

Article

Halogen Bonding vs. π -Stacked (Charge-Transfer) Interaction of Phenothiazine

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Abstract

Phenothiazine is a heteroaromatic molecule capable of various noncovalent interactions, including halogen bonding and π -stacked association. Despite its broad use in functional materials and pharmaceutical ingredients, a systematic comparison of these interaction modes has been lacking. Here, we report a combined experimental and computational study of intermolecular interactions of phenothiazine with a prototypical halogen-bond (HaB) donor (tetrabromomethane), planar π -electron acceptors (tetracyanopyrazine and tetrafluoro-*p*-benzoquinone), and multifunctional species capable of both interaction types (iodo- and bromo-3,5-dinitrobenzenes). X-ray structural analysis revealed that CBr₄ forms exclusively C–Br $\cdots\pi$ halogen bonds with the aromatic rings of phenothiazine, whereas all π -acceptors yield alternating donor–acceptor stacks characterized by multiple short contacts indicative of multicenter interactions. Notably, co-crystals of iodo- and bromodinitrobenzenes with phenothiazine display only π -stacked architectures. Density-functional calculations showed that isolated HaB complexes involving N, S, or π sites of phenothiazine possess comparable binding energies (≈ -3 kcal mol^{−1}), whereas π -stacked complexes are substantially stronger (≈ -9 – -12 kcal mol^{−1}). QTAIM, NCI, NBO, and energy-decomposition analyses indicated that while amounts of charge transfer in halogen-bonded and π -stacked complexes are comparable, the enhanced stability of the latter originates primarily from a large dispersion contribution. These results rationalize the solid-state preference for π -stacking over halogen bonding in systems where both motifs are accessible and clarify the hierarchy and physical origin of noncovalent interactions involving phenothiazine, providing guidance for the design of supramolecular assemblies and functional materials based on this versatile electron donor.

Keywords: halogen bonding; π -stacking; phenothiazine; X-ray crystallography; DFT computations

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1. Introduction

Phenothiazine is a tricyclic heteroaromatic compound whose electronic structure and conformational flexibility make it a versatile building block in crystal engineering and materials science [1–3]. Owing to the presence of both sulfur and nitrogen heteroatoms embedded in a π -conjugated framework, phenothiazine exhibits rich redox, photophysical, and coordination behavior. These properties underlie its use in dyes, organic electronics, and photoactive systems [4,5]. Its derivatives are also widely utilized as pharmaceuticals to treat mental disorders, as well as for anti-nausea, anti-vomiting, and sedative purposes [6,7].

Central to many of these applications is the propensity of phenothiazine to form intermolecular complexes with a variety of molecular partners. In particular, its sulfur and nitrogen atoms, as well as electron-rich aromatic rings provide hydrogen- or halogen-bond acceptor sites. Furthermore, although phenothiazine is a non-planar molecule with a distinctive bent, butterflylike shape, it can form π -stacked charge-transfer complexes, and hydrogen substituents at its nitrogen atoms can participate in hydrogen bonding. Accordingly, evaluation of the relative strengths and geometric characteristics of its intermolecular associations is vital for understanding the behavior of this molecule in chemical and biological systems, as well as for the crystal engineering of functional materials.

The crystallographic literature contains several solid-state structures of hydrogen-bonded complexes of neutral and cationic phenothiazine [8–11]. There are also a few structures of its π -stacked charge-transfer associations with π -electron acceptors, such as tetracyanoquinodimethane (TCNQ) and trinitrobenzene (TNB) [12–15]. Yet, a systematic study of the nature of such π -bonding, as well as the strength and energetics of intermolecular complexes formed by this molecule, remains lacking. In particular, the relative contributions of different noncovalent interactions and their dependence on the nature of the electron acceptors, as well as the effects of such interactions on the structure of phenothiazine, require further clarification.

It is also notable that the crystallographic database contains only one structure showing halogen bonding involving phenothiazine, namely, its solid-state association with diiodotetrafluorobenzene [16]. In this structure, one iodine substituent forms short contacts with the nitrogen and sulfur atoms, while the other iodine forms short contacts with the aromatic ring carbons. In contrast, interaction of phenothiazine with the prototypical HaB donor, I_2 , resulted in a redox reaction and crystallization of salts of polyiodides and the phenothiazine radical cation or 10-(3-phenothiazinylidene)-phenothiazinium (product of the radical coupling) [17].

Among the possible modes of interaction, the present work focuses on halogen bonding and π -stacked charge-transfer interactions involving phenothiazine as an electron donor (a Lewis base). We report the results of combined X-ray structural and computational analyses of complexes of phenothiazine with three types of counterparts: (i) tetracyanopyrazine and tetrafluoro-*p*-benzoquinone, planar organic π -acceptors capable of forming π -stacked charge-transfer complexes [18,19], (ii) tetrabromomethane, a well-known HaB donor [20,21], and (iii) iodo- and bromo-3,5-dinitrobenzenes, which are capable of forming both HaB and π -stacked complexes [22–26]. Structures and acronyms of some of these molecules are shown in Chart 1.

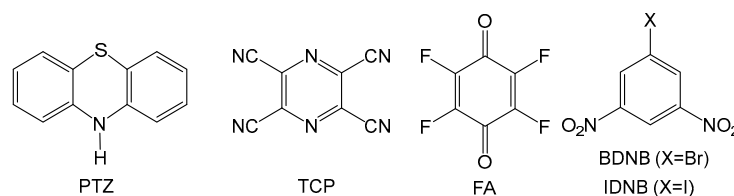


Chart 1. Structures and acronyms of the molecules used in this study.

The goal of this work is to clarify the hierarchy and physical origin of noncovalent interactions involving phenothiazine. In particular, this study aims at determining the relative preference between halogen bonding and π -stacked charge-transfer interactions of phenothiazine with partners capable of both interaction types, to establish the preferred halogen-bonding sites (N, S, or π -system), and to elucidate the nature of the resulting noncovalent interactions.

