7	4	1.11000070	0.69203946	1.06863458

END

TITLR = AV

CELL 1.0 15.2332 12.1631 3.6934 90.0000 90.0000 90.0000

ZERR 4 0.0 0.0 0.0 0.0 0.0 0.0

LATT -1

SYMM -X , -Y , +Z +1/2

SYMM -X +1/2, +Y +1/2, +Z +1/2

SYMM +X +1/2, -Y +1/2, +Z

SFAC O N C H

O1	1	0.75261270	0.73826444	0.80720978
O2	1	0.65513190	1.03884835	1.09842021
O3	1	0.77758162	0.93413521	1.16772590
N1	2	0.46475411	0.58205808	0.94943068
C1	3	0.63844140	0.84765129	1.07227937
C2	3	0.66781919	0.74948862	0.91897282
C3	3	0.52308703	0.67124655	0.99065213
C4	3	0.61013880	0.66128410	0.87819571
C5	3	0.55138661	0.85759051	1.18475993
C6	3	0.49372567	0.76939578	1.14396468
C7	3	0.69766048	0.94065697	1.11755594
H1	4	0.63329563	0.58529035	0.75891144
H2	4	0.52684789	0.93233426	1.30784944
H3	4	0.42634028	0.77803419	1.23300937
H4	4	0.40176412	0.58922825	1.03054956
H5	4	0.48594137	0.51105182	0.83844837
H6	4	0.78474266	0.80703220	0.83856818

H7 4 0.69689556 1.10315046 1.13021072
END

TITLR = AY

CELL 1.0 16.5870 3.6285 11.0156 90.0000 90.0000 90.0000

ZERR 4 0.0 0.0 0.0 0.0 0.0 0.0

LATT -1

SYMM -X, -Y, +Z +1/2

SYMM -X +1/2, +Y, +Z +1/2

SYMM +X +1/2, -Y, +Z

SFAC O N C H

O1	1	0.63310783	0.90504103	0.23044699
O2	1	0.78660837	0.86234786	-0.05978744
O3	1	0.76779745	1.18089515	0.11562018
N1	2	0.41079930	0.63987616	-0.03562393
C1	3	0.65487843	0.90659719	0.01517333
C2	3	0.60433936	0.86272043	0.11538469
C3	3	0.49274542	0.72943591	-0.01854456
C4	3	0.52328414	0.77416797	0.09850936
C5	3	0.62434906	0.86187677	-0.10188614
C6	3	0.54327702	0.77331087	-0.11874089
C7	3	0.73967260	0.99944713	0.03087189
H1	4	0.48435140	0.74036738	0.17664498
H2	4	0.66185826	0.89756423	-0.18149568
H3	4	0.52023217	0.74003968	-0.21007370
H4	4	0.38867816	0.60727389	-0.12027184
H5	4	0.37421752	0.60795239	0.03680049
H6	4	0.69102179	0.95250017	0.22939439
H7	4	0.84556591	0.92832889	-0.04810397

END

TITL starting1 starting1 starting1 R=0.0 AZ

CELL 1.0 25.3055 3.6439 6.9892 90.0000 90.0000 90.0000

ZERR 4 0.0 0.0 0.0 0.0 0.0 0.0

LATT -1

SYMM +X +1/2, -Y +1/2, -Z

SYMM -X, +Y +1/2, -Z +1/2

SYMM -X +1/2, -Y, +Z +1/2

SFAC O N C H

O1	1	0.83145037	0.97991598	0.35687384
O2	1	0.98823509	1.15159185	0.46726591
O3	1	0.93472306	0.76570728	0.30067045
N1	2	0.79014657	1.32718362	1.00343760
C1	3	0.90210375	1.06604008	0.58121087
C2	3	0.84836712	1.06484443	0.53665410
C3	3	0.82773563	1.23948948	0.86164330

C4	3	0.81118578	1.15154178	0.67688072
C5	3	0.91866110	1.15400744	0.76596192
C6	3	0.88147306	1.24067237	0.90617699
C7	3	0.94154506	0.97592204	0.43685949
H1	4	0.76952267	1.15026899	0.64145471
H2	4	0.96004727	1.15385348	0.80541998
H3	4	0.89479747	1.30774481	1.04921632
H4	4	0.80209033	1.39099660	1.13709550
H5	4	0.75127461	1.32650727	0.97129803
H6	4	0.86142560	0.93881973	0.27165308
H7	4	1.01546155	1.08720771	0.36604507

