Quantitative Analysis the Weak Non-Covalent Interactions of the Polymorphs of Donepezil

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ABSTRACT: Donepezil has polymorphism. Different crystalline forms can exhibit different physicochemical properties and biological activities. Exploration of intermolecular interactions is essential to reveal the formation mechanism and differences in properties of polymorphs. This study explores the weak non-covalent intermolecular interactions of donepezil polymorphs through fully ab initio quantum mechanical methods, semi-empirical methods, and Hirshfeld surface analysis. The results show that the Hirshfeld surface analysis method can clearly and intuitively reveal the intermolecular interactions. Theoretical calculations using the atom−atom Coulomb−London−Pauli (AA-CLP) method were also performed to understand the interaction energies toward the total lattice energy. The value of the lattice energy was in accordance with the melting points of the donepezil polymorphs and brought to light the nature of thermal stability. In the specific energy distribution, the contribution of the dispersion force is the most prominent. Further interaction energy analysis found that within a distance of 3.8 Å from the center of the donepezil molecule, different crystalline forms of donepezil molecules have different interaction energies with surrounding molecules. The different interaction energies between polymorphs may lead to polymorphs with different physical−chemical properties.
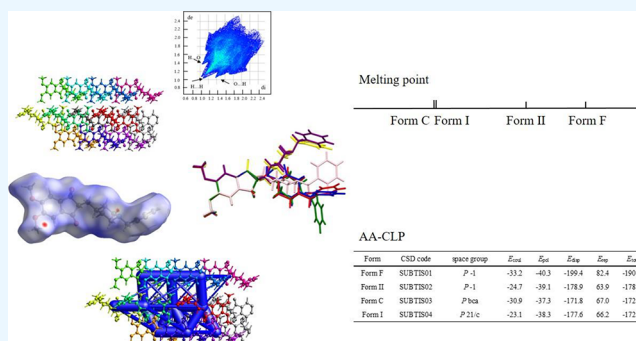
1. INTRODUCTION

Polymorphism is universally present and extensively investigated in the pharmaceutical industry. Understanding the properties of active pharmaceutical ingredients (APIs) in the solid state is utmost. Polymorphism was defined as "molecules with the same chemical composition adopt different crystal structures".[1,2] Various polymorphs of a drug could exhibit different physical and chemical properties including color, melting point, density, solubility, dissolution rate, stability, and bioavailability, which eventually lead to the different clinical efficacy and drug security.[3,4] The famous case of ritonavir can illustrate the polymorphic form affects the therapeutic effect of the drug. Ritonavir was marketed in 1996 as oral liquid solution and semi-solid capsule formulations (the API is Form I) for the treatment of AIDS. During the storing process, a second, previously unseen, polymorphic Form II appeared within the formulated drug product, resulting in a significant reduction in bioavailability and product withdrawal.[5]

Donepezil (Figure 1) is a reversible noncompetitive acetylcholine esterase inhibitor first launched by the Eisai Company Limited, Japan.[6] The U.S. Food and Drug Administration (USFDA) and the European Medicines Agency (EMA) have approved it to be extensively used worldwide for mild, moderate, and severe Alzheimer's disease in 1996 and
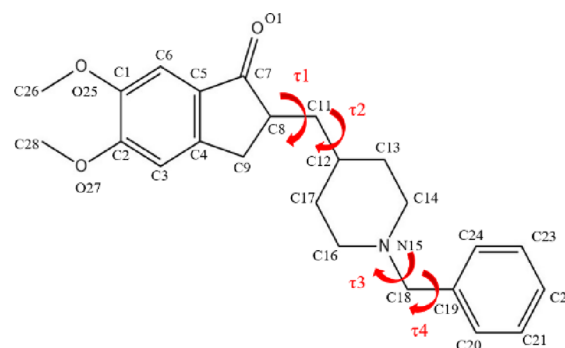

Figure 1. Structure of donepezil.

