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Chalcogen Bonding

Chalcogen Bonding “2S–2N Squares” versus Competing Interactions: Exploring the Recognition Properties of Sulfur

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Abstract: Chalcogen bonding (CB) is the focus of increased attention for its applications in medicinal chemistry, materials science, and crystal engineering. However, the origin of sulfur's recognition properties remains controversial, and experimental evidence for supporting theories is still emerging. Here, a comprehensive evaluation of sulfur CB interactions is presented by investigating 2,1,3-benzothiadiazole X-ray crystallographic structures gathered from the Cambridge Structure Database (CSD), Protein Data Bank (PDB), and own laboratory findings.

Through the systematic analysis of substituent effects on a subset library of over thirty benzothiadiazole derivatives, the competing interactions have been categorized into four main classes, namely 2S–2N CB square, halogen bonding (XB), S...S, and hydrogen-bonding (HB). A geometric model is employed to characterize the 2S–2N CB square motifs and discuss the role of electrostatic, dipole, and orbital contributions toward the interaction.

Introduction

Chalcogen bonding (CB), categorized as the interaction between Group VI elements (O, S, Se, Te, Po)^[1–12] and a Lewis-basic partner atom,^[13–19] has received significant attention in the past decade, largely in response to the advances made in understanding halogen bonding (XB).^[20–27] Seminal work^[28–30] led to the realization that polarizable halogens can be tuned to exploit the electron-poor regions of their surfaces, now defined as σ -holes,^[31–34] for efficient intermolecular interactions with Lewis-basic atoms. Unlike XB, the deliberate application of CB is still emerging. This is especially true for sulfur, which retains a large degree of atomic dipole polarizability (2.90 Å³) compared to oxygen (0.80 mÅ³), but less than the heavier selenium or tellurium atoms (3.77 and 3.9 Å³).^[35]

Recent reports have highlighted the importance of sulfur's role in recognition and the major aspects that still remain to be explored. The comprehensive Review by Meanwell and co-workers reports the wide diversity of sulfur recognition in biological systems and in protein–ligand interactions for medicinal chemistry applications.^[36] CB has been applied to anion transport^[37] and organocatalysis^[38] for the first time by Matile and co-workers. Yet, solution-phase binding constants for individual

intermolecular organosulfur interactions with Lewis-basic atoms remain elusive, and intramolecular association constants have only been reported in 2017.^[39] Earlier progress was made by the Taylor group, which obtained intermolecular binding constants for 2,1,3-benzotelluradiazole complexes with anionic and neutral Lewis bases (quinuclidine) in organic solvents using UV/Vis and NMR spectroscopies.^[40,41] Their results were rationalized on the basis of *N*-nucleophile→Te σ -hole attraction, which was not strong enough to produce measurable benzoseleno- and thiadiazole binding constants.

The solution-phase challenges of unlocking the underpinnings of organosulfur recognition can be compensated, at least in part, by closely analyzing interactions in the solid state, as had been done in the early days of halogen bonding.^[20,42] Dunitz, Parthasarathy, and co-workers reported the first X-ray crystallographic investigations on the intermolecular interactions of divalent sulfur and observed distinct directionality at close proximity, as expected for intermolecular CB interactions.^[43,44] Yet, large gaps still remain in the understanding of how the electronic environments of the interacting groups influence these interactions. For instance, it is now recognized that factors such as the hybridization state of sulfur can alter its interactions.^[12,15–17,19,37,38,45,46]

1,2,5-Thiadiazoles present interesting systems,^[47,48] although the nature of their S...N interactions and the involved structural boundaries remain largely unexplored. Most knowledge has been derived from computational analysis.^[49] Early density functional theory (DFT) studies concluded that close-range S...N orbital–orbital interactions (i.e., charge transfer) were primarily responsible for the interactions between 2,1,3-thiadiazoles.^[50] More recently, *ab initio* coupled-cluster single-double and perturbative triple (CCSD(T)) calculations, which account for dispersion, revealed that S...N orbital–orbital interactions are repulsive and that the longer-range dispersion interaction

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is most influential.^[51] The primary driving force switches to electrostatics (i.e., σ -hole interactions) for the more polarizable Se and Te diazoles. The energy gain for 2S–2N thiadiazole squares is calculated to be $-3.14 \text{ kcal mol}^{-1}$, as compared to Se ($-5.29 \text{ kcal mol}^{-1}$) and Te ($-12.42 \text{ kcal mol}^{-1}$) dimers. Finally, the influence of molecular dipoles for these systems has not been reported.