2. Materials and Methods

2.1. Materials

Commercially available phenothiazine (PTZ), tetrafluoro-*p*-benzoquinone (FA), tetracyanopyrazine (TCP), iodo-3,5-dinitrobenzene (IDNB), and bromo-3,5-dinitrobenzene (BDNB) were used as received. Tetrabromomethane (CBr₄) was purified by sublimation.

2.2. Crystallization and X-Ray Structural Analysis

To prepare co-crystals of PTZ with CBr₄, 20.3 mg (0.10 mmol) PTZ was combined with 33.2 mg (0.10 mmol) of CBr₄ and dissolved in 2 mL of acetonitrile with stirring. Slow cooling of the solution to −30 °C produced orange co-crystals (compound 1, FT-IR (cm^{−1}): 3363, 3050, 1593, 1569, 1464, 1443, 1030, 933). Cooling of a similar mixture containing 20.6 mg of PTZ and 17.9 mg of FA dissolved in 1 mL of acetonitrile resulted in the formation of their co-crystals (compound 3, FT-IR (cm^{−1}): 3576, 3499, 3069, 1692, 1465, 1301, 1080, 957, 743). An analogous procedure using a mixture of PTZ and 25.1 mg of BDNB resulted in the formation of red and colorless crystals. X-ray structural analysis (*vide infra*) showed that the red crystals contain PTZ–BDNB complexes (compound 5, FT-IR (cm^{−1}): 3389, 3339, 3101, 1595, 1529, 1445, 1340, 1034, 929, 730), whereas the colorless crystals consist solely of BDNB. To prepare co-crystals of PTZ with IDNB, 49.8 mg of PTZ was dissolved in 10 mL of a 3:1 DCM/hexane mixture, and 2 mL of this solution was added to 29.3 mg of IDNB dissolved in 1 mL of the same solvent mixture. Slow evaporation at room temperature yielded co-crystals (compound 4, FT-IR (cm^{−1}): 3383, 3342, 3081, 1528, 1444, 1340, 1305, 1036, 925, 728). Evaporation of a similar mixture of PTZ with 17.7 mg of TCP dissolved in 500 µL of acetone produced co-crystals (compound 2, FT-IR (cm^{−1}): 3345, 2241, 1601, 1445, 1356, 1164, 1054, 887, 745). Solid-state UV-Vis spectra of compounds 1–5 are shown in the Supporting Information. Note that the spectra of compounds 2–5 containing π -stacked associations (*vide infra*) show absorption bands extended into NIR range. These features are consistent with the appearance of the new low-energy absorption bands of π -stacked complexes, which are observed in solutions (see Supplementary Materials).

Single-crystal X-ray diffraction measurements were carried out using a Bruker AXS D8 Quest diffractometer with graphite-monochromated Mo K α radiation ($\lambda = 0.71070$ Å) at 150 K. Reflections were indexed and processed, and the data were scaled and corrected for absorption using APEX4, 5 or 6 [27]. Space groups were assigned using XPREP within the SHELXTL program suite. The structures were solved by dual methods using ShelXT and refined by full-matrix least-squares against F^2 using ShelXL-2019 with the graphical interface ShelXle [28–30]. Crystallographic data collection and refinement details are summarized in the Supporting Information (Table S1). Complete crystallographic data in CIF format have been deposited with the Cambridge Crystallographic Data Centre; CCDC 2526248–2526253 contain the supplementary crystallographic data for this paper. These data can be obtained free of charge via www.ccdc.cam.ac.uk/data_request/cif.

UV-Vis-NIR measurements were performed on a CARY 5000 spectrophotometer. To measure solid-state spectra, the co-crystals were carefully grinded and mixed with a drop of mineral oil (Nujol). This suspension was placed between microscope slides which were pressed together to form a thin uniform layer.

2.3. Computations

Geometries of the complexes and their individual components were optimized without constraints in dichloromethane (using a polarizable continuum model) at the M06-2X/def2-TZVPP level with the Gaussian 09 program package [31–34]. Energies, structures, and atomic coordinates of the optimized complexes are provided in the Supporting Information. Default convergence criteria were satisfied in all cases, and the absence of imaginary

frequencies confirmed that the optimized structures correspond to true minima. (Note that the initial optimizations of complexes of IDNB and BDNB with PTZ formed via I...N and Br...N bonds produced associations showing imaginary frequencies (-3.04 cm^{-1} and -3.87 cm^{-1} , respectively. The displacement of the reactants along IF mode of vibration, and subsequent re-optimization produced complexes without imaginary frequencies.) Previous computational benchmarks have shown that the M06-2X functional is among the most accurate and reliable DFT methods for modeling halogen-bonded associations [35,36]. The triple- ζ def2-TZVPP basis set includes two sets of polarization functions for heavy atoms and one set for hydrogen atoms. Inner-shell electrons are treated using effective core potentials, which reduce basis-set size and account for scalar relativistic effects, important for systems containing iodine [33]. Our previous studies also demonstrated that M06-2X/def2-TZVPP calculations reproduce experimental features of HaB complexes well [37].

Binding energies were calculated as: $\Delta E = E_C - (E_D + E_A)$, where E_C , E_D , and E_A are sums of the electronic and ZPE of the complex, donor, and acceptor. ZPEs (zero-point energies) represent the vibrational contributions to the total energies of the complex and the isolated reactants. Including these contributions provides a more realistic estimate of the energy required for dissociation of the complex. The ΔE^* values that do not include ZPE corrections are reported in the Supporting Information. These values are approximately 0.5–1 kcal/mol more negative (because additional vibrational modes present in the complexes increase their ZPE relative to the sum of the ZPEs of the separated reactants). Because complex formation involves distortion of the reactants, the binding energy comprises the preparation (distortion) energy ΔE_{prep} and the interaction energy between distorted fragments, ΔE_{int} . Time-dependent DFT calculations (M06-2X/def2-TZVPP) were performed using the optimized geometries of the HaB and π -stacked complexes. QTAIM and NCI analyses [38–40] were carried out with Multiwfn [41] using wavefunction files generated by Gaussian 09. For the NCI analysis, an isovalue of 0.5 was used, with color coding by $\text{sgn}(\lambda_2)\rho$ from -0.04 a.u. (blue, strong attractive interaction) to 0.02 a.u. (red, strong nonbonded overlap). Visualization was performed using VMD [42]. Energy-decomposition analyses (EDA) were carried out using the Amsterdam Density Functional (ADF) program within the Amsterdam Modeling Suite [43–45]. Single-point calculations were performed using the B3LYP-D3 functional (to evaluate dispersion contributions) and the TZ2P basis set, employing geometries optimized at the M06-2X/def2-TZVPP level. Natural Bond Orbital (NBO) analysis was performed using the Gaussian 09 suite of programs [46,47].

