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Article

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Crystal and Electron Properties of Carbamazepine- Aspirin Co-crystal

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Notes

The authors declare no competing financial interest.

In memory of our colleague and friend Slimane Dahaoui who passed away in 2018, April, 28th.

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3 **ABSTRACT:** Carbamazepine (CBZ) and aspirin (ASP) drug molecules in their 1:1 co-crystal
4 interact by relatively strong hydrogen bonds and aromatic-aromatic contacts. The crystal
5 structure and the experimental electron density in the CBZ:ASP co-crystal were derived from a
6 high resolution X-ray diffraction experiment at 100 K and the results are compared to those
7 previously obtained for the CBZ form III. The isobaric thermal expansion tensor appears to be
8 much more anisotropic for the co-crystal than for CBZ form III. The thermal expansion
9 coefficients α_V are found equal to 1.3 for CBZ III and $1.5 \times 10^{-4} \text{ K}^{-1}$ for CBZ:ASP co-crystal. The
10 interactions in the CBZ:ASP co-crystal have also been analyzed through the electrostatic
11 properties derived from both experimental and theoretical electron densities: topological
12 features, atomic charges and electrostatic potential. A very good agreement was found for the
13 values of the electron density at the critical points $\rho(\mathbf{r}_{\text{CP}})$ obtained from both experiment and
14 theory. This is not, however, true for the Laplacian values which are systematically weaker in the
15 theoretical approach. In contrast, the integrated atomic charges have higher magnitudes for the
16 theoretical density. Additionally, it is shown here that the total molecular energies can be
17 obtained from the electrostatic potential at the nuclei (EPN) within the Thomas-Fermi
18 approximation. The best agreement with the conventional quantum calculations (Restricted
19 Hartree-Fock RHF or Density Functional Theory DFT) was surprisingly obtained for the
20 promolecule (superposition of Independent Atomic Model, IAM) density and not from the
21 multipole model which overestimates or underestimates the energies.
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INTRODUCTION

The design of multi-component crystals or co-crystals is a powerful technique to modify physico-chemical properties of active pharmaceutical ingredients (API's) such as solubility, chemical and physical stability, dissolution rate or hygroscopicity.¹⁻⁵ Traditionally, the properties of an API are modified by forming a salt but there is a limited number of available counter-ions and molecules with no acid or base functions are also difficult to ionize. A pharmaceutical co-crystal contains a therapeutic molecule with at least one counter molecule (or coformer), bound together via non-covalent intermolecular interactions. US Food and Drug Administration (FDA) provides a list of substances that have precedence as food ingredient ("generally recognized as safe" substance or GRAS). Moreover, multidrug co-crystals have been the subject of growing interest in the pharmaceutical industry because they may offer a tandem therapeutic effect. Recently the FDA approved the first multidrug co-crystal for chronic heart failure: Entresto gathers Sacubitril and Valsartan in a single dose.⁶

The general aim of crystal engineering is the understanding of the intermolecular interactions in a crystal packing for an ulterior design of new crystalline compounds with the desired physicochemical properties. The packing is described in terms of supramolecular synthons giving rise to particular spatial arrangements. Then, the goal of crystal engineering is also to recognize and design synthons that are robust enough to be exchanged from one crystalline structure to another. In early studies, hydrogen bond synthons have been identified in molecular crystals.⁷ For this purpose, Etter *et al* proposed the concept of graph set annotations based on the geometric motifs of the hydrogen bond networks in the crystal structure.^{8,9} Several other types of synthons have been identified, but their real implications in a crystal structure still remain subjective.¹⁰ For example the strength of sandwich herringbone or stacking of aromatic

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3 molecules are known to be rather weak but they appear to play an important role to establish
4 stable packing arrangement.¹⁰ Moreover, the same intermolecular interaction may be a
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6 constituent of different supramolecular synthons.
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10 The solid state of carbamazepine (5H-Dibenzo[b,f]azepine-5-carboxamide) (hereafter
11 CBZ), an antiepileptic drug (Tegretol[®]), has been extensively studied. CBZ is known to exhibit
12 polymorphism (forms I, III, IV and V).¹¹⁻¹⁴ It has been recently revealed that form II of CBZ is in
13 fact a THF solvate.¹⁵⁻¹⁶ A survey of the Cambridge Structural Database (CSD) indicates that
14 CBZ crystallizes in numerous solvated and co-crystal forms.¹⁷ The analysis of the published
15 crystalline structures indicates that the primary supramolecular synthon in CBZ is the
16 carboxamide moiety (CONH₂). This chemical group most commonly forms a cyclic
17 homosynthon with another CBZ molecule or cyclic heterosynthons (amide...acid but also
18 amide...acid...H₂O etc.) with a carboxylic group such as that of aspirin. Aspirin (acetylsalicylic
19 acid, hereafter ASP) is the well-known API used to treat pain, fever and inflammation.¹⁸ Aspirin
20 presents two crystalline forms, form II being found during attempts to obtain the co-crystal
21 CBZ:ASP.¹⁹ Indeed, it has been demonstrated that the crystallization of aspirin form II can occur
22 in the presence of certain amides, such as in CBZ, whereas a co-crystallization with CBZ can
23 also occur.¹⁹ In the co-crystals of CBZ involving molecules with carboxylic acids, there are
24 generally extensive hydrogen bonding networks as O-H...O, N-H...O, C-H...O and C-H... π but
25 also aromatic group stackings.¹⁸ CBZ co-crystals exhibit polymorphism as for CBZ-nicotinamide
26 and CBZ-saccharin compounds.^{20, 21} In the two forms of CBZ-saccharin, the crystal packings
27 display both homosynthon (double hydrogen bonds involving the carboxamide group of CBZ)
28 and heterosynthon (hydrogen bonds between the respective N-H and C=O moieties of CBZ and
29 saccharine molecules) arrangements.
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3 Accurate crystal structures and electron densities of CBZ III have been recently studied
4 by X-ray and neutron diffraction experiments at 100 K.^{22, 23} ASP electron density features were
5 also reported from accurate X-ray data and theoretical calculations.²⁴ In the present paper, we
6 present an analysis of the electron density in the 1:1 co-crystal CBZ:ASP (triclinic, $P\bar{1}$). In the
7 crystallogensis attempts of the CBZ III and this co-crystal, two new solvates of CBZ were
8 fortuitously obtained. The thermal expansion of the co-crystal was analyzed from 100 K to
9 ambient temperature and compared to that of pure CBZ III in order to get more insight into the
10 preferred intermolecular interactions. The electron density of CBZ:ASP was derived from a high
11 resolution X-ray diffraction at 100 K and from periodic theoretical calculations. Topological
12 analysis based on Bader's theory of *Atoms In Molecules* (AIM) was carried out to characterize
13 the covalent and hydrogen bonds in the crystal lattice.²⁵ The obtained atomic charges are
14 discussed as well as the total energy of molecule derived from the electrostatic potential at the
15 nuclei (EPN).
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36 EXPERIMENTAL AND METHODOLOGICAL SECTION

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39 **Crystallization.** White powders of carbamazepine (CBZ) and aspirin (ASP) were
40 purchased from Spectrum & Cooper laboratories. Powder diffraction analyses of the commercial
41 samples reveal that they correspond to form III of CBZ and form I of ASP. Prismatic single co-
42 crystal CBZ:ASP (1:1 stoichiometry) was obtained by a slow evaporation at ambient
43 temperature of a solution of CBZ with an excess of ASP (stoichiometry 1:2 in the solution) in
44 ethyl acetate (CarloErba reagents). Other initial stoichiometries did not lead to single crystals of
45 CBZ:ASP with suitable size for high resolution X-ray diffraction or to CBZ form III. During our
46 several attempts to obtain a co-crystal, we never obtained the form II of aspirin contrary to what
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3 was observed in a recent study.²⁶ Several solvents were tested, and a prismatic single crystal of
4 an ethanol solvate of CBZ was obtained from an ethanol solution (absolute VWR Chemical,
5 99.7%) at room temperature and a prismatic single crystal of a solvate methanol was obtained
6 from a methanol solution (CarloErba for HPLC-Plus-gradient, 99.9%) of CBZ and PEG400. We
7 have fully determined the crystal structure (see Supplementary Information) of these solvates by
8 single crystal X-ray diffraction and they were found to be isostructural to the THF solvate
9 (former form II of CBZ).¹⁵⁻¹⁶ The presence of water in the ethanol or methanol solvent leads
10 systematically to the CBZ dihydrate.
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21 **X-ray data Collection.** Diffraction data of the CBZ-ASP were collected at 100.0(2) K on
22 a Kappa CCD APEX II diffractometer using graphite monochromated MoK α X-radiation. 17015
23 unique reflections were collected up to a resolution of $\sin\theta_{\max}/\lambda = H/2 = 1.00 \text{ \AA}^{-1}$ ($\theta = 45.5^\circ$),
24 where H is the Bragg vector modulus. An empirical absorption correction was applied using
25 SADABS²⁶ computer program. SORTAV²⁷ program was used for sorting and averaging data
26 revealing the good quality of the measurements (internal $R_{\text{int}} = 0.0442$ for a high data
27 redundancy around 17). The details of the X-ray diffraction experiment and the crystallographic
28 data for the CBZ:ASP co-crystal are given in Table 1.
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40 **Thermal expansion.** The anisotropy of the intermolecular interactions can be investigated
41 using the isobaric thermal expansion tensor, which is a measure of the interaction changes with
42 temperature.^{28,29} The tensor is calculated from the temperature-dependent cell parameters with
43 the PASCAL program.³⁰ Details of the calculation procedure can be found elsewhere.³¹ The
44 thermal expansion tensor is a symmetrical second-rank tensor with nonzero diagonal eigenvalues
45 α_{11} , α_{22} , α_{33} . A small value of an eigenvalue is commonly referred to a “hard” direction
46 corresponding to a small deformation; conversely, a large value is associated to a “soft”
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direction i.e. a large deformation. The eigenvectors can be expressed as a function of the cell parameters a , b and c . The anisotropy of the thermal expansion can be expressed as a single value by the aspherism coefficient A , related to the three eigenvalues of the thermal tensor³²

$$A(T) = \frac{2}{3} \sqrt{1 - \frac{3(\alpha_{11}\alpha_{22} + \alpha_{11}\alpha_{33} + \alpha_{22}\alpha_{33})}{\alpha_v^2}} \quad (1)$$

with $\alpha_v = \frac{1}{V} \left(\frac{\partial V}{\partial T} \right)$, the thermal expansion coefficient, and V the unit cell volume. When $A = 0$, the thermal expansion is totally isotropic. The graphical representations of the tensor at a given temperature are drawn using WinTensor program.³³