1997, respectively. Donepezil has a long half-life, few clinically problematic drug interactions, and generally good safety and tolerance. What is more, it could be used in the treatment of

Table 1. Crystal Structure Parameters of Six Donepezil Polymorphs

form	Form F	Form II	Form C	Form I	Form K	Form VII
molecular formula	$C_{24}H_{29}NO_3$	$2C_{24}H_{29}NO_3$	$C_{24}H_{29}NO_3$	$C_{24}H_{29}NO_3$	$C_{24}H_{29}NO_3$	$C_{24}H_{29}NO_3$
crystal system	triclinic	triclinic	orthorhombic	monoclinic	triclinic	triclinic
space group	$P\text{-}1$	$P\text{-}1$	$Pbca$	$P2_1/c$	$P\text{-}1$	$P\text{-}1$
a (Å)	5.9523(8)	10.365(6)	10.408(2)	16.610(14)	5.7888(3)	19.364(6)
b (Å)	11.8173(18)	14.306(8)	11.342(2)	9.549(8)	12.9301(8)	9.468(3)
c (Å)	15.072(2)	16.199(9)	35.927(7)	14.357(12)	14.5967(9)	11.656(8)
α (°)	79.253(3)	67.375 (10)	90	90	111.899 (5)	90
β (°)	84.287(2)	79.079(7)	90	112.545(12)	95.370(2)	93.04(5)
γ (°)	75.024(2)	71.988(7)	90	90	90.725(1)	90
Z	2	4	8	4	2	4
CSD code	SUBTIS01	SUBTIS02	SUBTIS03	SUBTIS04	SUBTIS05	SUBTIS

ischemic stroke and vascular dementia and could protect against glutamate neurotoxicity at the same time.[7] Donepezil has polymorphism. The first reported crystal structure of donepezil was published in 1992.[8] During the past 20 years, six polymorphs have been reported.[9,10] Clinical research reports show that the therapeutic efficacy of donepezil varies largely from 20 to 60%. Recent studies reveal that the polymorphic form difference may be the important influencing factor to affect the pharmaceutical performance. The intermolecular weak interactions such as van der Waals interactions, hydrogen bonding, and electrostatic interactions may be the important factors to drive and determine molecule packing behavior and polymorph formation. Analyzing and exploring the nature of intermolecular weak interactions in the crystal structure are critical to understand the relationship between new drug design and desirable physicochemical properties.

The present study explores the weak non-covalent intermolecular interaction of the polymorphs of donepezil by the fully ab initio quantum mechanical method, semi-empirical methods, and Hirshfeld surface analyses.[11−14] Ab initio quantum structure methods are designed to solve the full electronic Hamiltonian. One very successful method to do this is density functional theory (DFT). DFT computes directly ground-state properties from its charge density.[15] Semi-empirical methods are based on the same theoretical framework as ab initio MO theory, but they aim at reducing the computational cost by neglecting or approximating time-consuming two-electron integrals. They are being used for massive crystal structure generation and possible prediction.[16] The Hirshfeld surface is created based on the electron distribution of a molecule, and it has been calculated as the sum of spherical atom electron densities.[17] It was used to quantify the contribution of intermolecular interactions that stabilize the crystal packing and to understand the nature of intermolecular interactions.[18] The results show that, even with the same chemical structure, different polymorphs of donepezil have different spatial arrangements, interaction energies, and conformation. AA-CLP can be used as powerful tools to predict the crystal structure stability in different polymorphs.

2. MATERIAL AND METHODS

2.1. Single-Crystal XRD Data. For crystal structure sources, the crystal structure data of the polymorph of donepezil were obtained from the Cambridge Structural Database (CSD). There are six anhydrous crystal forms, and the crystal structure parameters are listed in Table 1.