END

TITLR = BA

CELL 1.0 25.3436 7.3548 3.6582 90.0000 90.0000 90.0000

ZERR 4 0.0 0.0 0.0 0.0 0.0 0.0

LATT -1

SYMM +X +1/2, -Y +1/2, -Z

SYMM -X, +Y +1/2, -Z

SYMM -X +1/2, -Y, +Z

SFAC O N C H

O1	1	0.91638607	0.39124338	0.99318794
O2	1	0.76109477	0.24721638	1.08696850
O3	1	0.81517120	0.48875782	1.18643061
N1	2	0.96681000	-0.21118968	1.36495098
C1	3	0.84992118	0.18662143	1.21393079
C2	3	0.90234682	0.22525308	1.12735291
C3	3	0.92756593	-0.07759322	1.31421398
C4	3	0.94116455	0.09313151	1.17753185
C5	3	0.83632290	0.01590669	1.35063071
C6	3	0.87515094	-0.11619548	1.40079025
C7	3	0.80882213	0.32279950	1.16386799
H1	4	0.98179443	0.12386661	1.10974537
H2	4	0.79606641	-0.01758386	1.42363241
H3	4	0.86411934	-0.24811527	1.50783458
H4	4	0.95699235	-0.33474978	1.46363323
H5	4	1.00473127	-0.18337961	1.30225347
H6	4	0.88533925	0.46786460	0.95872939
H7	4	0.73271012	0.34305528	1.05252061

END

TITLR = BB

CELL 1.0 25.3297 7.3654 3.6571 90.0000 90.0000 90.0000

ZERR 4 0.0 0.0 0.0 0.0 0.0 0.0

LATT -1

SYMM +X +1/2, -Y, -Z

SYMM -X, -Y +1/2, +Z

SYMM -X +1/2, +Y +1/2, -Z

SFAC O N C H

O1	1	0.83357372	0.64106066	0.00553124
O2	1	0.98896462	0.49751543	-0.08823990
O3	1	0.93480472	0.73851439	-0.18833982
N1	2	0.78320646	0.03910406	-0.36429563
C1	3	0.90009315	0.43672100	-0.21479828
C2	3	0.84763912	0.47523844	-0.12817928
C3	3	0.82244987	0.17262661	-0.31407731
C4	3	0.80882217	0.34317729	-0.17785666
C5	3	0.91372051	0.26617053	-0.35103759
C6	3	0.87490373	0.13412844	-0.40070476
C7	3	0.94119759	0.57282246	-0.16525938
H1	4	0.76816765	0.37382706	-0.11004391
H2	4	0.95400215	0.23276533	-0.42404752
H3	4	0.88596354	0.00234338	-0.50739770
H4	4	0.79304641	-0.08433451	-0.46264232
H5	4	0.74526125	0.06681967	-0.30157454
H6	4	0.86462057	0.71768690	0.03969272
H7	4	1.01734454	0.59331911	-0.05413944

END

TITLR = BD

CELL 1.0 16.7880 8.9669 4.7097 90.0000 90.0000 90.0000

ZERR 4 0.0 0.0 0.0 0.0 0.0 0.0

LATT -1

SYMM -X, -Y, +Z +1/2

SYMM -X +1/2, +Y +1/2, +Z +1/2

SYMM +X +1/2, -Y +1/2, +Z

SFAC O N C H

O1	1	0.96826730	0.56309397	0.72193983
O2	1	0.82873177	0.48547397	1.41830260
O3	1	0.86047165	0.38055223	0.99376570
N1	2	0.91062839	1.08687534	0.79526976
C1	3	0.86854714	0.64518687	1.05151468
C2	3	0.92558137	0.67541707	0.84387561
C3	3	0.89650475	0.93855899	0.88129625
C4	3	0.93955399	0.82209972	0.75878496
C5	3	0.82550689	0.76164350	1.17399979
C6	3	0.83947527	0.90832558	1.08889079
C7	3	0.85301976	0.49278287	1.14305410
H1	4	0.98391326	0.84489723	0.59756744
H2	4	0.78032521	0.74163450	1.33364975
H3	4	0.80556299	0.99777402	1.18512880
H4	4	0.87953869	1.17117265	0.88391527