Spherical and Electron Density Refinements. The crystal structure of the CBZ:ASP compound was solved using SIR94 program³⁴ and refined using SHELX97³⁵ implemented in WinGX³⁶ package. For the electron density refinements, the Hansen-Coppens model³⁷ was used. The frozen core and normalized valence spherical densities are obtained from the Hartree-Fock wave functions of the free atoms or ions.³⁸ The aspherical part of the pseudo-atom electron density is described by the real normalized harmonics $y_{lm\pm}$ basis set ($l = 0$ (monopole) to 4 (hexadecapole)) and modulated by a Slater-type radial function $R_{nl}(r) = Nr^{n_l} \exp(-\xi_l r)$, where N is a normalization factor. The exponents ξ_l (in bohr⁻¹) of the radial functions are chosen equal to 3.18, 4.47, 3.84 and $n_l = 2, 2, 3$ up to octupoles ($l = 3$) for C, O and N atoms, respectively; $\xi_l = 2.00$ bohr⁻¹ and $n_l = 1$ (dipole level, $l = 1$) for the hydrogen atoms.³⁹ MOPRO program^{40, 41} was used for the refinements of the electron density $\rho(\mathbf{r})$. At the end of the refinement cycles, SHADE3 software was used to empirically estimate the anisotropic thermal parameters of hydrogen atoms.⁴² These parameters were kept fixed to refine the electron density of CBZ:ASP compound.

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3 **Topological Analysis of the Electron Density.** The topological features of the electron
4 density were analyzed following the Bader's *Atoms in Molecules* theory.²⁵ This analysis allows a
5 quantitative description of the bonds and the electronic structure of atoms in molecules. The
6 gradient of the electron density $\nabla\rho(\mathbf{r}_{\text{CP}})$ vanishes at the critical points (CP) corresponding to the
7 extrema (maximum and minimum) and saddle points of $\rho(\mathbf{r})$. Each CP is therefore characterized
8 by two numbers: the number of the eigenvalues (for non-degenerate cases) and the signature of
9 the eigenvalues triplet $(\lambda_1, \lambda_2, \lambda_3)$. The ellipticity defined as $\varepsilon = (\lambda_1 - \lambda_2)/\lambda_2$ is a quantitative
10 measurement of the anisotropy of the electron density at the CP and reveals the character of the
11 chemical bonds (σ or π).
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24 **Experimental Electrostatic Potential and Electrostatic Potential at the Nuclei (EPN).**

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26 The electrostatic potential is based on the Hansen-Coppens electron density model.^{37, 40, 41} The
27 maps or the 3D views of the electrostatic potential reveal the nucleophilic (negative potential)
28 and electrophilic (positive potential) regions of a molecule in relation with its chemical
29 reactivity. The electrostatic potential can also be calculated at the nuclei positions. The
30 expression of the electrostatic potential at the nucleus (EPN) have been extensively described by
31 Coppens *et al.*⁴³ From the Hansen-Coppens model, only the monopole population (P_{val}) and its κ
32 parameter contribute to the EPN since all higher multipoles of a given atom create a zero
33 potential at its nucleus. Several molecular properties such as correlation energies in relation with
34 the values of EPN have been described by Politzer *et al.*⁴⁴⁻⁴⁵ Furthermore, the correlation
35 between the EPN and the atomic or molecular energy was evaluated within the statistical
36 approximation of Thomas-Fermi.⁴⁶⁻⁴⁷ The proposed energy relation for the total energy of a
37 system $E^{\text{tot}} = T + V$ (kinetic and potential energies) is
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$$E^{tot} = \sum_A k_A Z_A V_{0,A} \quad (2) \quad Z_A \text{ and } V_{0,A} \text{ are the nuclear charge and the potential at the}$$

nucleus of atom A, respectively; k_A is a proportional and adjustable factor for each atom A close to the value 3/7 suggested by the theory of Thomas-Fermi except for H atom ($k_A = 0.531278$).⁴⁶⁻
⁴⁷ The values obtained from the empirical equation (2) given above for the molecular energy of a set of several small organic molecules are in excellent agreement with those obtained by direct DFT calculations.⁴⁵⁻⁴⁶ This theory was also recently reported in an excellent book.⁴⁸ In this work, our program POTNUC⁴⁹ was used to compute the electrostatic potential (EPN) $V_{0,A}$ at each nucleus A. From the values of EPN, the previous equation was used to estimate E^{tot} energy.

Politzer has also proposed the decomposition of E^{tot} as $E^{tot} = \frac{3}{7}$

$$(E_{ne} + 2E_{nn}) \quad (3)$$

where E_{ne} and E_{nn} are the total nuclear-electronic attraction and the total nuclear-nuclear repulsion energies, respectively.⁴⁶⁻⁴⁷ E_{nn} is easy to calculate from the nuclear point charges, then an estimate of the total energy and that of nuclear-electronic interaction can be obtained from the equations (2) and (3). From the experimental electron density approach, a more detailed expression based on the multipole model was also given in the pioneering work of J. Bentley.⁵⁰

Theoretical calculations. Periodic quantum-mechanical calculations using *CRYSTAL14* were performed using the DFT method with the B3LYP hybrid functional and two different basis sets: 6-31G(d,p) and cc-pvdz.⁵¹⁻⁵⁴ The crystal geometry from the refined charge density model has been used in these single-point calculations. The level of accuracy in evaluating the bi-electronic Coulomb and exchange series was controlled by five parameters for which the used values were chosen from 10^{-7} to 10^{-14} . The shrinking factor of the reciprocal space was set to 8,

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3 corresponding to 260 k-points in the irreducible Brillouin zone. The convergence on total energy
4 was managed with a threshold of 10^{-7} . The XFAC option was used to generate from the
5 computed population matrix, the theoretical structure factors (hereafter *theoretical structure*
6 *factors* TSF) on the set of the observed Miller indices (17015 data, see Table 1). Both basis sets
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8 yield the same results; hereafter we will only discuss those originating from the cc-pvdz one.
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15 Non-periodic theoretical calculations were also performed using GAUSSIAN09.⁵⁵ The
16 single-point calculations were managed on isolated molecules and on dimers considering the
17 experimental molecular geometry. Different levels of theory have been considered: (i) restricted
18 Hartree-Fock (RHF) with 6-31G basis set, (ii) density functional theory (DFT) method using the
19 hybrid functional B3LYP with 6-31G(d,p) basis set and (iii) with cc-pvdz basis set. The total
20 energies are given in *hartrees* (1 H = 1 atomic unit (a.u.) = 2625.5 kJ/mol). The experimental
21 geometries were used as input.
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31 32 33 RESULTS AND DISCUSSION