2.2. Software Data Analysis. The conformational analysis and hydrogen bond analysis of the donepezil crystal form were

carried out using Mercury 4.3.1 (Cambridge Crystallographic Data Centre Inc., USA). The cif files of the five crystal forms were imported into Mercury, the hydrogen bond information of donepezil was obtained through "H-bond" and "contacts list", and the conformational differences of the five crystal forms were obtained through the analysis of "multiple structures". The Hirshfeld surface analysis of donepezil polymorphs was performed using CrystalExplorer 21.5, and the Hirshfeld surface analysis map of the visible structure of donepezil was obtained through "generate surface" and "transparency" using the cif file. The 2D fingerprint of donepezil is obtained using the "display fingerprint plot" in CrystalExplorer 21.5, and the ratio of different forces of donepezil to the total force can be obtained by selecting different element types. Using the B3LYP/6-31g(d,p) basis set in CrystalExplorer 21.5, the intermolecular interaction energies of polymorphic molecules in the range of 3.8 Å can be calculated. The energy frameworks can perform energy framework analysis of intermolecules in the 3.8 Å range of donepezil. The scale factor in the energy framework is 200, and the interaction energy less than 5 kJ/mol is ignored.[19] The CLP-PIXEL software package can be used to calculate the lattice energy of AA-CLP. The intermolecular potential energy in the crystal was calculated using the following equation (eq 1):

$$E_{ij}(kJ/mol) = A \exp(-BR_{ij}) - CR_{ij}^{-6} + 1389.36 q_i q_j / R_{ij}$$
(1)

where R_{ij} is the intermolecular distance between nuclear positions, A, B, and C are the empirical parameters, and q_i is the atomic charge parameter at the nuclear positions. The total lattice energy is the sum of these terms for all atom−atom distances in the crystal.[20,21]

3. RESULTS AND DISCUSSION

3.1. Conformational Analysis of Donepezil. Each polymorph differs in four torsion angles C9−C8−C11−C12 (τ1), C8−C11−C12−C13 (τ2), C14−N15−C18−C19 (τ3), and N15−C18−C19−C24 (τ4) (Figure 1). The torsion angles are shown in Table 2. The conformational superposition of each crystal form is shown in Figure 2 (yellow: Form F; red: molecule 1 of Form II; blue: molecule 2 of Form II; pink: Form C; green: Form I; purple: Form K). Form VII (CSD code SUBTIS) only has unit cell parameters without atomic coordinates, so the subsequent related analysis is not performed.

τ1 represents how the piperidyl ring is bent with respect to the bond C8−C11, and τ2 represents how the 2,3-

Table 2. Torsional Angles (τ, Degree) of Various Crystal Forms of Donepezil

	form	$\tau 1$	$\tau 2$	$\tau 3$	$\tau 4$
Form F		−179.06	−178.59	172.46	93.88
Form II	molecule 1	75.96	174.80	66.93	35.31
	molecule 2	82.57	177.47	72.20	25.61
Form C		−69.81	71.43	73.67	69.75
Form I		58.26	146.90	173.79	126.76
Form K		178.85	−178.94	174.34	96.32
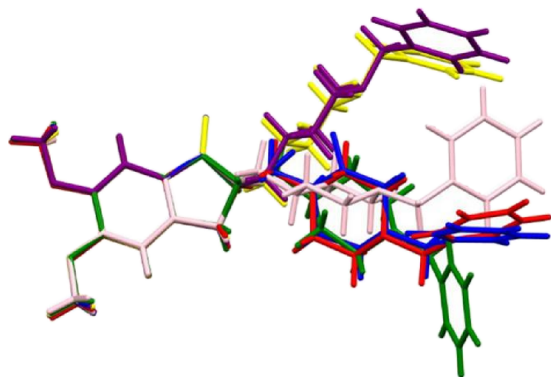
Figure 2. Overlay of the molecular conformation of donepezil.

dihydroinden-1-one ring is bent with respect to the bond of C11−C12. $\tau 1$ differs from −179.06 to 178.85°, making the piperidyl ring from being tilted to perpendicular to nearly coplanar to the bond C8−C11 (Table 2). It can be seen from Figure 2 and Table 2 that the torsion angles of the two molecules of Form II are basically the same, and their conformational diagrams are basically overlapped. $\tau 3$ and $\tau 4$ differ greatly between Form I and Form II, and the difference is about 100°. Form K has a similar molecular conformation as Form F and as such may be regarded to be a packing polymorph with respect to Form F. Only the $\tau 1$ and $\tau 2$ of Form F, $\tau 1$ of Form C, and $\tau 2$ of Form K have the negatively signed torsion angles, and the other polymorphs all have the positively signed torsion angles. Molecular conformation is a subtle but important property in the chemistry of the organic solid state, and the different conformations in the polymorph may result in quantitative differences in interaction energy values.