H5	4	0.95189272	1.10882250	0.64521340
H6	4	0.95481476	0.46733657	0.80800309
H7	4	0.81805980	0.37891092	1.48023030

END

TITL starting1 R=0.0 BF

CELL 1.0 8.4230 22.3853 3.7312 89.3191 90.0000 90.0000

ZERR 4 0.0 0.0 0.0 0.0 0.0 0.0

LATT -1

SYMM -X +1/2, +Y +1/2, +Z +1/2

SFAC O N C H

O1	1	0.86401733	0.22246969	-0.13819746
O2	1	1.19911464	0.09101963	-0.04258352
O3	1	1.13208712	0.16881083	-0.40927117
O4	1	0.33793690	0.77479755	0.36736488
O5	1	-0.13708261	0.81263704	0.35440934
O6	1	0.04727837	0.76080135	0.03999679
N1	2	0.46810523	0.08543191	0.30241233
N2	2	0.44443322	0.97410546	0.76891592
C1	3	0.93136455	0.11892928	-0.06472888
C2	3	0.82234156	0.16565676	-0.04237397
C3	3	0.62365548	0.09668090	0.17914645
C4	3	0.66848369	0.15452908	0.07952896
C5	3	0.88653256	0.06109033	0.03485023
C6	3	0.73268929	0.04997101	0.15672184
C7	3	1.09252291	0.12962026	-0.19172275
C8	3	0.12590032	0.84630408	0.37526759
C9	3	0.28435389	0.83099993	0.43494840
C10	3	0.33748007	0.93119198	0.63675042
C11	3	0.39014261	0.87344728	0.56565360
C12	3	0.07325603	0.90404177	0.44633178
C13	3	0.17904629	0.94647897	0.57700904
C14	3	0.01363330	0.80264203	0.23850651
H1	4	0.58435388	0.19097240	0.09645765
H2	4	0.96797758	0.02380438	0.01723964
H3	4	0.69917731	0.00485656	0.23257523
H4	4	0.43562873	0.04360771	0.37467046
H5	4	0.38920039	0.11920382	0.31879836
H6	4	0.97594582	0.22436170	-0.20504391
H7	4	1.31103063	0.09879605	-0.13255093
H8	4	0.51300049	0.86131817	0.61160425
H9	4	-0.04861530	0.91743213	0.39949915
H10	4	0.13684987	0.99119599	0.63048083
H11	4	0.40640374	1.01586999	0.82055928
H12	4	0.55903593	0.96306888	0.81228904
H13	4	0.25095602	0.74914737	0.29052073

H14 4 -0.21445743 0.78201646 0.25786544
END

TITLR = BH

CELL 1.0 13.1120 3.7726 13.3083 90.0000 90.0000 90.0000

ZERR 4 0.0 0.0 0.0 0.0 0.0 0.0

LATT -1

SYMM -X , -Y , +Z +1/2

SYMM -X +1/2, +Y , +Z +1/2

SYMM +X +1/2, -Y , +Z

SFAC O N C H

O1	1	0.29378576	0.60423496	0.09912485
O2	1	0.00355367	0.64737127	0.21107095
O3	1	0.14810216	0.31801353	0.22436098
N1	2	0.16749806	0.97266804	-0.22354814
C1	3	0.11308904	0.63292411	0.07218997
C2	3	0.21293769	0.67338778	0.03781762
C3	3	0.14923973	0.85857629	-0.12423370
C4	3	0.23100365	0.78619376	-0.06039967
C5	3	0.03133156	0.70530161	0.00834258
C6	3	0.04940822	0.81808712	-0.08986106
C7	3	0.09263570	0.51504271	0.17444763
H1	4	0.30866561	0.81725514	-0.08666839
H2	4	-0.04699183	0.67314915	0.03251593
H3	4	-0.01468890	0.87275443	-0.13879018
H4	4	0.10838382	1.02525206	-0.26974240
H5	4	0.23968493	1.00214165	-0.24845008
H6	4	0.27054179	0.54101436	0.16645082
H7	4	-0.01006481	0.56391427	0.28232485