3. Results and Discussion

3.1. X-Ray Structural Characterization of Intermolecular Complexes of Phenothiazine

Co-crystallization of PTZ and CBr_4 from a solution containing equimolar quantities of these molecules produced yellow orthorhombic crystals **1** (space group $P2_12_12_1$). X-ray structural analysis showed that the crystals comprise both components in a 2:1 PTZ: CBr_4 ratio. The four bromine substituents of each CBr_4 molecule are directed toward the outer aromatic C–C bonds of four neighboring phenothiazine molecules, and the distances between bromine and the pairs of carbon atoms forming these bonds are shorter than the corresponding van der Waals separations (Figure 1).

In turn, the same pair of carbon atoms in each PTZ molecule forms short contacts with a bromine atom from another CBr_4 molecule located on the opposite side of the aromatic ring. Overall, columns of CBr_4 molecules (forming layers parallel to the ac plane) alternate with layers of phenothiazine (Figure S1 in the Supporting Information). These layers show edge-to-face contacts between PTZ molecules, i.e., N–H...C and C–H...C contacts of $2.625\text{ \AA}$ and $2.841\text{ \AA}$, respectively, on one edge of PTZ, and C–H...N contact of $2.718\text{ \AA}$ on its opposite edge (Figure S1C in the Supporting Information).

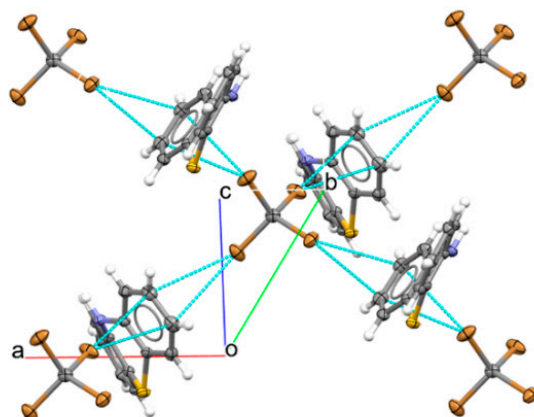


Figure 1. Fragment of the X-ray structure of **1** showing short contacts (blue lines) between bromine substituents of CBr_4 and aromatic carbon atoms of PTZ. Color code: dark grey—carbon, light grey—hydrogen, brown—bromine, blue—nitrogen, and yellow—sulfur.

All crystallographically non-equivalent distances between bromine and aromatic carbon atoms (3.4422(0.0037) and 3.4687(0.0040) Å, 3.4708(0.0039) and 3.4519(0.0039) Å; see the shortest contact in Table 1) are very similar. They are about 5% shorter than the sum of the van der Waals separations [48]. The bromine atoms are directed toward the midpoints of the C–C bonds, which is consistent with the formation of $\text{C–Br}\cdots\pi$ halogen bonds between CBr_4 and the aromatic systems of phenothiazine. The corresponding $\text{C–Br}\cdots\text{C}$ angles vary from 146.7° to 165.4° (see Figure S1 in the Supplementary Materials for atom labeling).

Table 1. Selected geometric characteristics of the solid-state intermolecular association of phenothiazine.

Compound	Type	Contacts, ^a Å	$d_{\text{cen-cen}}$, ^{b,c} Å	d_{shift} , ^{d,c} Å
$\text{CBr}_4\cdot\text{PTZ}$ (1)	$\text{Br}\cdots\pi$	3.4422(0.0037) ($\text{Br}\cdots\text{C}$)	–	–
$\text{TCP}\cdot\text{PTZ}$ (2)	$\pi\cdots\pi$	3.0102 (0.0033) ($\text{C}\cdots\text{N}$)	3.164 4.298	0.080 2.662
$\text{FA}\cdot\text{PTZ}$ (3)	$\pi\cdots\pi$	2.9508 (0.0016) ($\text{C}\cdots\text{N}$)	3.428 3.619	1.319 1.275
$\text{IDNB}\cdot\text{PTZ}$ (4)	$\pi\cdots\pi$	3.4436 (0.0037) ($\text{C}\cdots\text{C}$)	4.020 3.947	2.040 1.969
$\text{BDNB}\cdot\text{PTZ}$ (5)	$\pi\cdots\pi$	3.4190 (0.0031) ($\text{C}\cdots\text{S}$)	3.429 3.650	0.360 1.512

(a) Shortest contact relative to their van der Waals separations [48]. (b) Distance between the centroids of electron acceptor and the central ring of PTZ. (c) The distances in the pair in which aromatic rings of PTZ are directed from (first value) and toward (second value) the electron acceptor. (d) Shift in the centroids of PTZ relative to centroids of the electron acceptor.

The $\text{C–Br}\cdots\pi$ bonding induces only minor changes in the geometries of CBr_4 and PTZ (see Table S2 in the Supplementary Materials) as compared to those measured in the reported earlier individual molecules [49,50].

Evaporation of solutions containing PTZ and TCP produced monoclinic red plates (crystals **2**) in the $\text{C2}/c$ space group. These molecules form alternating stacks with multiple contacts between neighboring donors and acceptors that are shorter than the corresponding van der Waals separations (Figure 2A). A closer inspection of the crystal structure reveals that the donor–acceptor stacks consist of pairs in which the distances between the centroids of the aromatic ring of TCP and the central ring of PTZ of the TCP molecule is 3.164 Å. The centroids of PTZ are shifted with respect to the centroid of TCP (in the plane of the latter) by 0.080 Å (Table 1). The aromatic “wings” of PTZ are directed away from TCP in these pairs, and the $\text{N}\cdots\text{C}$ distances between PTZ and two aromatic carbon atoms of TCP are 3.0102 (0.0033) and 3.0441 (0.0033) Å, and the $\text{C}\cdots\text{S}$ distances are 3.2356 (0.0028) and 3.2392 (0.0028) Å.