Herein we investigate 2,1,3-benzothiadiazoles^[52] for the nature of their sulfur interactions, the factors controlling CB geometry, and how these forces compete with other crystal packing forces.^[53] 2,1,3-Benzothiadiazole (**1b**; Figure 1 a) and its derivatives serve as an effective test-case because of their affinity for crystallization, relevance to medicinal chemistry^[54–56] and materials science.^[57–68] Furthermore, many structural derivatives are capable of forming 2S–2N square dimeric^[69,70] or polymeric interactions within their crystalline lattices (Figures 1 b,c), and the scaffold allows for the systematic substitution of positions 4–7 on the benzo ring.

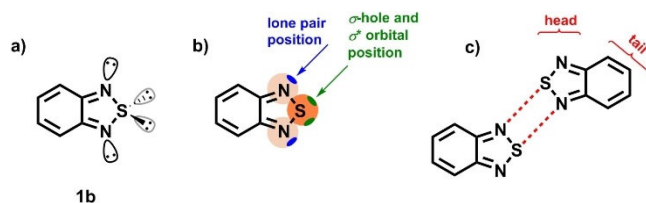


Figure 1. a) Top view of the 2,1,3-benzothiadiazole core structure and location of lone pair electrons: N in plane, S out of plane. b) Top view showing the in-plane position of the nitrogen lone pairs, sulfur σ -holes and σ^* orbitals. c) Square dimer interaction.

We present an analysis of 2,1,3-benzothiadiazoles **2a–9h** from our synthetic work and from the Cambridge Structure Database (CSD)^[71,72] (Figure 2). They contain a diversity of small, non-aromatic substituents, some of which can act as H-bond donor/acceptors. These substituents may attenuate sulfur in-

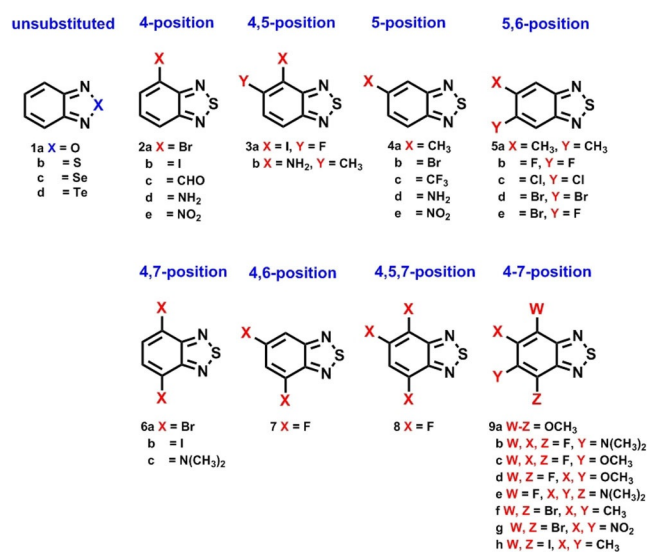


Figure 2. 2,1,3-Benzothiadiazole structures investigated in the present study.

teractions and impose other intermolecular contacts, different from the 2S–2N square interactions.

Results and Discussion

To geometrically define the alignment of two thiadiazole edges, we constructed a practical description for the 2S–2N square contact shown in Figure 3. This contact involves three critical angles θ , ϕ , and Φ , representing the three dimensions of available freedom when the thiadiazole edges converge and pair the sulfur with nitrogen through CB.

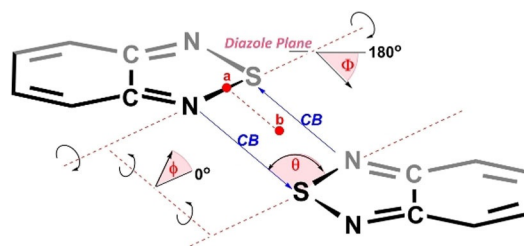


Figure 3. Geometric parameters of the 2S–2N square interaction. Parameter θ is the N–S–N angle, ϕ is the S–N–S–N torsion angle, and Φ is the diazole plane C–N–S–N torsion angle. The point $\bullet_a$ is the center of the N–S bond, and point $\bullet_b$ is the midpoint between point $\bullet_a$ of one thiadiazole and point $\bullet_a$ of a second thiadiazole.

We applied the ConQuest^[73] module (v. 1.19) to the CSD (v 5.38) to determine the abundance of 2,1,3-benzothiadiazole square contacts by constraining the maximum and minimum allowable CB distance to be $2.50 \leq \text{CB} \leq 4.00 \text{ \AA}$ and an R factor of ≤ 0.1 . Each CSD structure hit was analyzed further using Mercury software^[74] to determine (θ , ϕ , and Φ), and then rendered using PyMOL software^[75] to isolate the interactions of interest.