END

TITLR = CA

CELL 1.0 8.0159 6.8575 6.9624 111.1814 75.0469 105.8365

ZERR 2 0.0 0.0 0.0 0.0 0.0 0.0

LATT 1

SFAC O N C H

O1	1	0.66752793	0.72866683	0.30866239
O2	1	0.76443264	1.37931523	0.46539824
O3	1	0.57077388	1.08663743	0.31364304
N1	2	1.29138079	0.74852282	0.12723288
C1	3	0.86553834	1.05877638	0.29719937
C2	3	0.83480766	0.84217779	0.27534477
C3	3	1.14837104	0.85269164	0.18430931
C4	3	0.97622867	0.73915265	0.21888342
C5	3	1.03766930	1.17231178	0.26259777
C6	3	1.17908755	1.06927001	0.20615732

C7	3	0.71964268	1.16922482	0.35581980
H1	4	0.95158698	0.57100406	0.20221331
H2	4	1.06568474	1.34003325	0.27637784
H3	4	1.31211997	1.15900226	0.17929182
H4	4	1.41593084	0.83058491	0.10230636
H5	4	1.26925557	0.59189228	0.11147382
H6	4	0.58207670	0.82130349	0.35464814
H7	4	0.66202127	1.45495215	0.50557580

END

TITLR = CB

CELL 1.0 16.4670 11.9587 6.8246 90.0000 90.0000 90.0000

ZERR 8 0.0 0.0 0.0 0.0 0.0 0.0

LATT 1

SYMM +X +1/2, -Y +1/2, -Z

SYMM -X, +Y +1/2, -Z +1/2

SYMM -X +1/2, -Y, +Z +1/2

SFAC O N C H

O1	1	0.04506577	0.23305134	0.10412488
O2	1	0.03555344	-0.10339645	0.20915225
O3	1	-0.02993333	0.05712262	0.29185019
N1	2	0.33670582	0.21430406	0.10013830
C1	3	0.11051417	0.06292486	0.20275595
C2	3	0.11420853	0.17317644	0.13651516
C3	3	0.26074912	0.16348243	0.13459289
C4	3	0.18933009	0.22345023	0.10245373
C5	3	0.18193342	0.00296775	0.23489425
C6	3	0.25705531	0.05324129	0.20082349
C7	3	0.03267559	0.00897162	0.23938732
H1	4	0.19182142	0.30904866	0.05098959
H2	4	0.18106703	-0.08235424	0.28804877
H3	4	0.31209096	0.00591123	0.22670396
H4	4	0.38839162	0.17095166	0.12326636
H5	4	0.33943209	0.29402521	0.05216959
H6	4	-0.00290911	0.18684542	0.12641736
H7	4	-0.01891833	-0.14027542	0.23500786

END

TITLR = CC

CELL 1.0 7.5318 7.1228 27.2592 90.0000 90.0000 90.0000

ZERR 8 0.0 0.0 0.0 0.0 0.0 0.0

LATT 1

SYMM +X +1/2, -Y +1/2, -Z

SYMM -X, +Y +1/2, -Z +1/2

SYMM -X +1/2, -Y, +Z +1/2

SFAC O N C H

O1	1	0.15100495	0.66245564	0.11186963
O2	1	-0.17960948	0.87729007	0.21682743
O3	1	0.05988342	0.68505353	0.20959308
N1	2	-0.34500218	0.60899941	0.00173553
C1	3	-0.14301831	0.71665801	0.14257093
C2	3	-0.02764226	0.67183223	0.10428428
C3	3	-0.27716405	0.64515610	0.04902290
C4	3	-0.09473412	0.63608777	0.05751301
C5	3	-0.32543988	0.72572859	0.13408072
C6	3	-0.39252112	0.68997539	0.08730680
C7	3	-0.07561976	0.75427163	0.19168379
H1	4	-0.00455188	0.60141741	0.02792418
H2	4	-0.41848709	0.75839153	0.16314361
H3	4	-0.53444426	0.69705627	0.08119772
H4	4	-0.47694224	0.61564718	-0.00443778
H5	4	-0.26165036	0.57665243	-0.02598237
H6	4	0.18031724	0.69733017	0.14553452
H7	4	-0.13163559	0.90264909	0.25098660