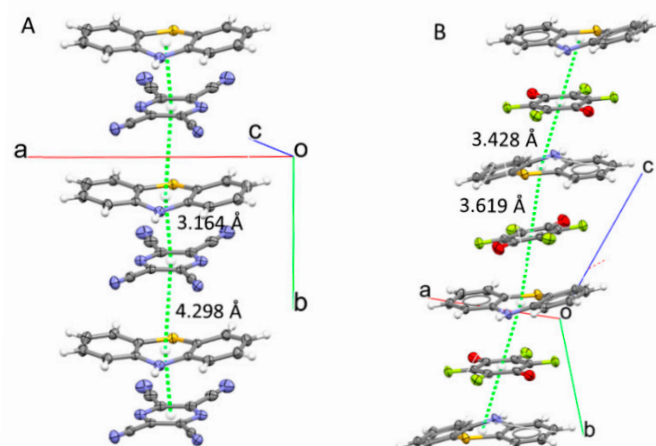


Figure 2. Fragments of X-ray structures of **2** (A) and **3** (B) showing alternating stacks of PTZ with TCP or FA molecules (light-green lines indicate distances between centroids, see contacts shorter than van der Waals separations in Figure S3 in the Supporting Information). Color code: dark grey—carbon, light grey—hydrogen, brown—bromine, blue—nitrogen, yellow—sulfur, red—oxygen, and light green—fluorine.

Between these pairs, the aromatic “wings” of phenothiazine are directed toward TCP molecules, and PTZ is arranged above the cyano groups of neighboring acceptors. The distances between centroids and lateral shifts between these neighbors are larger than those in the pairs described above (Table 1). As a result, the distances between sulfur atoms of PTZ and aromatic carbon atoms of TCP (3.4777(0.0027) and 3.5123(0.0027) Å) are close to their van der Waals separations, while nitrogen atoms do not form short contacts with TCP in these dyads. The angle between the aromatic rings in the PTZ moieties (14.5°) is smaller, while the C–S and C–N bond lengths are close to those in the isolated PTZ molecule [50] (Table S2 in the Supporting Information).

Evaporation of solutions containing PTZ and FA resulted in the formation of black triclinic crystals **3** (space group $P\bar{1}$). These crystals comprise alternating stacks of donors and acceptors (Figure 2B) and include acetonitrile molecules hydrogen-bonded to the N–H group of phenothiazine. The donor–acceptor stacks in crystals **3** can be described as 2:1 PTZ:FA triads separated by FA molecules. The distances between centroids of PTZ and FA are listed in Table 1. The aromatic “wings” of PTZ within the triads are directed outward, and there are multiple intermolecular contacts shorter than the van der Waals separations. The shortest of these distances (2.9508 (0.0016) and 3.1617 (0.0016) Å) correspond to contacts between nitrogen atoms of PTZ and carbonyl carbon atoms of FA, and between aromatic carbon atoms of PTZ and side carbon atoms of FA, respectively. The wings of both PTZ neighbors are directed toward the FA molecule separating the triads. The distances between centroids in these pairs are larger than those measured within triads, but the lateral shifts in the TCP and FA molecules are somewhat smaller (Table 1). The number of short intermolecular contacts between these molecules is smaller than within the triads; specifically, the shortest C...C and C...S distances between FA and these PTZ molecules are 3.2444 (0.0017) and 3.4395 (0.0013) Å, respectively.

As in crystals **2**, the C–S and C–N bond lengths in the PTZ moiety in crystals **3** are similar to those in the isolated molecule, and the angle between the aromatic rings is smaller than in free PTZ (Table S2 in the Supporting Information). The C–O bond length of 1.217(2) Å in the FA moiety within the triad is slightly longer than that of 1.212(2) Å in the FA molecule separating the triads. Since bond elongation in *p*-benzoquinones is usually associated with partial quinonoid-to-benzenoid transformation upon reduction [51], this

difference suggests a somewhat higher electron density on FA molecules located within the triads.

While CBr_4 forms only HaB complexes and TCP or FA are planar π -acceptors involved in π -stacking interactions, bromo- and iodo-3,5-dinitrobenzenes (BDNB and IDNB) are capable of forming both types of interactions. Indeed, the literature reports co-crystals of these molecules exhibiting halogen bonding and/or π -stacking with suitable counterparts [23–26]. Furthermore, PTZ can participate in both interactions. Nevertheless, its co-crystals **4** and **5** of PTZ with IDNB or BDNB, respectively, display only π -stacked donor–acceptor interactions (Figure 3).

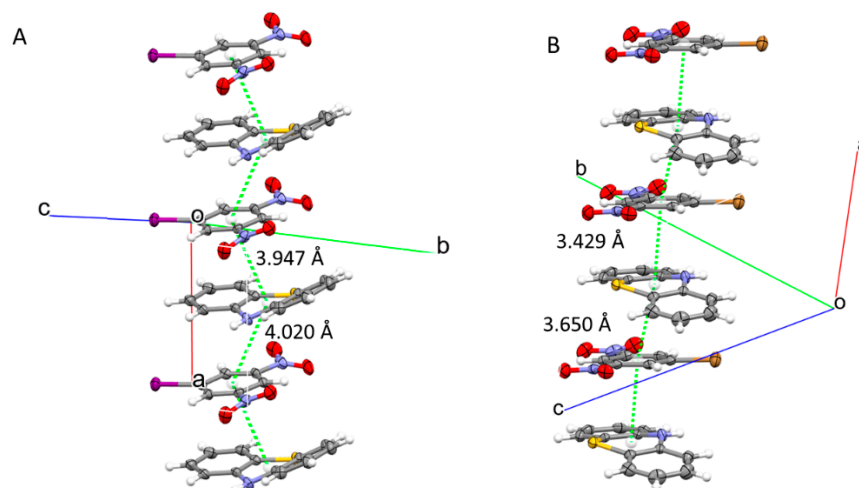


Figure 3. Fragments of X-ray structures of co-crystals **4** (A) and **5** (B) showing alternating π -stacks of phenothiazine with IDNB and BDNB, respectively. Color code: dark grey—carbon, light grey—hydrogen, purple—iodine, brown—bromine, blue—nitrogen, yellow—sulfur, and red—oxygen.