3.2. Theoretical Methods. *3.2.1. AA-CLP Calculation of Donepezil.* Lattice energies and intermolecular interaction energies were calculated using the semi-empirical computational technique Coulomb−London−Pauli model (AA-CLP) proposed by Gavezzotti.[22] The CLP-PIXEL software package was used for calculation, and the calculation results are summarized in Table 3.

Table 3 shows the individual contributions of different types of interactions to the lattice energy of donepezil. According to

the AA-CLP calculation results, the energy values clearly signify that Form F has the smallest total lattice energy and it is more stabilizing than that of Form C. According to the melting point reported, the stability order is Form F (98.20 °C) > Form II (96.40 °C) > Form I (93.21 °C) ≈ Form C (92.16 °C), and the theoretical calculation of different crystal forms of donepezil is in good agreement with the thermal stability. Form K (90.15 °C) is an exception. The inconsistency can be ascribed to the fact that Form K is very unstable.

3.2.2. Interaction Energy Calculation of Donepezil. Energies of intermolecular interactions were also investigated using the energy frameworks method implemented in CrystalExplorer.[23] Using the B3LYP/6-31g(d,p) wave function, a donepezil molecule is specified, and all molecules within a distance of 3.8 Å around the donepezil are used to analyze the intermolecular interaction energy.[24,25] The total energy (E_{tot}) of interaction between molecules is commonly expressed in terms of four key components: electrostatic (E_{ele}), polarization (E_{pol}), dispersion (E_{dis}), and exchange-repulsion (E_{rep}); the total energy was calculated using eq 2

$$E_{tot} = k_{ele}E_{ele} + k_{pol}E_{pol} + k_{dis}E_{dis} + k_{rep}E_{rep} \quad (2)$$

where the k values are the scale factors provided by the software. In this paper, the scale factors for electrostatic, dispersion, polarization, and repulsion are 1.057, 0.740, 0.871, and 0.618, respectively.

The analysis results are shown in Figure 3. The different colored molecules represent different interaction energies with
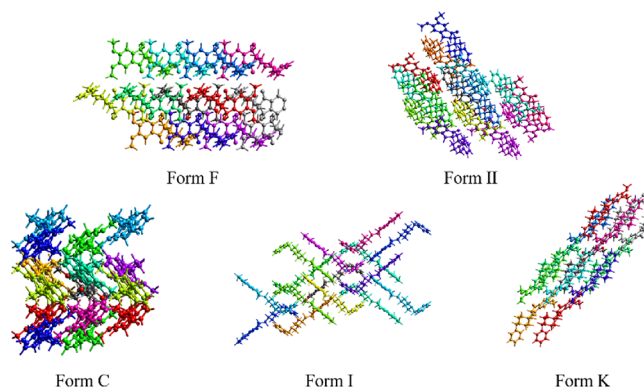
Figure 3. Interaction energy relationship centered on donepezil.

the central donepezil molecule (viewed from the *c*-axis direction). Within a distance of 3.8 Å with donepezil as the center, there are 10 different interaction energies around Form K and Form F, 9 different interaction energies around Form C, 11 different interaction energies around Form I, and 15 different interaction energies around Form II. The details of different interaction energies are listed in Tables S1−S6. The total energies of Form F, Form I, and Form C are −303.5,

Table 3. AA-CLP Calculation Results of Donepezil (kJ/mol)

form	CSD code	space group	E_{coul}	E_{pol}	E_{disp}	E_{rep}	E_{tot}
Form F	SUBTIS01	*P-1*	−33.2	−40.3	−199.4	82.4	−190.5
Form II	SUBTIS02	*P-1*	−24.7	−39.1	−178.9	63.9	−178.8
Form C	SUBTIS03	*Pbca*	−30.9	−37.3	−171.8	67.0	−172.9
Form I	SUBTIS04	*P2₁/c*	−23.1	−38.3	−177.6	66.2	−172.9
Form K	SUBTIS05	*P-1*	−29.2	−40.4	−198.6	83.4	−184.8

−224.0, and −247.8 kJ/mol, respectively, which also agree with the thermal stability of different crystal forms of donepezil.