END

TITL CD

CELL 1.0 13.5447 6.7812 14.6768 90.0000 90.0000 88.6515

ZERR 8 0.0 0.0 0.0 0.0 0.0 0.0

LATT -1

SYMM +X +1/2, +Y +1/2, -Z +1/2

SFAC O N C H

O1	1	0.24759138	0.91101339	0.04320459
O2	1	-0.04369456	0.80571877	0.09230760
O3	1	0.10716707	0.75949729	0.15778102
O4	1	0.75963471	0.61315036	0.88250302
O5	1	0.46453004	0.68486038	0.82946291
O6	1	0.61344463	0.76475052	0.77031263
O7	1	0.74673531	0.89321961	0.38250302
O8	1	1.04183999	0.82150960	0.32946291
O9	1	0.89292540	0.74161945	0.27031264
O10	1	0.25877864	0.59535658	0.54320459
O11	1	0.55006459	0.70065120	0.59230760
O12	1	0.39920296	0.74687268	0.65778102
N1	2	0.19685341	0.77113759	-0.27426958
N2	2	0.69299331	0.68490204	1.20268423
N3	2	0.81337671	0.82146793	0.70268424
N4	2	0.30951662	0.73523238	0.22573042
C1	3	0.09333797	0.77835184	-0.00449989
C2	3	0.18783587	0.84393802	-0.02419209
C3	3	0.16209973	0.77357261	-0.18368094
C4	3	0.22221438	0.84152482	-0.11377851

C5	3	0.03323512	0.71038665	-0.07441054
C6	3	0.06761363	0.70797346	-0.16399695
C7	3	0.05612317	0.77949983	0.08861311
C8	3	0.59691359	0.71354831	0.93080950
C9	3	0.69446745	0.65840440	0.95054288
C10	3	0.66073728	0.69451007	1.11138843
C11	3	0.72637560	0.64890909	1.04082910
C12	3	0.53128603	0.75916233	1.00137785
C13	3	0.56319417	0.74966702	1.09166406
C14	3	0.56219090	0.72455296	0.83698009
C15	3	0.90945644	0.79282166	0.43080950
C16	3	0.81190257	0.84796558	0.45054288
C17	3	0.84563274	0.81185990	0.61138843
C18	3	0.77999442	0.85746088	0.54082911
C19	3	0.97508400	0.74720765	0.50137785
C20	3	0.94317585	0.75670296	0.59166407
C21	3	0.94417912	0.78181701	0.33698010
C22	3	0.41303206	0.72801813	0.49550011
C23	3	0.31853416	0.66243197	0.47580791
C24	3	0.34427029	0.73279736	0.31631905
C25	3	0.28415564	0.66484516	0.38622149
C26	3	0.47313490	0.79598333	0.42558946
C27	3	0.43875640	0.79839652	0.33600305
C28	3	0.45024685	0.72687014	0.58861311
H1	4	0.29562515	0.89267733	-0.12865070
H2	4	-0.04007673	0.65676918	-0.06118606
H3	4	0.02033346	0.65449203	-0.21766009
H4	4	0.15338663	0.72209290	-0.32487451
H5	4	0.26517399	0.81863041	-0.28856141
H6	4	0.21328157	0.91175656	0.10168525
H7	4	-0.06894629	0.80633240	0.15742125
H8	4	0.80218291	0.60595032	1.05572718
H9	4	0.45538780	0.80427062	0.98821931
H10	4	0.51159909	0.78581614	1.14585064
H11	4	0.64553650	0.71777462	1.25376043
H12	4	0.76352654	0.64494915	1.21700269
H13	4	0.72694361	0.61846437	0.82326265
H14	4	0.44100587	0.69285480	0.76387746
H15	4	0.70418712	0.90041965	0.55572718
H16	4	1.05098222	0.70209936	0.48821931
H17	4	0.99477093	0.72055385	0.64585065
H18	4	0.86083352	0.78859537	0.75376043
H19	4	0.74284348	0.86142082	0.71700270
H20	4	0.77942641	0.88790559	0.32326266
H21	4	1.06536415	0.81351517	0.26387746
H22	4	0.21074488	0.61369265	0.37134930