The distances between centroids and lateral shifts (as well as interatomic contacts between adjacent BDNB and PTZ molecules) in co-crystals **5** are somewhat shorter (Table 1) than those between PTZ and IDNB in co-crystals **4**. The shortest interatomic distances are 3.4190 (0.0031) Å ($R = 0.93$) for $\text{S}\cdots\text{C}$ contacts in the BDNB co-crystals and 3.4436 (0.0037) Å ($R = 0.97$) for $\text{C}\cdots\text{C}$ contacts in the IDNB co-crystals. Short contacts are also present between N–H and/or aromatic hydrogen atoms of phenothiazine and oxygen atoms of the electron acceptors in both co-crystals (Figure S2, Supporting Information). In particular, on the nitrogen-containing edge, phenothiazine shows the $\text{N-H}\cdots\text{O}$ and $\text{C-H}\cdots\text{O}$ contacts with two oxygens of one of the nitro groups of IDNB with $\text{H}\cdots\text{O}$ distances of 2.377 Å and 2.563 Å, respectively, and $\text{N-H}\cdots\text{O}$ and $\text{C-H}\cdots\text{O}$ angles of 192.8° and 149.7° , respectively. This bonding produces eight-membered ring ($R_2^2(8)$ motif). On the sulfur containing edge of PTZ molecule, there is $\text{C-H}\cdots\text{O}$ contact with another nitro group with $\text{H}\cdots\text{O}$ distance of 2.241 Å and $\text{C-H}\cdots\text{O}$ angle of 158.8° . Overall, hydrogen bonding between two nitro substituents of IDNB and hydrogens on both edges of PTZ results in formation of PTZ/IDNB chains propagating in the plane perpendicular to the direction of the π -stacks. In addition, iodine substituents of IDNB form short contacts with oxygen atoms of IDNB (from the group which is involved in the one $\text{C-H}\cdots\text{O}$ hydrogen bonding). The $\text{I}\cdots\text{O}$ distance of 3.2542(0.0021) Å (which is 8% shorter than the van der Waals separations) and the $\text{C-I}\cdots\text{O}$ angle of $160.86(0.08)^\circ$ are consistent with halogen bonding (type II contacts). The $\text{I}\cdots\text{O}$ halogen bonding provides links between neighboring hydrogen-bonded chains and π -bonded stacks of IDNB and PTZ molecules. (Note, that the in-plane distances between iodine and any atom of PTZ molecules are much larger than the van der Waals separation, i.e., there is no halogen bonding between these species). The bromine atoms in crystals **5** do not form contacts shorter than the van der Waals separations (this distinction

is probably related to the stronger halogen bonding abilities of iodine atoms as compared to the bromine analogues related to the larger size and polarizability of the former [21]). However, the C-H and N-H hydrogens on one edge of PTZ and C-H hydrogen on another edge are involved in hydrogen bonding with nitro-groups' oxygens from the adjacent BDNB nitro pattern similar to that in the co-crystals formed by PTZ and IDNB.

In the π -stacks of both co-crystals, IDNB or BDNB molecules are slightly shifted relative to the PTZ moieties. The angles between the aromatic rings in phenothiazine are 23.37° in complexes with IDNB and 17.88° in co-crystals with BDNB. These shifts likely allow a closer approach of the electron acceptors to the butterfly shaped PTZ molecule. Multiple short contacts between neighboring molecules are observed in both co-crystals; however, most are close to the van der Waals separations.

3.2. Computational Analysis of Bonding in Intermolecular Complexes of Phenothiazine

Supramolecular interactions have in recent years been commonly rationalized using the σ - and π -hole concepts [52,53]. Alternatively, many studies stress the contribution of HOMO/LUMO interactions to intermolecular bonding [21]. Accordingly, electrostatic potentials mapped on molecular surfaces, showing regions of positive and negative potential, and their HOMO and LUMO shapes provide valuable information about the propensity of a species to engage in different types of noncovalent bonding.

The highest positive electrostatic potential on the surface of phenothiazine (Figure 4) is located on the hydrogen atom bound to nitrogen. The surfaces of the adjacent carbon-bound hydrogen atoms are also positive. These features are consistent with the participation of these atoms in hydrogen bonding observed in crystal structures.

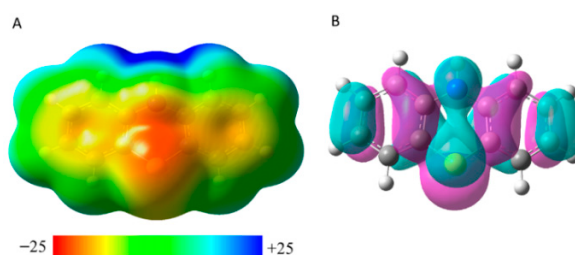


Figure 4. Molecular electrostatic potential (kcal mol^{-1} , 0.001 a.u. electron density) (A) and HOMO (B) of phenothiazine. (Note that blue and purple colors in B represent different phases (signs) of the electronic wave function).

The present work, however, focuses on intermolecular interactions in which phenothiazine serves as an electron-rich partner, i.e., as a halogen-bond (HaB) acceptor and an electron donor in charge-transfer π -stacked associations. The region of most negative electrostatic potential is located above the convex central ring of PTZ, somewhat closer to the sulfur atom. Less negative regions are also present above the aromatic rings. Within the σ -hole framework, this distribution suggests that the strongest halogen bonding should involve the sulfur site. However, in the crystal structure CBr_4 forms a halogen bond with the outside of the aromatic ring. Such location could be related to the presence of HOMO fragments of phenothiazine suitable for the interaction with the LUMO of electron acceptor. However, since such arrangements may be influenced by crystal packing forces, we first evaluated the relative binding energies of $\text{Br}\cdots\pi$, $\text{Br}\cdots\text{N}$, and $\text{Br}\cdots\text{S}$ interactions in (isolated) optimized HaB complexes.