3.2.3. Energy Frameworks Analysis of Donepezil. The "energy framework" of donepezil is shown in Figure 4. From
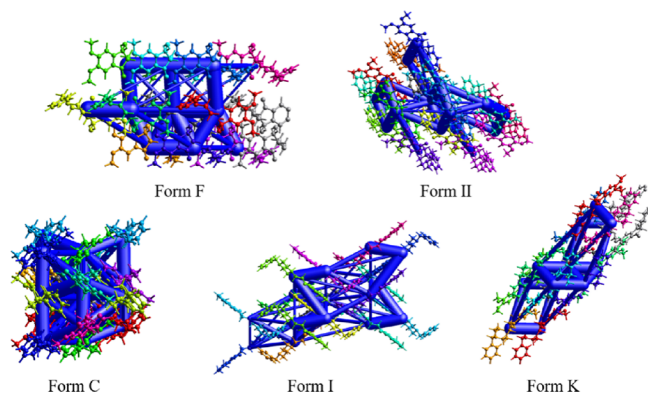

Figure 4. Energy frame diagram viewed from the *c*-axis direction.

the figure, we can see that the overall energy frameworks of different crystal forms of donepezil are mainly composed of different geometrical monomers, and there is a small interaction energy (smaller cylinder radius) connection inside the geometrical energy framework monomers. Among all the crystal forms, Form I is the most unstable crystalline form and shows the smallest diameter in the energy frame. The energy framework visualizes the role-energy relationship in the crystal structure of donepezil, which makes it more efficient and convenient to explore the intermolecular energy relationship in the crystal structure of donepezil.

3.2.4. DFT Study of Donepezil. DFT is suitable for lattice energy calculations with salt and covalently bonded framework structures.[26] All DFT calculations in this study were performed using the Gaussian 16W software package. In this study, lattice energy calculations were performed for the five crystal forms using B31yp/def2TZVP, B31yp/6-311+g(d,p), and Mp2/6-31g(d,p) basis sets to study the stable structure and electronic properties of donepezil; the coordinates of all non-hydrogen atoms were frozen during the calculation process.[27,28] The calculation results are shown in Table 4.

From the results, we can see that DFT calculation values influenced by the basis set selected and the lattice energies are almost always intertwined with differences between chosen geometries.[29] The lattice energies obtained from the calculations indicate that the most stable crystallographic structure of donepezil is Form II and the most unstable is Form I. The literature shows that Form I has the lowest heat of fusion and is the most unstable. Slurry conversion experiments show that, above 53 °C, among the crystal Form C, Form II, and Form I, Form II is the most stable form. This is consistent with the DFT calculated results. However, for Form F and

Form C, there is a violation of the thermal stability order by the melting point. The reason may be owing to the fact that during the DFT energy calculation, no dispersion energies were considered during the optimization processes. DFT energies are responsible for the conformation of individual molecules in a crystal, while the dispersion energies can affect the volume of the unit cell or relative intermolecular distances, particularly when the dispersion energy is dominant in the lattice energy.[26,30] In this case, the dispersion energies are the important contribution to the total energy.