H23	4	0.54644675	0.84960080	0.43881394
H24	4	0.48603657	0.85187794	0.28233991
H25	4	0.35298340	0.78427708	0.17512549
H26	4	0.24119604	0.68773956	0.21143859
H27	4	0.29308845	0.59461341	0.60168524
H28	4	0.57531631	0.70003756	0.65742124

END

TITL CE

CELL 1.0 15.5222 8.5864 11.3064 88.8204 90.0000 90.0000

ZERR 8 0.0 0.0 0.0 0.0 0.0 0.0

LATT 1

SYMM +X +1/2, -Y +1/2, -Z

SFAC O N C H

O1	1	0.84556045	0.40902753	0.60563418
O2	1	0.89868266	0.69575745	0.88069613
O3	1	0.93797093	0.65731751	0.68983314
O4	1	0.17812958	0.17560085	0.88324107
O5	1	0.09058296	0.46855782	0.61993862
O6	1	0.07576047	0.42502363	0.81788274
N1	2	0.81713827	-0.02197695	0.88107709
N2	2	0.17330101	-0.24844440	0.61218148
C1	3	0.88582974	0.44330922	0.80825435
C2	3	0.85444022	0.35061527	0.71796877
C3	3	0.84018861	0.13426217	0.85660436
C4	3	0.83162558	0.19607886	0.74215812
C5	3	0.89440293	0.38146442	0.92270315
C6	3	0.87158523	0.22696213	0.94687178
C7	3	0.91008488	0.60488001	0.78478167
C8	3	0.11311560	0.21442346	0.69244788
C9	3	0.15559441	0.11983320	0.77557601
C10	3	0.15310913	-0.09301765	0.63914977
C11	3	0.17558359	-0.03389995	0.74891442
C12	3	0.09063091	0.15527760	0.58268355
C13	3	0.11062557	0.00157810	0.55604110
C14	3	0.09159418	0.37519467	0.71862604
H1	4	0.80727475	0.12468411	0.67172726
H2	4	0.91933095	0.45003544	0.99438560
H3	4	0.87868574	0.18017262	1.03602257
H4	4	0.82326103	-0.06674286	0.96386312
H5	4	0.79438767	-0.08907281	0.81584444
H6	4	0.86062375	0.51937980	0.60198768
H7	4	0.91572361	0.80808630	0.86352239
H8	4	0.20858398	-0.10677524	0.81377871
H9	4	0.05691556	0.22535315	0.51676751
H10	4	0.09269013	-0.04311324	0.47061574

H11 4 0.15711437 -0.29125723 0.53276599
H12 4 0.20406315 -0.31690964 0.67222807
H13 4 0.16336960 0.28572604 0.88856234
H14 4 0.07555160 0.58030797 0.63902267
END

TITLR = DA

CELL 1.0 3.5780 16.8319 11.0321 90.0000 90.8176 90.0000

ZERR 4 0.0 0.0 0.0 0.0 0.0 0.0

LATT -7

SYMM +X, -Y, +Z +1/2

SFAC O N C H

O1 1 -0.02590845 0.11360020 0.77507824
O2 1 0.10101596 -0.03387178 1.06742614
O3 1 -0.21857493 -0.02615764 0.88825407
N1 2 0.06840441 0.33943150 1.04059599
C1 3 -0.02816112 0.09290803 0.99018580
C2 3 -0.01152823 0.14328834 0.88998956
C3 3 0.03599081 0.25665395 1.02365107
C4 3 0.02051843 0.22516204 0.90673563
C5 3 -0.01271677 0.12439997 1.10709436
C6 3 0.01932675 0.20627300 1.12382061
C7 3 -0.06203277 0.00726346 0.97461447
H1 4 0.03341617 0.26398390 0.82862156
H2 4 -0.02858682 0.08690058 1.18662681
H3 4 0.03028147 0.23003385 1.21503128
H4 4 0.07980749 0.36224735 1.12514475
H5 4 0.08060549 0.37590451 0.96817699
H6 4 -0.03390327 0.05564674 0.77637716
H7 4 0.07608853 -0.09346569 1.05580950
END