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36 **Crystal Structure.** CBZ and ASP co-crystallize in the centrosymmetric P-1 space group,
37 with one molecule of CBZ and one molecule of ASP in the asymmetric unit corresponding to a
38 1:1 stoichiometry in the solid state. The crystalline structure of this CBZ:ASP co-crystal has
39 been solved in 2005 at room temperature and published together with the polymorph II of
40 aspirin, but without a proper description of the crystalline structure.¹⁹ The numbering schemes of
41 the CBZ:ASP asymmetric unit are given Figure 1. Details on the crystallographic data and the
42 refinements are listed in Table 1. Table 2 lists the main distances and angles obtained at the end
43 of the multipole refinement of CBZ:ASP.
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3 As in polymorphs I and IV of CBZ, there is a pyramidalization of the amide group NH_2
4 in the co-crystal: the $\text{N}_1\text{-C}_{15}\text{-N}_2\text{-H}_{14}$ dihedral angle being $-12.2(6)^\circ$ which is lower than the one
5 computed in the gas phase (-24.3°).⁵⁶ Previous periodic molecular modeling calculations also
6 demonstrate that, in these carbamazepine polymorphs, the deformation of the amide geometry
7 may occur in order to optimize hydrogen-bond interactions; and the neglect of the amide
8 pyramidalization introduces significant errors in the crystal structure predictions for
9 carbamazepine.⁵⁶
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20 In the co-crystal, both CBZ and ASP molecules act as a donor and an acceptor of
21 hydrogen bond. The packing diagram shows an heterosynthon between the acid group COOH of
22 aspirin and the carboxamide group (CONH_2) of CBZ and an additional heterosynthon between
23 the acetyl group COCH_3 of aspirin and the NH_2 amine group of CBZ (see Figure 2).
24 Consequently, two CBZ molecules and two ASP molecules form quadrimers with graph sets
25 $D^1_1(2)$ for the two strong hydrogen bonds ($\text{O}_2\text{-H}_{25}\cdots\text{O}_1$, $\text{N}_2\text{-H}_{15}\cdots\text{O}_3$) and one weaker ($\text{N}_2\text{-H}_{14}\cdots\text{O}_5$,
26 see Table 2 and Figure 2); each nitrogen atom is involved in a bifurcated H-bond with two
27 different CBZ molecules. Besides these hydrogen bonds, weak $\text{CH}\cdots\text{O}$ ($\text{C}_8\text{-H}_8\cdots\text{O}_2$ and $\text{C}_5\text{-}$
28 $\text{H}_5\cdots\text{O}_5$) interactions have also been found (Table 2). There are $\pi\text{-}\pi$ interactions between the
29 aromatic rings of the CBZ molecules forming the so-called sandwich herringbone (SH) stacking
30 as found in CBZ III (Figure 2).²² The ring centroid-centroid distances are found equal to 3.93 Å
31 in CBZ:ASP and to 3.79 Å for CBZ III, respectively.
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49 **Thermal expansion of CBZ III and CBZ:ASP.** The cell parameter values of the single
50 crystals of CBZ form III and CBZ:ASP were determined from 100 K to ambient temperature
51 with a step of 10 K. The variation of the cell parameters as a function of temperature for CBZ III
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3 is in relatively good agreement with those previously published.⁵⁷ No phase transition was
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5 observed in both cases. The eigenvalues of the thermal expansion tensor have been compiled in
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7 Table 3 and the graphical representation of the tensor at ambient temperature is presented in
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9 Figure 2.³³ Since the cell parameters increase linearly with temperature, the isobaric thermal
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11 expansion tensor is constant with temperature.
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16 All the unit cell parameters and volumes increase with temperature for CBZ III and
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18 CBZ:ASP co-crystal. Consequently, the thermal expansion is positive in all directions in both
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20 crystals (see Table 3 and Figure 2). The thermal expansion coefficients α_V are found equal to 1.3
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22 and $1.5 \times 10^{-4} \text{ K}^{-1}$ for CBZ III and CBZ:ASP, respectively. These values are similar to that of L-
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24 ascorbic acid but smaller than the average value of $2.0 \times 10^{-4} \text{ K}^{-1}$ found for small organic
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26 molecules.^{57, 58} The aspherism coefficient A, calculated according to equation 1, has a value of
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28 0.49 for CBZ:ASP which is comparable to the one of tienoxolol and L-ascorbic acid.^{58, 59} A
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30 small value of 0.28 was found for CBZ III indicating that the thermal expansion is more
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32 anisotropic in the co-crystal than in CBZ form III over the entire measured temperature range.
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37 For the CBZ:ASP co-crystal, the main part of the expansion is along the eigenvector \mathbf{e}_3
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39 (see Table 3, Figure 2). It is 4.5 to 25 times larger than the expansion along the two other axes.
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41 This high value emphasizes the “soft” direction in the crystal, along which the intermolecular
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43 interactions are the weakest; this \mathbf{e}_3 direction is more or less perpendicular to the infinite chains
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45 of quadrimers (see Figure 2).
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49 In polymorph III of CBZ, each molecule of CBZ acts as donor and acceptor of hydrogen
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51 bonds: the molecules are involved in a dimeric homosynthon $\text{NH} \cdots \text{O}$ hydrogen bond (Figure 2).
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53 The two carboxamide groups of the CBZ molecules involved in a hydrogen bonded dimer are
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55 coplanar. There are SH (sandwich herringbone) aromatic interactions as shown in Figure 2 and
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3 previously reported.²² These aromatic group interactions between dimers of CBZ molecules also
4 form infinite chains, however, unlike the co-crystal, these chains are along two different
5 directions in approximately the (e_1 , e_2) plane of tensor (see the dotted arrows in Figure 2). These
6 chains are linked via weak $\text{CH}\cdots\text{O}$ hydrogen bonds and van der Waals interactions. The isobaric
7 thermal expansion is almost isotropic in the (e_2 , e_3) plane (see Figure 2 and Table 3) and is
8 smaller along e_1 .
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12 **Electron Deformation Density Maps.** Figure 3 depicts the experimental static electron
13 deformation density maps obtained at the end of the multipole refinement. Different planes of
14 CBZ and ASP molecules have been chosen (see Figure 1). The shared electrons in the single and
15 double covalent bonds are clearly shown. On average, double bond in $\text{C}=\text{O}$ or aromatic $\text{C}=\text{C}$
16 bonds display a density peak value of 0.6 to 0.8 $\text{e}\text{\AA}^{-3}$ whereas C-N and other C-C bonds have an
17 average peak values ranging from 0.35 to 0.45 $\text{e}\text{\AA}^{-3}$. In the NH_2 group, the hydrogen atoms are
18 characterized by higher dipoles ($\text{N}_2\text{-H}_{14}$ and $\text{N}_2\text{-H}_{15}$) than those of the C-H groups in the
19 aromatic rings. The oxygen lone pairs of O_1 and O_5 oxygen atoms are almost symmetrical in
20 contrast to those of O_3 atom. This is clearly shown in the hydrogen bonds ($\text{N}_2\text{-H}_{15}\cdots\text{O}_3$ and $\text{O}_2\text{-}$
21 $\text{H}_{25}\cdots\text{O}_1$, bottom of Figure 3). In the plane of this last map, O_3 display a higher lone pair directed
22 toward the depletion of the electron density of atom C_{23} involved in the $\text{C}_{23}=\text{O}_5$ double bond.
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43 In Figure 4, the electron deformation density obtained after the theoretical structure
44 factors (TSF) refinement is depicted; Figures 3 and 4 display the same molecular parts for
45 comparison. The peak bond accumulations are globally comparable for the covalent bonds.
46 Discrepancies appear, however, for the oxygen lone pairs which are more populated and
47 symmetrical in the theoretical maps, even for O_3 involved in strong hydrogen bonds (Bottom of
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Figure 4). Moreover, the dipoles of H atoms are slightly less pronounced for the theoretical refinement especially for H₁₄ and H₁₅ atoms.

Topological Analysis of the Total Electron density. The total electron (core and valence) density has been characterized by its topological features reported in Table 4. The negativity of the Laplacian of the electron density in C-C, C=C, C=O, N-H, O-H and C-H bonds show the shared shell or covalent character. Conversely, in the hydrogen bonds and the O₃⋯O₄ close contact (bottom of Table 4), the Laplacian is positive (close shell interaction) and low valued (from 0.7 to 4.2 e.Å⁻⁵). For the peak height of the electron density at the bond critical points, the interacting chemical groups display the highest values: for CBZ molecule, C₁₅-O₁ (2.7 e.Å⁻³) and C₁₅-N₁ and C₁₅-N₂ (2.2 e.Å⁻³); for ASP molecule, C₁₆-O₃ (2.9 e.Å⁻³), C₁₆-O₂ (2.3 e.Å⁻³) compared to C₂₃-O₅ (2.9 e.Å⁻³). As expected N-H and O-H groups exhibit higher values of $\rho(\mathbf{r}_{\text{CP}})$ (2.2 e.Å⁻³ for N₂-H₁₄ and N₂-H₁₅ bonds) compared to 2.1 e.Å⁻³ for O₂-H₂₅ bond; on average 1.8 e.Å⁻³ was found for C-H bonds. All these values are in good agreement with those previously reported for CBZ III.²² The values of $\rho(\mathbf{r}_{\text{CP}})$ at the bond critical points for hydrogen bonds and atomic close contact are obviously lower: 0.4 e.Å⁻³ for O₂-H₂₅⋯O₁ and 0.1 e.Å⁻³ for N₂-H₁₅⋯O₃ hydrogen bonds and for O₃⋯O₄ contact (see Figure 1). These two last H-bonds display, however, different Laplacian values (2.4 vs 1.6 e.Å⁻⁵). The oxygen atoms O₂ and O₅ are also involved in weaker C-H⋯O intra-molecular hydrogen bonds: C₈-H₈⋯O₂ ($\rho(\mathbf{r}_{\text{CP}}) = 0.07$ e.Å⁻³ and $\nabla^2\rho(\mathbf{r}_{\text{CP}}) = 0.7$ e.Å⁻⁵) and C₅-H₅⋯O₅ ($\rho(\mathbf{r}_{\text{CP}}) = 0.05$ e.Å⁻³ and $\nabla^2\rho(\mathbf{r}_{\text{CP}}) = 0.8$ e.Å⁻⁵). In Table 4, the strength of the hydrogen bonds and atomic contacts was quantified by the interaction energies E_{NC} (for non-covalent (NC) interactions) which differentiate between O-H⋯O (-81.9 kJ/mol), N-H⋯O (-9.2 to -22.7 kJ/mol) and C-H⋯O bonds (-6 kJ/mol on average).⁶⁰ In comparison, O₃⋯O₄ intramolecular