Optimization of CBr_4/PTZ pairs starting from geometries in which a bromine atom was directed toward an aromatic C–C bond, the nitrogen atom, or the sulfur atom produced structures that retained their initial orientations. These optimized structures, together with the results of their QTAIM and NCI analyses, are shown in Figure 5.

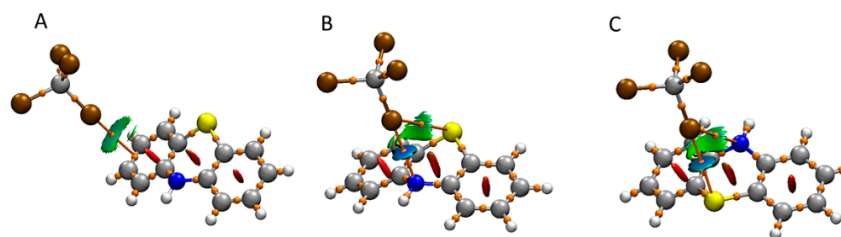


Figure 5. Superposition of the results of QTAIM and NCI analyses onto the optimized complexes of HaB complexes of CBr_4 with PTZ formed via $\text{Br}\cdots\pi$ (A), $\text{Br}\cdots\text{N}$ (B), and $\text{Br}\cdots\text{S}$ (C) interaction. Bond paths and critical (3, −1) points (from QTAIM) are shown as orange lines and spheres, respectively, and blue–green regions indicate bonding interactions (from NCI). Color code: dark grey—carbon, light grey—hydrogen, brown—bromine, blue—nitrogen, yellow—sulfur.

The QTAIM and NCI analyses revealed several notable features. First, the bond path in Figure 5A is directed from the bromine atom toward the midpoint of an aromatic C–C bond, confirming the $\text{Br}\cdots\pi$ nature of this interaction. The characteristics of the corresponding (3, −1) bond critical point (BCP) (Table S3, Supporting Information) are consistent with weak supramolecular bonding. The NCI analysis shows a blue–green region around this BCP, confirming a relatively weak noncovalent attraction between bromine and the aromatic system.

Second, the optimized complexes in Figure 5B,C each show two bond paths (and corresponding BCPs) between the bromine atom and the nitrogen and sulfur atoms of PTZ. Their characteristics differ markedly. In Figure 5B, the $\text{Br}\cdots\text{N}$ distance is 3.015 Å and the C– $\text{Br}\cdots\text{N}$ angle is 175.4°, typical of halogen bonding. The BCP along the $\text{Br}\cdots\text{N}$ path is characterized by an electron density $\rho(r) = 0.015$ a.u., a potential energy density $V(r) = -0.0095$ a.u., and an ELF value of 0.053, consistent with a moderate supramolecular interaction. In contrast, the $\text{Br}\cdots\text{S}$ distance in this structure is 3.912 Å, exceeding the van der Waals separation, the C– $\text{Br}\cdots\text{S}$ angle is 128.1°, outside the range typical for halogen bonding, and the corresponding $\rho(r)$, $V(r)$, and ELF values are three to five times smaller (Table S3, Supporting Information). The NCI analysis shows a dark blue region around the $\text{Br}\cdots\text{N}$ BCP, indicating a moderate attractive interaction, whereas the region around the $\text{Br}\cdots\text{S}$ BCP is light green, consistent with very weak, if any, attraction. These data indicate that the complex in Figure 5B is formed primarily via $\text{Br}\cdots\text{N}$ halogen bonding, with a weak secondary $\text{Br}\cdots\text{S}$ interaction.

The complex in Figure 5C is characterized by a $\text{Br}\cdots\text{S}$ distance of 3.306 Å and a C– $\text{Br}\cdots\text{S}$ angle of 175.9°, whereas the $\text{Br}\cdots\text{N}$ distance is 3.681 Å with a C– $\text{Br}\cdots\text{N}$ angle of 127.4°. These geometric parameters, together with the QTAIM and NCI analyses confirm that this structure is formed predominantly via $\text{Br}\cdots\text{S}$ halogen bonding with a weak secondary $\text{Br}\cdots\text{N}$ interaction. Binding energies for these complexes are listed in Table 2.

Notably, the energies of the optimized CBr_4 –PTZ complexes formed via $\text{Br}\cdots\pi$, $\text{Br}\cdots\text{N}$, and $\text{Br}\cdots\text{S}$ interactions are very similar. This suggests that all three types of complexes may coexist in solution, and that the interaction mode observed in co-crystals is determined by crystal packing forces, which outweigh the relatively weak and comparable supramolecular interactions.

Optimization of the IDNB–PTZ and BDNB–PTZ pairs produced HaB complexes formed via interaction of iodine or bromine with either the nitrogen or sulfur atoms. These optimized complexes, together with the corresponding QTAIM and NCI analyses, are illustrated in Figure 6.

Table 2. Short contacts, binding energies and charge transfer in the optimized complexes.

Complex	Type	Contact, Å	ΔE , ^c kcal/mol	q , e
CBr ₄ ·PTZ	Br··· π	3.442	−2.9	0.008
	Br···N	3.015	−2.9	0.022
	Br···S	3.306	−3.1	0.024
IDNB·PTZ	π - π ^a	3.297 (C···C)	−8.1	0.010
	π - π ^b	3.172 (C···C)	−9.7	0.020
	I···N	3.140	−3.7	0.010
	I···S	3.494	−3.4	0.030
BDNB·PTZ	π - π ^a	3.249 (C-C) 3.160 (C-N _{NO2})	−8.4	0.016
	π - π ^b	3.330 (C···C) 3.106 (C···N) 3.553 (C···S)	−11.6	0.014
	Br···N	3.131	−2.5	0.008
	π - π ^b	3.084 (C···C) 2.888 (C···N) 3.389 (C-S)	−10.7	0.123
FA·PTZ	π - π ^b	3.196 (C···C) 3.013 (C-N) 3.240 (C···S)	−10.5	0.127

(a) Wings of PTZ are directed from the partner; (b) Wings of PTZ are toward from the partner. (c) The corresponding values that do not include ZPE are listed in Table S3 in the Supporting Information.