TITLR = DB

CELL 1.0 14.6220 3.6069 12.7263 90.0000 83.4680 90.0000

ZERR 4 0.0 0.0 0.0 0.0 0.0 0.0

LATT -7

SYMM -X, +Y, -Z

SFAC O N C H

O1 1 0.07132072 0.91619602 0.68216760
O2 1 0.12435640 1.10335832 0.98637858
O3 1 0.02719008 1.29170287 0.86964476
N1 2 0.39612227 0.79411471 0.57609495
C1 3 0.17746733 1.06922691 0.80600882
C2 3 0.15943456 0.94769276 0.70634417
C3 3 0.32269087 0.88649137 0.65329552
C4 3 0.23205190 0.85634743 0.62999618

C5	3	0.26809583	1.09936792	0.82929927
C6	3	0.34072359	1.00802966	0.75294976
C7	3	0.10260874	1.16631379	0.88677947
H1	4	0.21763972	0.76206007	0.55277788
H2	4	0.28433004	1.19621570	0.90556782
H3	4	0.41081157	1.03329416	0.77189142
H4	4	0.46170106	0.81566557	0.59292010
H5	4	0.38313225	0.70604782	0.50401489
H6	4	0.02744017	0.97492133	0.74354111
H7	4	0.07181489	1.17174711	1.04211519

END

TITLR = DC

CELL 1.0 13.8080 3.5884 26.7601 90.0000 103.0586 90.0000

ZERR 8 0.0 0.0 0.0 0.0 0.0 0.0

LATT 7

SYMM -X , +Y , -Z +1/2

SFAC O N C H

O1	1	0.47443387	0.15608132	0.83773772
O2	1	0.61826076	-0.11897327	0.98401897
O3	1	0.48654126	0.22254252	0.94155781
N1	2	0.78911485	0.20742286	0.78950365
C1	3	0.62472473	0.11607863	0.90321632
C2	3	0.57565840	0.15118261	0.85180190
C3	3	0.73389470	0.17677692	0.82768741
C4	3	0.63025724	0.18154637	0.81403894
C5	3	0.72836070	0.11131207	0.91685307
C6	3	0.78295226	0.14169234	0.87909763
C7	3	0.56905775	0.08443500	0.94322270
H1	4	0.59176701	0.20864048	0.77419094
H2	4	0.76857221	0.08801325	0.95646370
H3	4	0.86339192	0.13840288	0.89016995
H4	4	0.86409003	0.20380659	0.79934853
H5	4	0.75368264	0.23270557	0.75231206
H6	4	0.44569900	0.11858998	0.86749846
H7	4	0.57893391	-0.13957607	1.01168708

END

TITLR = DD

CELL 1.0 13.7913 8.0135 14.8295 90.0000 62.1345 90.0000

ZERR 8 0.0 0.0 0.0 0.0 0.0 0.0

LATT 7

SYMM -X , +Y , -Z +1/2

SFAC O N C H

O1	1	0.39470482	1.43373242	0.97768349
O2	1	0.16511725	1.41411981	0.87669454

O3	1	0.29993506	1.25565100	0.88032212
N1	2	0.45335368	2.01474893	0.88734779
C1	3	0.31135763	1.55339234	0.88243899
C2	3	0.37639953	1.56787158	0.93117363
C3	3	0.40567487	1.85982358	0.88570293
C4	3	0.42355449	1.72108905	0.93280482
C5	3	0.29348806	1.69213256	0.83533676
C6	3	0.34064029	1.84534064	0.83696986
C7	3	0.26148188	1.39448481	0.87980805
H1	4	0.47394460	1.73159420	0.97077496
H2	4	0.24427977	1.68447988	0.79606733
H3	4	0.32636346	1.95208129	0.79994814
H4	4	0.44040278	2.11517060	0.85333728
H5	4	0.50036280	2.02533122	0.92261871
H6	4	0.35380853	1.33669165	0.97421723
H7	4	0.13097025	1.30280098	0.87486428