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3 contact interaction ($O_3 \cdots O_4 = 2.74 \text{ \AA} < 2 * R_{\text{van der Waals}} = 2.80 \text{ \AA}$) is characterized by $E_{\text{NC}} = -14.4$
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5 kJ/mol). All these values are consistent with those reported for CBZ III.²²
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9 The topological analysis was also carried out from the theoretical structure factors (TSF)
10 refinement density. The results are reported in Table 4 for comparison with the experimental
11 features. There is a good agreement for the values of the electron density at the critical points
12 $\rho(\mathbf{r}_{\text{CP}})$ obtained from the experiment and theory. However, differences between the two
13 approaches appear in the absolute Laplacian values which are systematically weaker in the TSF
14 refinement especially for C=O, O-H and N-H bonds: C16=O3 (-34.7 (exp) vs -26.2 (TSF) e.\AA^{-5}),
15 C23=O4 (-23.7 (exp) vs -17.7 (TSF) e.\AA^{-5}), O2-H25 (-31.2 (exp) vs -26.8 (TSF) e.\AA^{-5}), N2-H15
16 (-27.6 (exp) vs -22.0 (TSF) e.\AA^{-5}). This remark holds true for the ellipticity ε values for the
17 majority of the bonds. For the hydrogen bonds and intermolecular contacts, the Laplacian and
18 non-covalent energy values obtained by both experiment and theory are in good agreement
19 (bottom of Table 4).
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35 **Atomic Charges.** The total electron density has been numerically integrated over the
36 atomic basins for the two molecules in CBZ:ASP co-crystal.^{25, 61,62} The values of the atomic
37 charges are reported in Table 5. These charges were calculated for the CBZ \cdots ASP dimer (as in
38 Figure 1). The charges of the most important atoms in the molecular interactions are highlighted
39 in bold. The values obtained for CBZ molecule are globally in good agreement with those of
40 CBZ III.²² However, the absolute magnitudes of the atomic charges in CBZ III are higher than
41 those for CBZ in the co-crystal: for example in CBZ III, 1.6, -0.9, -1.0 -0.9 e were obtained for
42 atoms C₁₅, N₁, N₂, O₁, respectively.²² H₁₄ and H₁₅ hydrogen atoms of the amine group of CBZ
43 carry the same charges (0.4 to 0.5 e) in both crystalline structures. For the CBZ:ASP co-crystal,
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3 the integrations of the atomic charges were also carried out for isolated molecules (Table 5). No
4 significant differences of charges were found for the CBZ molecule in CBZ III and in the co-
5 crystal. However, low values for isolated ASP molecule were observed for C₂₃ (+1.0 vs +1.5 e),
6 O₃ (-0.5 vs -0.8 e), O₄ (-0.6 vs -0.9 e), O₅ (-0.7 vs -1.1 e) and H₂₅ (+0.4 vs + 0.5 e) atoms.
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8 Looking at the sum of the atomic charges, no charge has been transferred between the two
9 molecules in the co-crystal.
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18 For comparison, the integrated charges obtained from Independent Atom Model (IAM)
19 densities (promolecule) and from the theoretical structure factors (TSF) refinement are also
20 reported in Table 5. As can be expected from a charge transfer consideration, the atomic charge
21 absolute values from the promolecule are systematically weaker than those obtained from the
22 experimental multipole refinement. Conversely, the atomic charges obtained from the theoretical
23 approach are higher in their absolute values than those derived experimentally. This is
24 particularly observed in CBZ molecule: C₁₅ (1.62 e (TSF) vs 1.29 e (exp)), N₁ (-0.98 e (TSF) vs -
25 0.70 e (exp)), N₂ (-1.17 e (TSF) vs -0.98 e (exp)), O₁ (-0.94 e (TSF) vs -0.71 e (exp)).
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37 **Electrostatic Potential.** The electrostatic potential has been calculated around the isolated
38 molecules and for the CBZ:ASP dimers in the co-crystal. Figure 5 illustrates the electrostatic
39 potential using the iso-surface representation. For isolated CBZ (top of Figure 5), the negative
40 region of electrostatic potential (nucleophilic part at -0.03 eÅ⁻¹ cut-off) is extended around the
41 aromatic rings of the molecule showing the main contribution of the π -electrons. This also holds
42 true for the ASP molecule; the proximity of the methyl group (positive contribution) to the
43 carboxyl group counterbalances the negative contribution of the latter (at -0.03 eÅ⁻¹ cut-off). The
44 electrostatic potential features of the CBZ:ASP dimers in the co-crystal are also displayed in
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3 Figure 5. The aromatic-aromatic interaction between two CBZ molecules (sandwich herringbone
4 (SH), also observed in the lattice of CBZ III²²) is characterized by a large negative region of
5 electrostatic potential surrounding the external part of the aromatic rings. For the CBZ...ASP
6 dimer, at the chosen cut-off of $-0.03 \text{ e}\text{\AA}^{-1}$, the negative potential still remains in the vicinity of
7 the aromatic part of CBZ molecule. The right column of Figure 5 illustrates the electrostatic
8 potential obtained from the theoretical structure factors refinement. For the same cut-offs, the
9 negative theoretical electrostatic potential surfaces are more spatially extended for isolated
10 molecules and for dimers.
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23 **Electrostatic Potential at the nuclei (EPN) and molecular total energies.** Table 6 reports
24 the values of the EPN obtained for each atom of the molecules in the CBZ:ASP co-crystal.⁴⁹ As
25 mentioned before, only the parameters κ and P_{val} of the multipole model contribute to the EPN.
26 For the sake of comparison, the values of EPN of the promolecules (sum of neutral atoms) and
27 those obtained by the theoretical approach (TSF refinement) are also given. As for the atomic
28 charges, the most important atoms in the molecular interactions are highlighted in bold in Table
29 6. It is worthy to note that the highest absolute EPN values are obtained from the theory for C, O,
30 N elements and also H₁₄, H₁₅ and H₂₅ atoms (see Table 6), the remaining H atoms displaying
31 close values between experiment and theory.
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45 Equations (2) and (3) were used for estimating the total molecular energy E^{tot} (in *hartree*)
46 from experimental and theoretical (TSF) approaches. The results are reported in Table 7 for
47 isolated molecules and dimers and are compared to those obtained for CBZ III. The energy
48 values of isolated or a group of molecules estimated with Gaussian software from RHF *6-31*
49 G^{**} , DFT B3LYP *6-31 G^{**} and DFT B3LYP *cc-pvdz* levels of theory are also given in Table 7.
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3 These last two basis sets give very comparable values for the molecular energies. From the
4 theoretical calculations, the interacting CBZ molecules in both CBZ III and CBZ:ASP co-crystal
5 display the same average total energies: -1517.6 hartrees for RHF 6-31 G** and -1526.3 hartrees
6 for DFT B3LYP 6-31 G**. For comparison, the CBZ...ASP interaction is characterized by
7 energy values of -1403.8 and -1411.5 hartrees for the two theoretical approaches. Table 7 also
8 reports the energy estimates obtained after the experimental and TSF refinements. For both CBZ
9 III and CBZ:ASP co-crystal, the multipole refinements over-estimate the total molecular
10 energies. In CBZ:ASP co-crystal, we can notice that the TSF refinement leads systematically to
11 the highest energies in absolute values. Surprisingly, the values derived from the “promolecule”
12 density are those which are closest to the *ab initio* results especially those of DFT B3LYP (see
13 Table 7).
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29 CONCLUSIONS

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33 The structure of the CBZ:ASP co-crystal was here described through the geometrical properties
34 and also through the isobaric thermal expansion tensor. The comparison was made with the
35 previous results of the CBZ form III crystal. Both crystal structures (CBZ and CBZ:ASP co-
36 crystal) reveal strong hydrogen bonds and aromatic π - π interactions. CBZ III displays, however,
37 a more isotropic thermal expansion tensor than that obtained for the CBZ:ASP co-crystal. This
38 can be explained by several non-parallel molecular chains occurring in the former compound
39 crystal lattice which both involve hydrogen bonding and π - π interactions. The electron densities
40 were here derived from X-ray and theoretical structure factors based on the experimental
41 geometry using the B3LYP/cc-pvdz quantum chemistry model. The deformation electron density
42 maps obtained from these two approaches are very comparable for the covalent bonds except for
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3 the oxygen lone pairs and for the polarization of aromatic H atoms. The topological features of
4 the total electron density in the CBZ:ASP co-crystal were carefully analyzed. The values of the
5 electron density at the bond critical points (BCP) obtained for the experiment and theory are
6 similar. A disagreement on the Laplacian estimates at the BCP was observed; for all covalent
7 bonds, the theoretical Laplacian values are systematically slightly lower than those derived from
8 the experiment. For the hydrogen bonds and atomic contacts, however, all the topological
9 features are comparable. The integrated atomic charges were here estimated from the total
10 electron densities. The refinement against the TSF gives systematically higher magnitudes of the
11 atomic charges than those derived from the experimental structure factors. The same trend was
12 observed for the electrostatic potential derived from the TSF refinement which displays more
13 extended negative potential regions around the isolated molecules and the dimers in the
14 CBZ:ASP co-crystal. This feature also shows that the aromatic π -electron contribution is
15 significantly enhanced in the TSF refinement. The electrostatic potential at the nuclei (EPN) was
16 used here to estimate the total molecular energy following the Politzer *et al* approximation.⁴⁴⁻⁴⁶
17 The best agreement to reproduce the quantum *ab initio* total energy was here obtained with the
18 IAM electron density (promolecule) and not from the multipole refinements. Investigations to
19 elucidate this issue are in progress.
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47 **ASSOCIATED CONTENT**

48 49 50 **Supporting Information**

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3 Residual density maps after the multipole refinement, crystal data and structures of ethanol and
4 methanol solvates of carbamazepine are available free of charge via the internet at
5 <http://pubs.acs.org>. CCDC 1877787 contains the supplementary crystallographic data for this
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10 paper. These data can be obtained free of charge from The Cambridge Crystallographic Data
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13 Centre via www.ccdc.cam.ac.uk/structures/.

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Table 1. Data Collection and Refinement Details of CBZ:ASP Co-crystal.

Empirical formula	$C_{24}H_{20}N_2O_5$
Formula weight	1960.87
Temperature (K)	100.0(2)
Crystal system	Triclinic
Space group	P-1

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Unit cell dimensions	$a = 9.0161(1) \text{ \AA}$
	$b = 11.3400(2) \text{ \AA}$
	$c = 11.4142(2) \text{ \AA}$
	$\alpha = 60.340(2)^\circ$
	$\beta = 85.622(2)^\circ$
	$\gamma = 84.722(2)^\circ$
Volume	1009.17(3) \AA^3
Z	2
Density (calculated) (Mg/m^3)	1.370
Absorption coefficient (mm^{-1})	0.097
F(000)	436
Reflections collected	292549
Independent reflections	17015 [$R_{\text{int}} = 0.0442$]
Completeness to $\theta = 45.51^\circ$	92.8%
Spherical Refinement	
R_1 , wR_2 , gof [$I > 2\sigma(I)$]	3.39 %, 7.35 %, 0.81
Multipole Refinement	
$R_1(F)$, $wR_2(F)$, gof [$I > 2\sigma(I)$]	2.69 %, 3.00 %, 1.53
	1.00 %, 0.36 %, 3.26*

*refinement against 17015 theoretical structure factors (TSF) from cc-pvdz basis set.

Table 2. Selected Bond Lengths (Å), Angles and Torsion Angles (deg) in CBZ:ASP Co-crystal.