3.2.5. Hirshfeld Surface Analysis of Donepezil. Hirshfeld surface, 2D fingerprinting, and intermolecular interaction analysis of donepezil polymorphs were performed using the CrystalExplorer program.[31−33] The closest distances from a point on the Hirshfeld surface to the inner and outer atoms of the surface are defined as d_i and d_e, respectively, and the standard distance d_{norm} can be calculated using the following equation (eq 3):[34]

$$d_{norm} = (d_i - r_i^{vdW})/r_i^{vdW} + (d_e - r_e^{vdW})/r_e^{vdW} \qquad (3)$$

The surface analysis diagrams of the five crystal forms are shown in Figure 5. The red dots are generated by the formation of hydrogen bonds between the molecules inside the surface and the molecules outside. The stronger the hydrogen bonding force, the smaller the distance between the donor and the acceptor, the darker the red dot, and the larger the diameter. White areas represent connections longer than hydrogen bond distances, and blue areas represent connections that are longer relative to white areas. Donepezil has no hydrogen bond donors; therefore, the unsolvated polymorph cannot exhibit hydrogen bonds. Figure 5 shows that there is a C−H⋯C interaction force in the five crystal forms, and there is a C−H⋯O interaction force at the oxygen atom of the methoxy group of Form F, Form II, Form C, and Form K. Form F, Form I, and Form K also exist in the C−H⋯H interaction force. This is consistent with the interaction force information. Intermolecular interactions are shown in Table 5.

The 2D fingerprint of intermolecular interaction reflects the interaction mode between molecules within the structure and the contribution of each interaction mode to the overall effect.[35] The 2D fingerprint of donepezil is shown in Figure 6. It can be seen that the peak formed by the O atom as a hydrogen bond acceptor in the donepezil molecule is sharper, indicating that its O atom has a strong ability as a hydrogen bond acceptor. Among the five crystal forms, the carbonyl oxygen atom and the oxygen atom on the methoxy group of donepezil mainly act as hydrogen bond acceptors to form O⋯H−C. Therefore, the force of O⋯H is stronger than that of H⋯O, which are 8.0, 7.7, 9.1, 7.8, and 7.8%, respectively. H−H, C−H, and O−H forces are the main components of the full spectrum. H⋯H forces account for 63.5, 64.1, 65.1, 66.7, and 63.8% of Form F, Form II, Form C, Form I, and Form K, respectively. The C−H interaction forces of donepezil were 11.3, 8.3, 9.8, 7.9, and 11.3% in the five crystal forms. Figure 7

Table 4. DFT Calculation Results of Donepezil (kJ/mol)

form	F	II[a]	C	I	K	ΔE_{max}
B31yp/def2TZVP	10.17644	0	8.624768	11.07698	10.17644	11.07698
B31yp/6-311+g(d,p)	4.47910	0	18.15533	36.75437	7.19124	36.75437
Mp2/6-31g(d,p)	14.57940	0	30.88901	47.13560	19.89866	47.13560

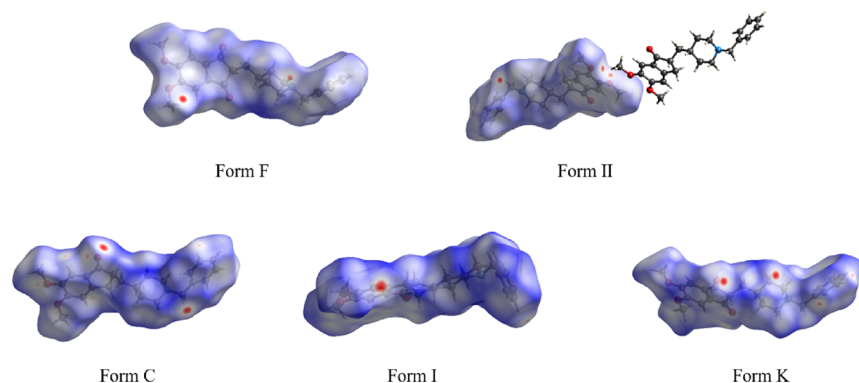[a]The lowest energy of polymorph Form II was normalized to zero.

Figure 5. Hirshfeld surface analysis diagram of donepezil.