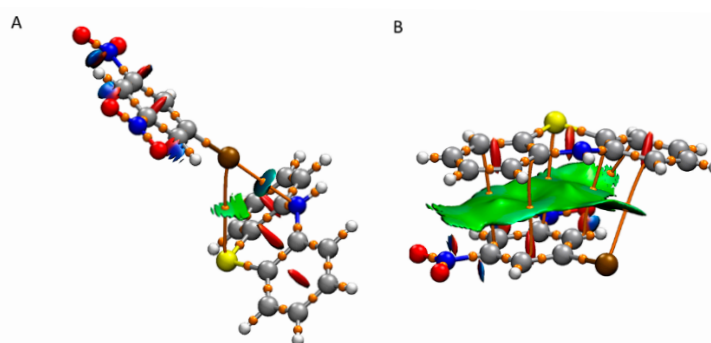


Figure 6. Superposition of the results of QTAIM and NCI analyses onto the optimized HaB (A) and π -stacked (B) complexes of BDNB with PTZ. Bond paths and critical (3, −1) points are shown as orange lines and spheres, respectively, and blue–green regions indicate bonding interactions. Color code: dark grey—carbon, light grey—hydrogen, brown—bromine, blue—nitrogen, yellow—sulfur, and red—oxygen.

As expected, halogen bonding between PTZ and IDNB is somewhat stronger. The binding energies of complexes formed via S or N atoms lie within 1 kcal mol^{−1} of those found for the CBr₄ complexes. QTAIM analyses further showed that HaB complexes of PTZ with BDNB or IDNB exhibits two bond paths and two BCPs, analogous to the CBr₄ complexes. Geometric parameters, electron-density topologies, and energy densities at the BCPs (Table S3, Supporting Information), together with NCI analyses, confirm that each complex is formed via one dominant halogen bond and a weak secondary interaction involving the same halogen atom.

In addition to HaB complexes, optimization also yielded π -stacked associations of IDNB and BDNB with PTZ illustrated in Figure 6B. The “wings” of PTZ are directed either toward or away from the electron acceptor molecules. These structures display multiple bond paths and BCPs, indicating multicenter bonding between the stacked donor and acceptor. NCI analysis reveals green regions with multiple blue inclusions around these BCPs, characteristic of attractive interactions. Although the individual BCP characteristics (Table S3 in the Supporting Information) indicate weak interactions, their combined effect results in strong overall binding. Indeed, the binding energies of the π -stacked complexes (Table 2) are substantially larger than those of the corresponding HaB complexes. The difference of approximately 5–7 kcal mol^{−1} corresponds, at room temperature, to a 4–5 orders-of-magnitude difference in formation constants in solution. Moreover, while

halogen bonding allows only 1:1 complexes, π -stacking enables the formation of infinite stacks in which each donor interacts with two acceptors and vice versa. These factors likely explain the preference for π -stacked complexes observed in the solid state.

It should also be mentioned that the optimized HaB dimer formed via $I\cdots O$ bonding similar to that observed in the solid-state is characterized by ΔE values of -1.9 kcal/mol, i.e., this bonding is somewhat weaker. Optimized hydrogen-bonded complex between IDNB and PTZ analogous to that in the crystal structure in Figure S2 is characterized by ΔE values of -1.9 kcal/mol (see Table S4 in the Supplementary Materials for details).

Optimization of π -stacked complexes formed by PTZ with TCP or FA also produced minimum-energy structures in which the PTZ “wings” are oriented toward or away from the acceptor molecules. (The binding energies of the two isomers are very similar; only one is discussed hereinafter for clarity.) QTAIM analyses revealed multiple bond paths and BCPs, as well as blue regions indicative of attractive interactions (Figure 7), confirming multicenter donor–acceptor bonding analogous to that in the IDNB and BDNB complexes. These π -stacked complexes also exhibit substantially higher charge transfer from PTZ to the acceptors. The binding energies of the FA and TCP complexes fall in the same range as those of the analogous π -stacked IDNB and BDNB complexes (Table 2).

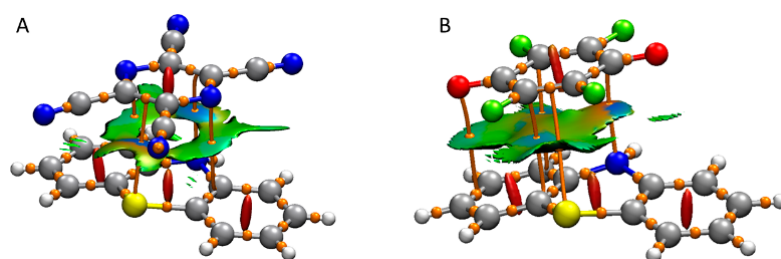


Figure 7. Superposition of the results of QTAIM and NCI analyses onto the optimized π -stacked complexes of PTZ with TCP (A) and FA (B). Bond paths and critical (3, -1) points (from QTAIM) are shown as orange lines and spheres, respectively, and blue–green regions indicate bonding interactions (from NCI). Color code: dark grey—carbon, light grey—hydrogen, blue—nitrogen, yellow—sulfur, red—oxygen, light green—fluorine.

To clarify the origin of the differences in binding energies between HaB and π -stacked complexes, we first evaluated charge transfer using NBO analysis. The amount of charge transfer in the three HaB complexes of PTZ with CBr_4 is small (0.008–0.024 e). Similar small values of charge transfer were found for all complexes with BDNB and IDNB. Most notably, HaB and π -stacked complexes of these acceptors exhibit comparable charge transfer, indicating that this factor is not responsible for the differences in binding energies. The complexes of PTZ with TCP and FA are characterized by the higher amounts of charge-transfer, but this distinction is consistent with the more positive reduction potentials of the latter as compared to nitrobenzene derivatives [25,54].