CBZ			
C15-O1	1.2490(6)	O1-C15-N2	122.26(4)
C15-N2	1.3471(9)	C1-N1-C14	116.94(3)
C15-N1	1.3657(6)	C6-C7-C8	126.73(5)
C1-N1	1.4264(9)	C7-C8-C9	127.45(4)
C14-N1	1.4287(7)	C1-C6-C7	123.40(5)
		C8-C9-C14	119.17(3)
C1-C2	1.3921(12)	C1-N1-C15-O1	-8.92(3)
C1-C6	1.4002(10)	C1-N1-C15-N2	172.85(4)
C2-C3	1.3911(9)	C1-N1-C14-C13	113.75(5)
C3-C4	1.3972(11)	C1-N1-C14- C9	-67.40(4)
C4-C5	1.3875(12)	N1-C15-N2-H14	-12.2(6)
C5-C6	1.4033(9)	N1-C15-N2-H15	-175.0(2)
C6-C7	1.4581(13)		
C7-C8	1.3513(8)		
C8-C9	1.4578(10)		
C9-C10	1.4035(7)		
C9-C14	1.4017(11)		
C10-C11	1.3853(10)		
C11-C12	1.3938(11)		
C12-C13	1.3903(7)		
C13-C14	1.3923(9)		
ASP			
C23-O5	1.2047(10)	O2-C16-O3	123.04(5)
C16-O3	1.2197(6)	C22-C17-C18	118.07(5)
C16-O2	1.3197(9)	O4-C22-C17	121.36(5)
C23-O4	1.3562(9)	C23-O4-C22	120.63(3)
C22-O4	1.3850(8)		
C16-C17	1.4875(6)	C18-C17-C16-O2	-11.87(4)
C17-C18	1.4017(8)	C18-C17-C16-O3	167.91(4)
C17-C22	1.4014(8)	C17-C22-O4-C23	80.40(4)
C18-C19	1.3887(6)	C22-O4-C23-C24	-168.60(4)
C19-C20	1.3943(9)		
C20-C21	1.3904(8)		
C21-C22	1.3883(6)		
C23-C24	1.4929(9)		
<i>Hydrogen bonds</i>			
H25...O1 ¹	1.601(7)	O2-H25...O1	168.18(19)
H15...O3 ¹	1.913(6)	N2-H15...O3	167.65(14)
H14...O5 ²	2.243(6)	N2-H14...O5	152.45(14)
H8...O2 ³	2.568(6)	C8-H8...O2	157.57(19)
H5...O5 ³	2.510(6)	C5-H5...O5	144.9(4)

symmetry operations : ¹-x,-y, 2-z ; ²1+x, y, z ; ³x, y, z

Table 3. Eigenvalues (α_{ii}), Eigenvectors (e_i with respect to the Cell Vectors a , b , c) and Aspherism Coefficient A of the Isobaric Thermal Expansion Tensors of CBZ III and CBZ:ASP Co-crystal.

	<i>CBZ III</i>	<i>CBZ:ASP</i>
α_{11} (MK ⁻¹)	27.1(31)	4.3(21)
α_{22} (MK ⁻¹)	46.3(29)	24.3(36)
α_{33} (MK ⁻¹)	47.5(26)	111.1(35)
e_1	-0.994 a + 0.110 c	0.370 a + 0.901 b + 0.227 c
e_2	1.0 b	0.906 a - 0.388 b + 0.171 c
e_3	0.418 a + 0.908 c	-0.261 a - 0.484 b + 0.835 c
α_V (MK ⁻¹)	131.6(8)	147.8(8)
A	0.28	0.49

Table 4. Topological Properties of the Electron Density of CBZ:ASP Cocrystal.^a The first and second Lines correspond to the values obtained from the experimental Electron Density and from the Theoretical Structure Factors (TSF) refinement, respectively.

bond A-B	$d(\text{CP-A}) (\text{\AA})$	$d(\text{CP-b}) (\text{\AA})$	$\rho(\Gamma_{\text{CP}}) (\text{e.\AA}^{-3})$	$\nabla^2\rho(\Gamma_{\text{CP}}) (\text{e.\AA}^{-5})$	ε
CBZ					
C15-O1	0.458	0.791	2.69	-34.0	0.120
	0.460	0.790	2.63	-27.7	0.131
C15-N2	0.533	0.814	2.25	-26.9	0.171
	0.554	0.794	2.29	-23.7	0.190
C15-N1	0.558	0.808	2.21	-24.2	0.212
	0.570	0.795	2.20	-20.6	0.216
C1-N1	0.599	0.827	1.87	-15.2	0.051
	0.599	0.827	1.86	-13.1	0.050
C14-N1	0.606	0.823	1.84	-13.7	0.055
	0.608	0.821	1.87	-12.7	0.034
C1-C2	0.678	0.715	2.16	-20.7	0.290
	0.724	0.668	2.08	-17.8	0.262
C1-C6	0.702	0.699	2.11	-19.9	0.266
	0.718	0.682	2.07	-17.6	0.203
C2-C3	0.712	0.680	2.12	-19.9	0.241
	0.669	0.722	2.10	-18.2	0.193
C3-C4	0.689	0.708	2.11	-19.4	0.221
	0.710	0.687	2.06	-17.5	0.217
C4-C5	0.707	0.680	2.16	-21.1	0.198
	0.681	0.707	2.09	-18.1	0.189
C5-C6	0.701	0.703	2.09	-19.6	0.192
	0.709	0.695	2.03	-16.3	0.179
C6-C7	0.732	0.726	1.84	-14.3	0.147
	0.731	0.727	1.85	-13.3	0.114
C7-C8	0.668	0.684	2.34	-23.0	0.293
	0.679	0.673	2.26	-21.6	0.309
C8-C9	0.750	0.708	1.84	-14.6	0.127
	0.738	0.720	1.84	-13.4	0.142
C9-C10	0.695	0.709	2.07	-18.4	0.161
	0.714	0.689	2.04	-16.8	0.180
C9-C14	0.676	0.726	2.04	-18.0	0.259
	0.701	0.701	2.07	-17.5	0.233
C10-C11	0.683	0.703	2.14	-20.3	0.191
	0.692	0.693	2.13	-17.8	0.228
C11-C12	0.718	0.676	2.13	-20.4	0.195
	0.673	0.721	2.09	-17.7	0.197
C12-C13	0.681	0.709	2.11	-20.2	0.178
	0.695	0.696	2.09	-17.9	0.228
C13-C14	0.692	0.700	2.11	-19.9	0.234
	0.674	0.719	2.12	-18.6	0.238
N2-H14	0.733	0.275	2.22	-28.9	0.067
	0.758	0.250	2.10	-25.2	0.075
N2-H15	0.725	0.290	2.24	-27.6	0.076
	0.757	0.258	2.04	-22.0	0.079
C2-H2	0.702	0.380	1.83	-18.4	0.086
	0.716	0.366	1.83	-16.3	0.006
C3-H3	0.717	0.360	1.79	-17.6	0.055
	0.715	0.362	1.85	-17.7	0.058
C4-H4	0.703	0.376	1.82	-18.7	0.003
	0.704	0.375	1.79	-15.7	0.000
C5-H5	0.718	0.356	1.80	-17.9	0.077
	0.713	0.362	1.84	-17.4	0.053
C7-H7	0.694	0.384	1.80	-17.9	0.040
	0.719	0.359	1.82	-16.3	0.032

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3	C8-H8	0.673	0.413	1.78	-16.9	0.025
4		0.720	0.366	1.81	-15.8	0.033
5	C10-H10	0.674	0.401	1.78	-17.2	0.070
6		0.700	0.375	1.85	-16.8	0.046
7	C11-H11	0.716	0.364	1.84	-19.2	0.043
8		0.709	0.371	1.83	-17.2	0.016
9	C12-H12	0.703	0.376	1.84	-19.0	0.033
10		0.707	0.372	1.86	-17.9	0.039
11	C13-H13	0.709	0.369	1.84	-19.0	0.071
12		0.714	0.364	1.81	-16.7	0.038
13	<i>ASP</i>					
14	C23-O5	0.416	0.789	2.93	-26.2	0.134
15		0.425	0.780	2.93	-27.2	0.139
16	C16-O3	0.437	0.783	2.90	-34.7	0.131
17		0.434	0.786	2.80	-26.2	0.108
18	C16-O2	0.497	0.822	2.27	-26.8	0.102
19		0.508	0.813	2.23	-22.2	0.096
20	C23-O4	0.507	0.850	2.06	-23.7	0.050
21		0.535	0.822	2.03	-17.7	0.093
22	C22-O4	0.550	0.837	1.90	-15.7	0.008
23		0.557	0.828	1.84	-11.2	0.023
24	O2-H25	0.753	0.217	2.13	-31.2	0.031
25		0.761	0.210	2.12	-26.8	0.009
26	C16-C17	0.772	0.715	1.81	-14.1	0.158
27		0.780	0.708	1.79	-13.0	0.157
28	C17-C18	0.704	0.698	2.07	-18.4	0.220
29		0.694	0.708	2.03	-16.2	0.198
30	C17-C22	0.685	0.716	2.13	-19.3	0.232
31		0.684	0.718	2.06	-17.1	0.241
32	C18-C19	0.688	0.701	2.15	-20.0	0.205
33		0.712	0.677	2.09	-17.8	0.208
34	C19-C20	0.680	0.715	2.14	-19.4	0.211
35		0.682	0.713	2.10	-18.1	0.149
36	C20-C21	0.714	0.676	2.12	-19.5	0.218
37		0.691	0.700	2.09	-17.5	0.182
38	C21-C22	0.679	0.710	2.17	-20.6	0.245
39		0.667	0.721	2.13	-18.5	0.224
40	C23-C24	0.795	0.698	1.75	-13.8	0.113
41		0.803	0.690	1.76	-12.2	0.095
42	C18-H18	0.712	0.369	1.80	-18.4	0.067
43		0.710	0.370	1.81	-16.6	0.047
44	C19-H19	0.698	0.379	1.83	-19.0	0.033
45		0.710	0.368	1.80	-15.5	0.054
46	C20-H20	0.730	0.348	1.79	-18.7	0.065
47		0.711	0.366	1.81	-16.2	0.034
48	C21-H21	0.711	0.373	1.86	-18.8	0.051
49		0.706	0.377	1.78	-15.3	0.037
50	C24-H22	0.716	0.360	1.67	-14.2	0.074
51		0.699	0.377	1.80	-15.7	0.010
52	C24-H23	0.703	0.375	1.75	-16.8	0.076
53		0.689	0.389	1.83	-16.6	0.005
54	C24-H24	0.707	0.365	1.75	-17.4	0.028
55		0.700	0.371	1.76	-15.3	0.023
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Hydrogen bonds and intermolecular contacts							E_{NC}
O2-H25...O1 ¹	0.523	1.078	0.38	4.2	0.006	-81.9	
N2-H15...O3 ¹	0.519	1.083	0.34	5.6	0.010	-77.2	
	0.666	1.261	0.14	2.4	0.197	-22.7	
N2-H14...O5 ²	0.685	1.230	0.16	3.0	0.023	-27.8	
	0.865	1.401	0.07	1.2	0.295	-9.2	
C8-H8...O2 ³	0.868	1.392	0.07	1.4	0.141	-9.6	
	1.082	1.517	0.07	0.7	0.495	-6.3	
C5-H5...O5 ³	1.059	1.595	0.04	0.8	0.824	-4.8	
	1.064	1.456	0.05	0.8	0.021	-5.8	
O3...O4 ¹	1.045	1.490	0.04	0.7	0.002	-4.9	
	1.352	1.396	0.10	1.6	1.558	-14.4	
	1.357	1.397	0.10	1.6	0.855	-14.1	