Table 5. Donepezil Intermolecular Interactions

form	intermolecular interaction
Form F	C18−H19···H11(2.319 Å, −x, −y, 2 − z , 165.82°); C8−H3···C1(2.847 Å, −1 + x, y, z, 132.38°); C23−H26···O1(2.548 Å, −1 + x, y, z, 140.75°)
Form II	C23−H24···O5(2.610 Å, 136.83°); C47−H53···O2(2.702 Å, 133.84°); C23−H24···O6(2.604 Å, 164.76°); C23−H25···C4(2.867 Å, 2 − x, −y, −z, 121.16°)
Form C	C7−H7···O1(2.500 Å, −0.5 + x, 1.5 − y, −z, 168.52°); C3−H2···C21(2.882 Å, −0.5 + x, 1.5 − y, −z, 162.50°)
Form I	C8−H3···C4(2.782 Å, 1 − x, 2 − y, 1 − z, 158.76°); C9−H4···H3(2.363 Å, 1 − x, 2 − y, 1 − z, 114.50°)
Form K	C14−H14···H23(2.319 Å, −1 + x, y, z, 125.42°); C23−H24···O1(2.664 Å, −1 + x, y, z, 148.99°); C9−H4···C2(2.319 Å, −1 + x, y, z, 135.79°)

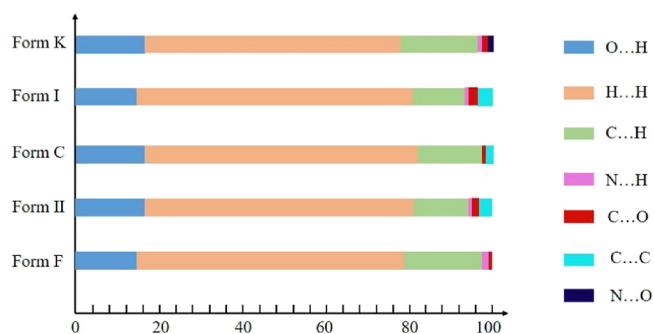**Figure 7.** Percentage contributions of the short intermolecular contacts to the Hirshfeld surface area in donepezil.

shows the percentage contribution of short intermolecular contacts in the donepezil molecule to the Hirshfeld surface area. It can be seen from the figure that H···H, O···H, and C···H contribute more than 95% to the entire Hirshfeld surface.
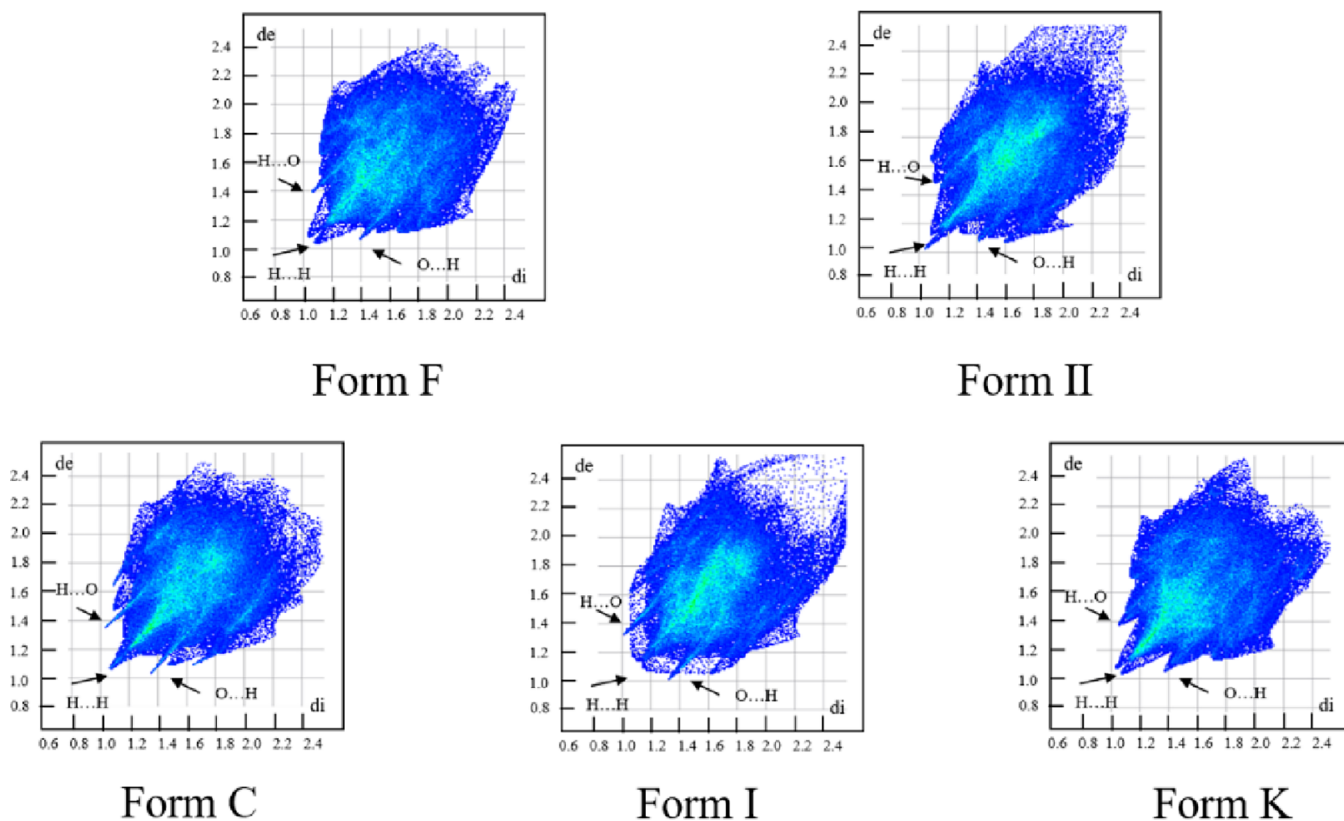