Since the change in charge transfer is not the dominant factor in the differences in binding energies, energy-decomposition analysis (EDA) was performed. The AMS suite of programs decomposes the intermolecular interaction energy, ΔE_{int} , into electrostatic, ΔE_{elstat} , Pauli repulsion, ΔE_{Pauli} , orbital interaction, ΔE_{oi} , and dispersion, ΔE_{disp} , components [42–44]:

$$\Delta E_{\text{int}} = \Delta E_{\text{elstat}} + \Delta E_{\text{Pauli}} + \Delta E_{\text{oi}} + \Delta E_{\text{disp}}$$

The values of ΔE_{int} and its components are listed in Table 3. Overall, variations in ΔE_{int} follow those of the binding energies ΔE in Table 2. Because ΔE includes deformation energies of the reactants and ZPEs (see Table S3 in the Supplementary Materials for the

value which do not include ZPEs), ΔE_{int} values are somewhat larger in magnitude. The donor–acceptor interactions in π -stacked complexes are therefore significantly stronger than in the corresponding HaB complexes. For CBr_4 –PTZ, interactions via $\text{Br}\cdots\text{N}$ and $\text{Br}\cdots\text{S}$ are about 2 kcal mol^{-1} stronger than via $\text{Br}\cdots\pi$; the similar overall binding energies are thus likely due to lower deformation energies in the latter case.

Table 3. Interaction energies and their components (in kcal/mol) in the π -stacked and HaB complexes.

Complex	Type	ΔE_{elstat}	ΔE_{oi}	ΔE_{disp}	ΔE_{Pauli}	ΔE_{int}
CBr_4 ·PTZ	$\text{Br}\cdots\pi$	−2.7	−1.8	−4.2	4.6	−4.1
	$\text{Br}\cdots\text{N}$	−5.5	−3.8	−5.6	8.8	−6.1
	$\text{Br}\cdots\text{S}$	−4.9	−3.6	−7.0	8.9	−6.7
IDNB·PTZ	π – π^a	−8.0	−3.4	−16.7	14.	−13.8
	π – π^b	−12.1	−4.9	−17.2	20.3	−14.0
	$\text{I}\cdots\text{N}$	−3.1	−1.5	−4.8	3.9	−5.5
	$\text{I}\cdots\text{S}$	−6.2	−3.9	−5.9	8.9	−7.0
BDNB·PTZ	π – π^a	−10.7	−4.4	−17.3	17.1	−15.2
	π – π^b	−6.3	−3.2	−13.9	11.3	−12.1
	$\text{Br}\cdots\text{N}$	−4.1	−2.1	−5.2	6.6	−4.7
FA·PTZ	π – π^b	−14.7	−12.5	−16.0	27.4	−15.8
TCP·PTZ	π – π^b	−15.5	−11.9	−18.4	24.0	−21.8

(a) Wings of PTZ are directed toward the partner; (b) Wings of PTZ are directed from the partner.

Consistent with the NBO results, the EDA shows that ΔE_{oi} values (associated with charge transfer) are similar for π -stacked and HaB complexes with the same electrophile. The largest differences arise in the dispersion component, indicating that the enhanced stability of π -stacked complexes is primarily driven by dispersion interactions.

In summary, X-ray crystallography reveals that CBr_4 forms exclusively $\text{C}–\text{Br}\cdots\pi$ halogen bonds with phenothiazine in the solid state, whereas DFT calculations indicate that $\text{C}–\text{Br}\cdots\text{N}$, $\text{C}–\text{Br}\cdots\text{S}$, and $\text{C}–\text{Br}\cdots\pi$ interactions have comparable intrinsic strengths, implying that crystal packing forces determine the observed motif. All π -acceptors form alternating donor–acceptor stacks with PTZ, characterized by multiple short contacts indicative of multicenter charge-transfer interactions. Although BDNB and IDNB are good HaB donors, their co-crystals with phenothiazine exhibit only π -stacked architectures, consistent with the higher binding energies predicted for such complexes. NBO and EDA show that the enhanced stability of stacked structures arises primarily from large dispersion contributions, augmented by electrostatic and orbital interactions. These results rationalize the solid-state preference for π -stacking over halogen bonding when both motifs are accessible and clarify the hierarchy and physical origin of noncovalent interactions involving phenothiazine, providing guidance for the design of supramolecular assemblies and functional materials based on this versatile donor.

Supplementary Materials: The following are available online at <https://www.mdpi.com/article/10.3390/cryst16030177/s1>, Table S1: Crystallographic, data collection, and structure refinement details. Table S2: Selected geometric characteristic of phenothiazine molecule. Table S3: Characteristics of the bond critical points (in a.u.) corresponding to short contacts in the optimized complexes of PTZ with various anion. Table S4: Energies, zero-point energies (ZPE) and free energies (in Hartree) of complexes and reactants. Figure S1: Fragments of X-ray structure of 1. Figure S2: X-ray structure of crystals 4 (left) and 5 (right). Figure S3: Fragments of the X-ray structures of 2. Figure S4: FT-IR spectra of compound 1. Figure S5: FT-IR spectra of compound 2. Figure S6: FT-IR spectra of compound 3. Figure S7: FT-IR spectra of compound 4. Figure S8: FT-IR spectra of compound 5. Figure S9: UV-Vis spectra of solid-state compounds 1. Figure S10: UV-vis spectra of solutions containing individual PTZ (dashed green) and TCP (dashed red), and their mixtures (purple). Figure S11: UV-vis spectra

of solutions containing individual PTZ (dashed green) and FA (dashed red), and their mixtures (purple). Figure S12: UV-vis spectra of solutions containing individual PTZ (dashed green) and BDNB (dashed red), and their mixtures (purple). Figure S13: UV-vis spectra of solutions containing individual PTZ (dashed green) and IDNB (dashed red), and their mixtures (purple). Figure S14: UV-vis spectra of solutions containing individual PTZ (dashed green) and CBr₄ (dashed red), and their mixtures (purple).

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