$\rho(r_{CP})$ and $\nabla^2\rho(r_{CP})$ are the electron density and the Laplacian values at the critical points (CP); ε is the ellipticity of the bond. E_{NC} (in kJ/mol) indicates the non-covalent interaction energy.

symmetry operations : ¹-x, -y, 2-z ; ²1+x, y, z ; ³x, y, z

Table 5. Integrated Atomic Charges (in e unit) in CBZ:ASP co-crystal. EXP and TSF correspond to the Refinements obtained from Experimental and Theoretical Structure Factors (TSF), respectively. "IAM" refers to the promolecule (Independent Atom Model) and "only" refers to molecules extracted from the crystal lattice.

	EXP CBZ in CBZ:ASP	EXP CBZ only	IAM CBZ only	TSF CBZ in CBZ:ASP	TSF CBZ only	EXP ASP in CBZ:ASP	EXP ASP only	IAM ASP only	TSF ASP in CBZ:ASP	TSF ASP only	
C1	0.38	0.37	0.20	0.32	-0.07	C16	1.11	0.75	0.76	1.00	0.75
C2	-0.13	-0.10	-0.18	0.07	0.10	C17	0.22	0.11	-0.00	0.19	0.21
C3	-0.32	-0.33	-0.06	-0.17	-0.25	C18	-0.31	-0.02	-0.05	-0.25	-0.29
C4	0.11	0.10	-0.07	-0.07	-0.29	C19	-0.12	-0.20	-0.21	-0.38	0.04
C5	-0.19	-0.19	-0.10	-0.09	-0.05	C20	-0.27	-0.15	-0.15	-0.07	-0.13
C6	-0.04	-0.02	0.02	-0.15	0.17	C21	0.08	-0.04	-0.04	-0.21	-0.13
C7	-0.14	-0.08	-0.02	-0.04	-0.06	C22	0.15	0.31	0.05	0.40	0.37
C8	-0.13	-0.11	-0.06	-0.16	-0.42	C23	1.50	0.97	0.74	1.09	1.16
C9	0.23	0.22	0.11	0.04	0.20	C24	-0.37	-0.36	-0.30	0.07	-0.45
C10	0.08	0.09	-0.15	-0.14	-0.31	O2	-0.71	-0.76	-0.76	-0.77	-0.79
C11	-0.45	-0.43	-0.39	0.03	-0.06	O3	-0.83	-0.46	-0.41	-0.85	-0.70
C12	0.09	0.07	-0.33	-0.17	-0.43	O4	-0.92	-0.63	-0.42	-0.46	-0.69
C13	0.02	-0.02	0.01	0.02	-0.16	O5	-1.11	-0.69	-0.59	-1.21	-0.87
C14	0.04	0.00	0.17	0.17	0.24	H18	0.18	0.05	0.15	0.27	0.21
C15	1.29	1.38	-0.10	1.62	0.86	H19	0.15	0.08	0.16	0.24	0.05
N1	-0.70	-0.64	-0.40	-0.98	-0.56	H20	0.17	0.14	0.14	0.15	0.12
N2	-0.98	-0.95	-0.83	-1.17	-1.00	H21	0.06	-0.01	0.16	0.27	0.20
O1	-0.71	-0.89	-0.69	-0.94	-0.93	H22	0.08	0.16	0.15	0.08	0.29
H2	0.07	0.05	0.16	0.14	0.24	H23	0.14	0.03	0.15	0.04	0.17
H3	0.11	0.09	0.16	0.10	0.16	H24	0.13	0.11	0.17	0.16	0.16
H4	0.02	0.02	0.14	0.11	0.16	H25	0.51	0.44	0.43	0.59	0.60
H5	0.14	0.14	0.17	0.11	0.15						
H7	0.08	0.08	0.16	0.13	0.22						
H8	-0.02	-0.04	0.18	0.09	0.25						
H10	-0.10	-0.07	0.12	0.09	0.24						
H11	0.24	0.23	0.15	0.09	0.15						
H12	0.02	0.03	0.15	0.08	0.18						
H13	0.09	0.10	0.12	0.13	0.26						
H14	0.45	0.43	0.33	0.50	0.53						
H15	0.40	0.37	0.33	0.47	0.47						
Sum	-0.05	-0.10	-0.69	0.24	-0.02		-0.16	-0.17	0.13	0.33	0.28

Table 6. Electrostatic Potential at the Nuclei $V_{0,A}$ (EPN) from Experimental data (EXP) and from the Refinement of Theoretical Structure Factors (TSF). $V_{\text{promol},A}$ is the EPN for the Independent Atom Model (promolecule). All values are in atomic unit.

	<i>CBZ</i>			<i>ASP</i>			
	$V_{\text{promol},A}$	$V_{0,A,EXP}$	$V_{0,A,TSF}$	$V_{\text{promol},A}$	$V_{0,A,EXP}$	$V_{0,A,TSF}$	
C1	-14.690	-14.600	-14.761	C16	-14.690	-14.558	-14.722
C2	-14.690	-14.673	-14.696	C17	-14.690	-14.483	-14.719
C3	-14.690	-14.765	-14.821	C18	-14.690	-14.533	-14.733
C4	-14.690	-14.700	-14.863	C19	-14.690	-14.676	-14.652
C5	-14.690	-14.717	-14.808	C20	-14.690	-14.711	-14.728
C6	-14.690	-14.630	-14.713	C21	-14.690	-14.663	-14.738
C7	-14.690	-14.766	-14.758	C22	-14.690	-14.591	-14.688
C8	-14.690	-14.797	-14.799	C23	-14.690	-14.545	-14.712
C9	-14.690	-14.625	-14.649	C24	-14.690	-14.636	-14.741
C10	-14.690	-14.678	-14.786	O2	-22.260	-22.139	-22.275
C11	-14.690	-14.725	-14.778	O3	-22.260	-22.126	-22.286
C12	-14.690	-14.650	-14.850	O4	-22.260	-22.165	-22.315
C13	-14.690	-14.597	-14.787	O5	-22.260	-22.013	-22.308
C14	-14.690	-14.599	-14.678	H18	-1.000	-0.951	-0.938
C15	-14.690	-14.524	-14.725	H19	-1.000	-1.022	-1.036
N1	-18.336	-18.193	-18.300	H20	-1.000	-1.035	-1.057
N2	-18.336	-18.318	-18.394	H21	-1.000	-0.961	-0.961
O1	-22.260	-22.203	-22.365	H22	-1.000	-0.934	-0.931
H2	-1.000	-1.057	-1.007	H23	-1.000	-0.954	-0.991
H3	-1.000	-1.041	-1.073	H24	-1.000	-0.936	-1.022
H4	-1.000	-1.052	-1.045	H25	-1.000	-0.865	-0.932
H5	-1.000	-0.993	-1.058				
H7	-1.000	-1.078	-0.997				
H8	-1.000	-1.077	-1.010				
H10	-1.000	-1.074	-0.969				
H11	-1.000	-0.961	-1.019				
H12	-1.000	-1.043	-1.006				
H13	-1.000	-0.973	-0.959				
H14	-1.000	-0.905	-0.964				
H15	-1.000	-0.934	-0.990				

Table 7. Comparison of the Total Molecular Energies (in *hartree*) in CBZ:ASP Co-crystal Compared to Those in CBZ Form III. “Promolecule” refers to IAM and corresponds to energy derived from EPN. *CBZ...ASP*, *CBZ...CBZ* are the dimers interacting through hydrogen bonds and *CBZ/CBZ SH* corresponds to the Sandwich Herringbone (*SH*) aromatic interactions.

<i>CBZ:ASP co-crystal</i>						
	<i>RHF</i> <i>6-31G**</i>	<i>DFT</i> <i>B3LYP</i> <i>6-31G**</i>	<i>DFT</i> <i>B3LYP</i> <i>cc-pvdz</i>	<i>EXP</i>	<i>TSF</i>	<i>Promolecule</i>
<i>CBZ</i>	-758.82	-763.12	-763.15	-762.18	-766.85	-763.44
<i>ASP</i>	-644.98	-648.36	-648.39	-644.14	-649.51	-648.57
<i>CBZ...ASP</i>	-1403.82	-1411.51	-1411.57	-1407.87	-1423.32	-1412.02
<i>CBZ/CBZ SH</i>	-1517.63	-1526.24	-1526.29	-1525.28	-1534.34	-1526.88
<i>CBZ III</i>						
	<i>RHF</i> <i>6-31G**</i>	<i>DFT</i> <i>B3LYP</i> <i>6-31G**</i>	<i>DFT</i> <i>B3LYP</i> <i>cc-pvdz</i>	<i>EXP</i>	<i>TSF</i>	<i>Promolecule</i>
<i>CBZ</i>	-758.82	-763.12	-763.15	-771.92	-	-763.44
<i>CBZ...CBZ</i>	-1517.65	-1526.28	-1526.33	-1543.93	-	-1526.89
<i>CBZ/CBZ SH</i>	-1517.63	-1526.25	-1526.30	-1544.22	-	-1526.88