END

TITLR = DE

CELL 1.0 24.0835 7.4280 13.2080 90.0000 40.2054 90.0000

ZERR 8 0.0 0.0 0.0 0.0 0.0 0.0

LATT 7

SYMM -X, +Y, -Z +1/2

SFAC O N C H

O1	1	0.13011861	0.26953430	0.20558276
O2	1	0.17985247	-0.19075780	-0.02319219
O3	1	0.22692175	-0.03900203	0.05008033
N1	2	0.07244187	0.57933142	-0.02639902
C1	3	0.16140355	0.12205096	0.00473073
C2	3	0.13125885	0.27049798	0.10082567
C3	3	0.10231401	0.42577787	-0.01593608
C4	3	0.10171827	0.42236312	0.09047972
C5	3	0.16198907	0.12548581	-0.10167626
C6	3	0.13245781	0.27734194	-0.11202012
C7	3	0.19259710	-0.03771959	0.01362726
H1	4	0.07837216	0.53718795	0.16539617
H2	4	0.18575893	0.01308412	-0.17887619
H3	4	0.13339592	0.27856783	-0.19531196
H4	4	0.07280957	0.58185894	-0.10328973
H5	4	0.05060246	0.68671311	0.04310638
H6	4	0.14932489	0.15336112	0.20492886
H7	4	0.20177052	-0.30134221	-0.01667140

END

TITLR = FA

CELL 1.0 7.2523 26.4439 3.6106 90.0000 71.7833 90.0000

ZERR 4 0.0 0.0 0.0 0.0 0.0 0.0

LATT 1

SYMM -X, +Y +1/2, -Z +1/2

SFAC O N C H

O1	1	0.59485252	0.83937836	0.35185177
O2	1	0.74561656	0.98504303	0.50669691
O3	1	0.53227784	0.94123100	0.28322432
N1	2	1.26731445	0.79147652	-0.00940576
C1	3	0.83728475	0.90405765	0.25374811
C2	3	0.78486237	0.85322584	0.26036064
C3	3	1.12290194	0.82927974	0.07897648
C4	3	0.92768291	0.81584274	0.17294711
C5	3	1.03249852	0.91749515	0.15975647
C6	3	1.17530737	0.88010133	0.07233986
C7	3	0.69035463	0.94367221	0.34373754
H1	4	0.88613470	0.77644255	0.17863834
H2	4	1.07786988	0.95663634	0.14851661
H3	4	1.32642045	0.89100766	-0.00100261
H4	4	1.40856367	0.80116147	-0.07721889
H5	4	1.22951388	0.75470294	-0.00453355
H6	4	0.51033557	0.86892181	0.42071364
H7	4	0.64238510	1.01242695	0.56841166

END

TITLR = FC (STR1)

CELL 1.0 6.9920 3.6688 24.8207 90.0000 90.9374 90.0000

ZERR 4 0.0 0.0 0.0 0.0 0.0 0.0

LATT 1

SYMM -X +1/2, +Y +1/2, -Z +1/2

SFAC O N C H

O1	1	0.39990063	-0.21134193	0.83237612
O2	1	0.27839972	-0.24582323	0.99291290
O3	1	0.45369276	-0.54718602	0.93076207
N1	2	-0.24920445	0.14728602	0.79353062
C1	3	0.17055637	-0.22702485	0.90315411
C2	3	0.21805286	-0.15859848	0.84973890
C3	3	-0.10823190	0.02159902	0.83033892
C4	3	0.07862923	-0.03431398	0.81331878
C5	3	-0.01630577	-0.17112476	0.92016421
C6	3	-0.15569732	-0.04684641	0.88376231
C7	3	0.31401239	-0.35727439	0.94177344
H1	4	0.11633789	0.01844937	0.77189692
H2	4	-0.05796952	-0.22510270	0.96123308
H3	4	-0.30038538	-0.00519550	0.89741683
H4	4	-0.38438191	0.18796263	0.80582010
H5	4	-0.21494495	0.19696676	0.75488766

H6	4	0.48404907	-0.28482068	0.86220030
H7	4	0.37903612	-0.33779466	1.01952980
END				

Figure S6. Crystallographic autostereograms[¶] of the predicted crystal packings made with MoProViewer.

[¶]: Katrusiak, A. (2001). Crystallographic autostereograms. *Journal of Molecular Graphics and Modelling*, 19(3-4), 363-367.)

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