Figure 6. Intermolecular interaction fingerprint of donepezil.

4. CONCLUSIONS

AA-CLP lattice energy calculations, DFT calculations, energy frame diagrams, and Hirshfeld surface analysis were used to enhance the analysis of the different conformations and interactions of crystals presented in 3D structures. The analysis showed that all the five crystal forms have the same configuration but have different molecular conformations. Donepezil has no hydrogen bond donor and mainly forms C—H···C, C—H···O, and C—H···H interaction forces. These three interacting forces account for more than 95% of the total energy. During the AA-CLP calculation, the dispersion energy is the key to interpret organic crystal structures. The calculation results clearly show the relative importance of dispersion force as molecular polarity. The contributions of various forces in donepezil crystals were successfully calculated by the AA-CLP method and DFT method to evaluate the importance of non-covalent interactions in the crystal assembly process. Except for the unstable crystal Form K, the energy calculation results of AA-CLP are consistent with the thermal stability. Except for Form F, the energy calculation results of DFT are also basically consistent with the thermal stability. The visualization of the interaction energies in the crystal structure was realized by using the energy framework model, which sheds light on the understanding of the intermolecular interaction energies in the crystal structure of donepezil. By calculating the Hirshfeld surface and two-dimensional fingerprints of donepezil, the intermolecular interactions can be intuitively revealed and the different force sizes and proportions in the unit cell can be distinguished.

■ ASSOCIATED CONTENT

ⓢ Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acsomega.2c04201.

> Table S1: Molecular pair wise interaction energies (kJ/mol) obtained from the energy framework calculation for Form F; Table S2: Molecular pair wise interaction energies (kJ/mol) obtained from the energy framework calculation for Form II (molecule 1); Table S3: Molecular pair wise interaction energies (kJ/mol) obtained from the energy framework calculation for Form II (molecule 2); Table S4: Molecular pair wise interaction energies (kJ/mol) obtained from the energy framework calculation for Form C; Table S5: Molecular pair wise interaction energies (kJ/mol) obtained from the energy framework calculation for Form I; Table S6: Molecular pair wise interaction energies (kJ/mol) obtained from the energy framework calculation for Form K (PDF)

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Author Contributions

W.X., H.Y., and M.L.: literature searches, data analysis, and writing of the initial manuscript. B.Z., L.Z., and F.W.: energy calculation and data analysis. N.G. and Y.L.: conceptualization, methodology, supervision, and review and editing.

Notes

The authors declare no competing financial interest.

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