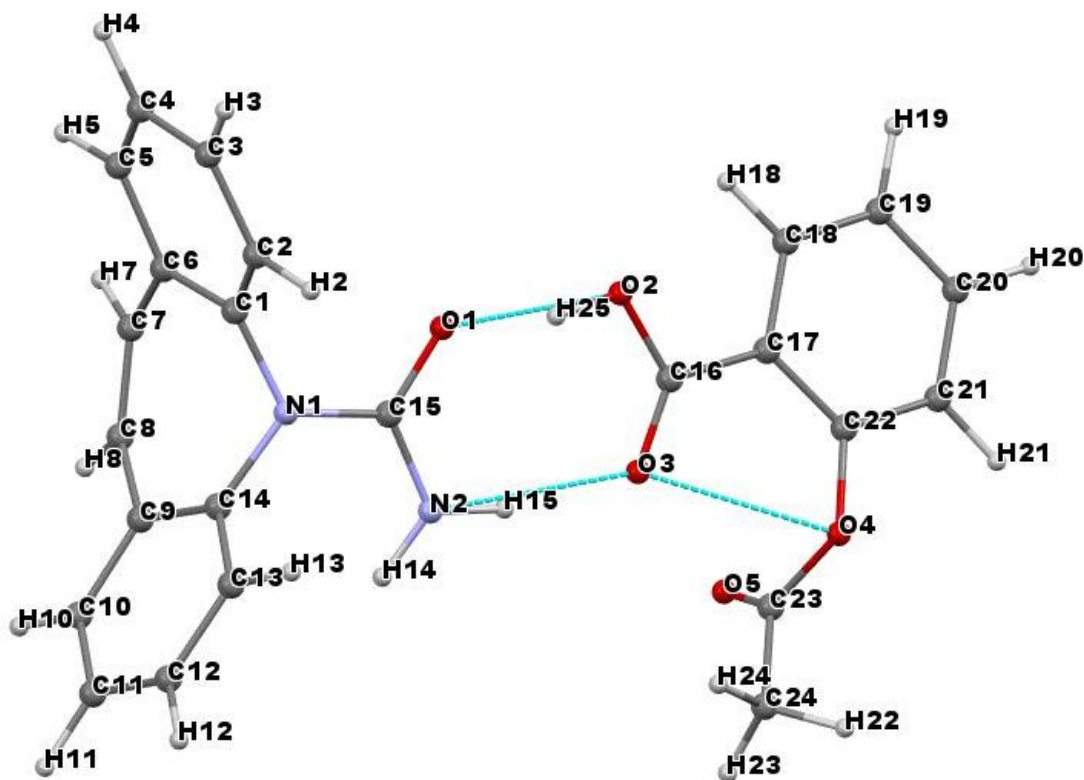


Figure 1. Molecular structure of CBZ:ASP with the numbering schemes of the atoms. Blue dotted lines indicate the hydrogen bonds.

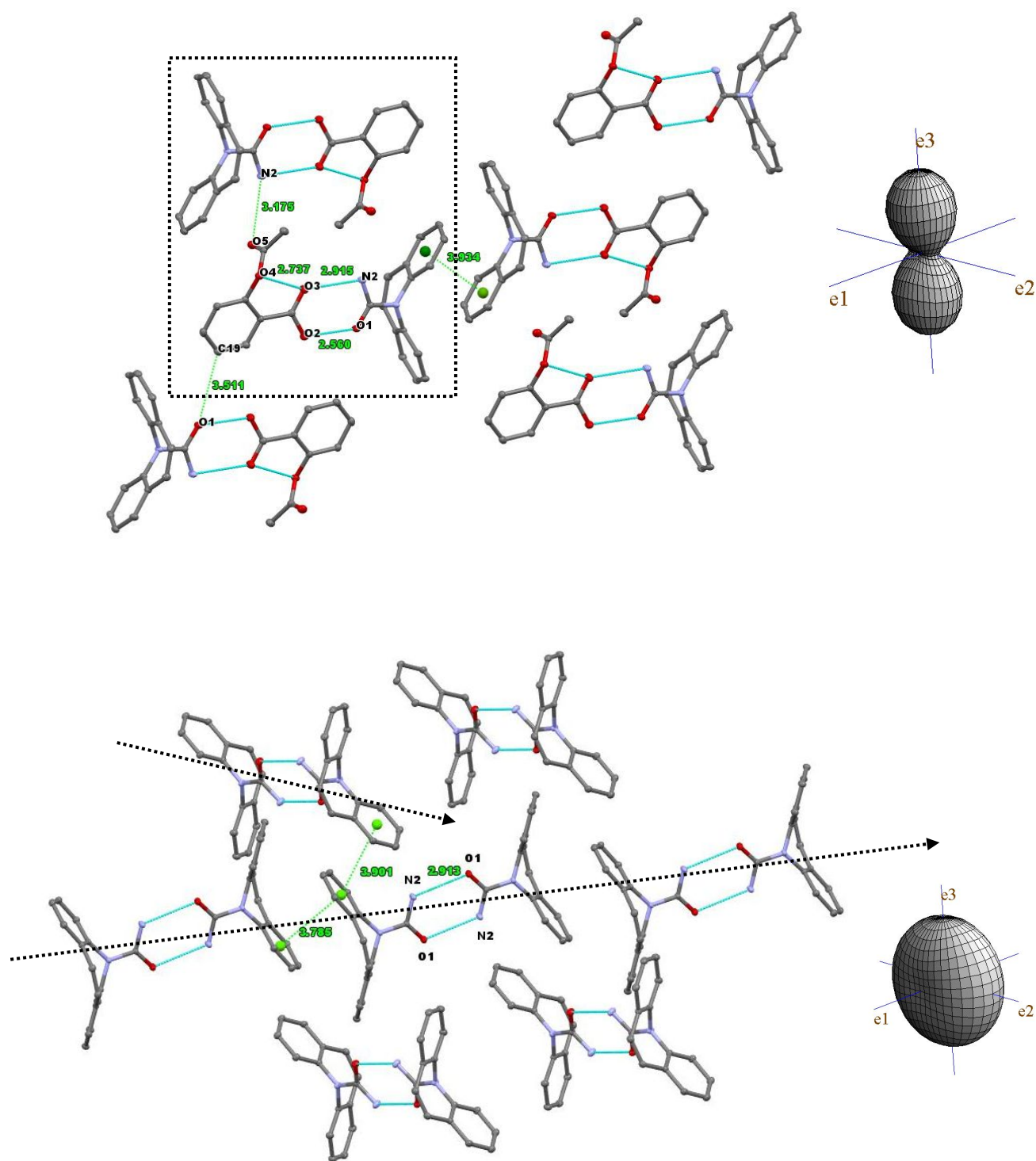


Figure 2. Molecular packing and hydrogen bonds in the crystal lattices of CBZ:ASP co-crystal (top) and CBZ III (bottom). H atoms are omitted. The main hydrogen bond (A-D) and benzene ring centroid-centroid distances are indicated in Å. The square in the CBZ:ASP structure groups together a quadrimer of interacting molecules, while in CBZ III structure, the lines indicate the two chains of aromatic group (SH) and H-bonds interactions. On the right column are given the graphical representation of the thermal expansion tensors of CBZ:ASP and CBZ III, e_1 , e_2 and e_3 are the principal directions of the tensors.

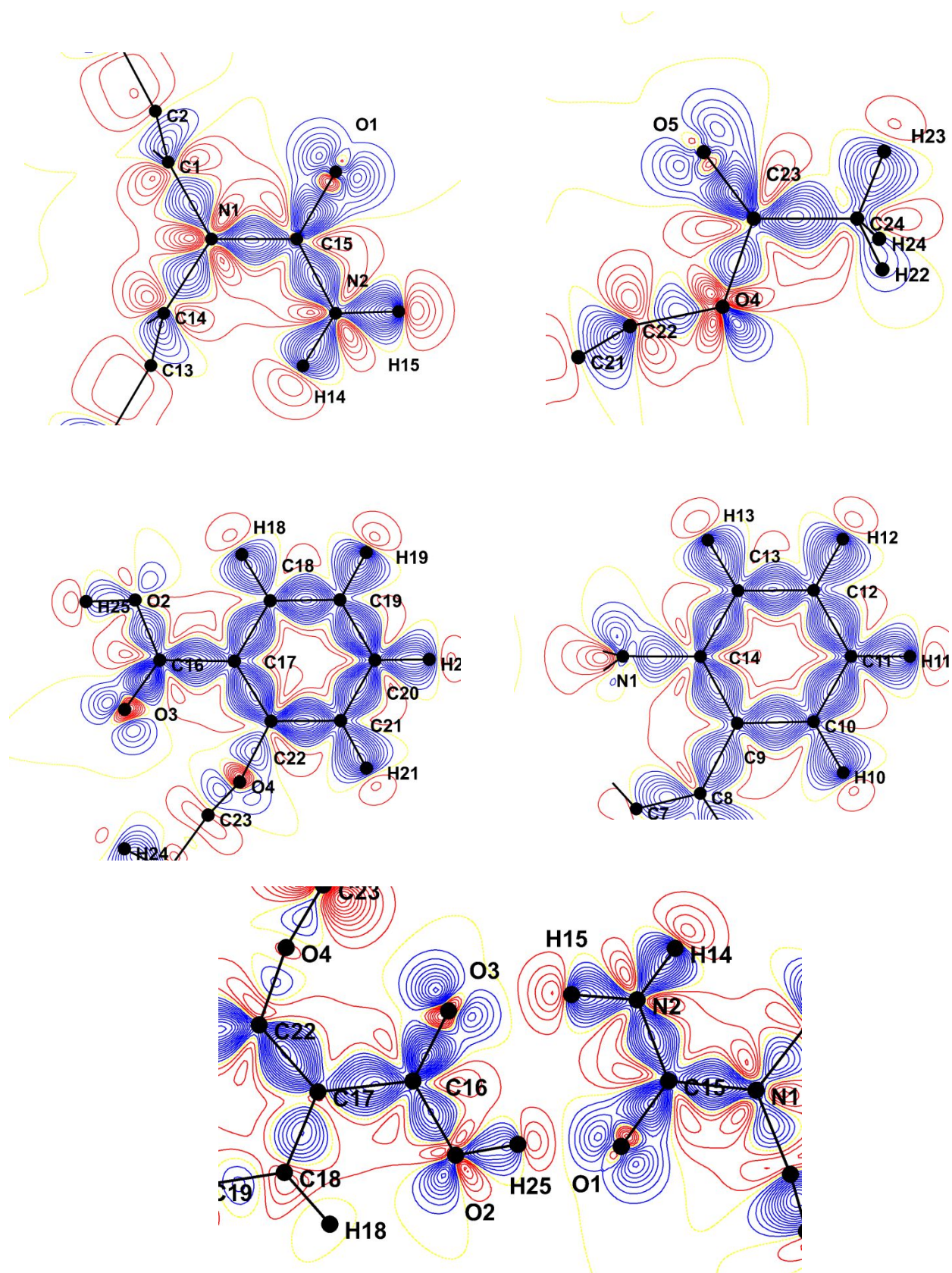


Figure 3. Experimental static electron deformation density in chosen planes of CBZ:ASP co-crystal. Contours are $0.05 \text{ e}\text{\AA}^{-3}$, positive contours are in blue and negative ones in red.

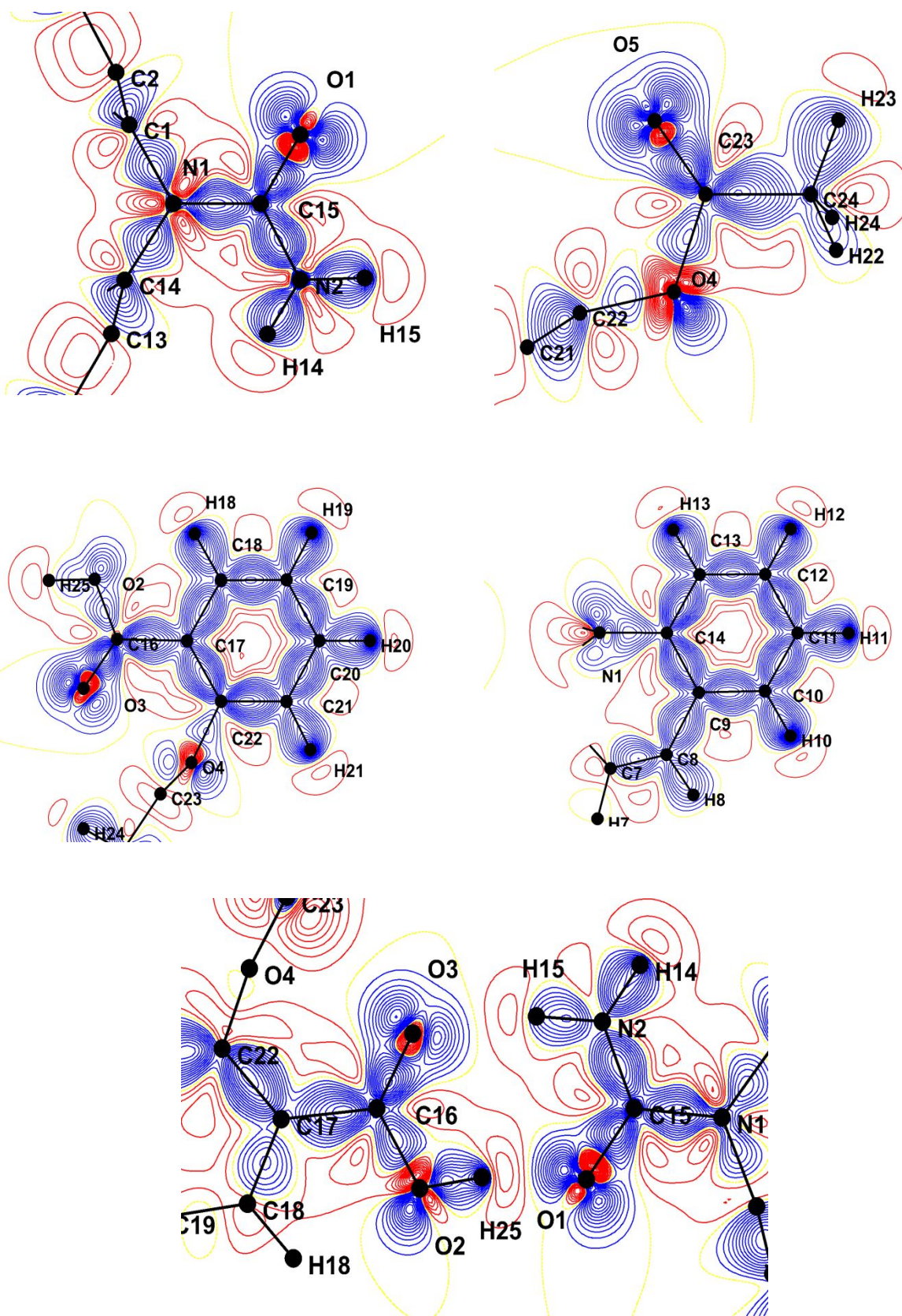


Figure 4. Static electron deformation density from the refinement of theoretical structure factors (TSF) in the same planes as in Figure 3 of CBZ-ASP co-crystal. Contours are $0.05 \text{ e}\text{\AA}^{-3}$, positive contours are in blue and negative ones in red.

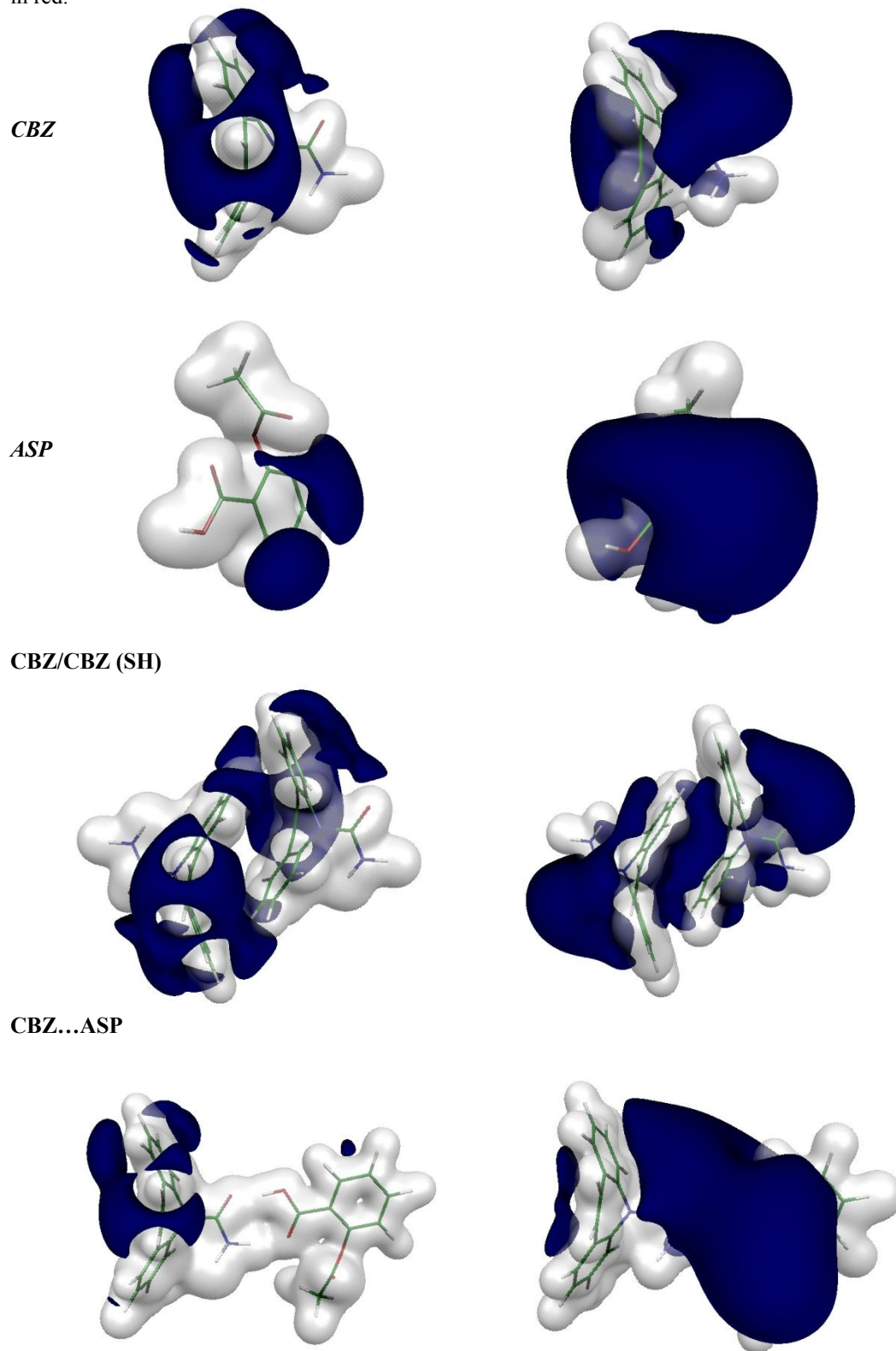


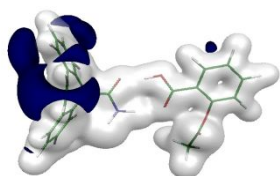
Figure 5. Electrostatic potential from experimental data (left column) and from the refinement of TSF (right column). Positive potential isosurface ($+0.05 \text{ e}\text{\AA}^{-1}$) is in grey and the negative one ($-0.03 \text{ e}\text{\AA}^{-1}$) is in blue.

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Crystal and Electron Properties of Carbamazepine-Aspirin Co-crystal

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TOC



Synopsis

Experimental and theoretical charge densities of the carbamazepine-aspirin co-crystal have been derived from high-resolution X-ray diffraction and DFT cc-pVDZ basis set structure factors. Topological features of the electron density, atomic charges, electrostatic potential and total energy obtained from the electrostatic potential at the nuclei (EPN) are discussed.