The CSD search revealed 197 structurally diverse organic and organometallic 2,1,3-benzothiadiazoles, 58 of which have contact distances $\leq 4.0 \text{ \AA}$ (Table S2 and Figure S10 in the Supporting Information). Within this subgroup, 20 contain two or more potential 2S–2N square interactions within their lattices, which raises the total number of such squares to 84. The contact S–N distance, which we define as the calculated CB average distance (CB_{ave}) between the monomers, spanned from $2.89 \text{ \AA}$ ^[76] to $3.95 \text{ \AA}$ ^[77] with the mean being $3.42 \text{ \AA}$ (see Figure S10 for structures).

An analysis of the correlation between CB_{ave} distance and the associated angles θ , ϕ , and Φ for each structure shows that those with close contacts ($\text{CB}_{\text{ave}} \leq \text{van der Waals radii sum N+S} = 3.35 \text{ \AA}$ ^[78]) have angular ranges of $\theta_{\text{ave}} = 67.7\text{--}89.7^\circ$ (mean 74.0°), $\phi_{\text{ave}} = 0\text{--}36.3^\circ$ (mean 1.7°) and $\Phi_{\text{ave}} = 149.6\text{--}179.5^\circ$ (mean 171.6°). Every structure in this category contains a highly aligned square planar interaction, with angles approaching $\phi \approx 0^\circ$, $\theta \approx 90^\circ$, and $\Phi \approx 180^\circ$. The shortest ($2.89 \text{ \AA}$)^[76] middle ($3.39 \text{ \AA}$)^[79] and longest ($3.95 \text{ \AA}$)^[77] CB_{ave} distances, respectively, illustrate the marked diversity in 2S–2N square 2,1,3-benzothiadiazole dimer structures that fall within the $2.89\text{--}4.0 \text{ \AA}$ CB_{ave} range (Figure S10). The strikingly high

prevalence of diverse structures (39) containing *both* sub-van der Waals S...N contacts *and* highly aligned square planar interactions suggests that the square attraction out-competes the myriad of other substituent interactions during packing.

The 2S–2N Square Class Assembled by Chalcogen Bonding

Of the four unsubstituted 2,1,3-benzochalcogenadiazoles (O, S, Se and Te) **1a–1d**, only the X-ray structure of tellurium **1d**^[81–83] contains highly aligned, sub-van der Waals 2Te–2N square interactions ($CB_{ave} = 2.70 \text{ \AA}$, $\theta_{ave} = 69.1^\circ$, $\phi_{ave} = 2.4^\circ$, $\Phi_{ave} = 178.7^\circ$) (Figure S8). Conversely, the sulfur **1b**^[84–86] and selenium **1c**^[87,88] isostructures have significantly out-of-plane, distorted squares that are nearly identical (S; Se, respectively: $CB_{ave} = 3.40 \text{ \AA}$; $3.41 \text{ \AA}$, $\theta_{ave} = 76.4^\circ$; 76.6° , $\phi_{ave} = 20.0^\circ$; 23.4° , $\Phi_{ave} = 145.5^\circ$; 144.4°). Cozzolino et al. attributed the robust Te...N nonbonding interactions as outcompeting the steric demands of its benzo- tail, while the cost remains too high for the sulfur and selenium derivatives.^[50] The oxygen derivative **1a**^[85] has no square interactions and aligns in head–tail columns.

Small, non-aromatic substituent additions to the benzo tail of **1b** results in significant changes to the square geometry. Unexpectedly, 74% (23 structures) of the sulfur derivatives **1b–9h** contain S...N contacts $< 4.0 \text{ \AA}$ and have at least one square interaction (Figure 4). Furthermore, the most highly aligned squares (17 structures with ranges $\theta_{ave} = 68.1\text{--}78.6^\circ$, $\phi_{ave} = 0\text{--}23.4^\circ$, $\Phi_{ave} = 162.8\text{--}179.1^\circ$), representing 81% of the subset, contain sub-van der Waals S...N contacts. This is in agreement with the CSD population shown in Figure S9, where a strong correlation between sub-van der Waals contacts and square alignment exists, but the high degree of alignment does not discriminate between substituent types.

While the calculations by Tsuzuki et al.^[51] show that S...N thiazole contacts stabilize the squares, the diversity of substituents (in Figure S9) indicates that they have a role in stabilizing dimerization in other ways besides tuning sulfur's polarization, such as through substituent...substituent or substituent...benzothiadiazole tail interactions. The substituent position on the benzo- tail is not relevant in this regard. For instance, **5a** and

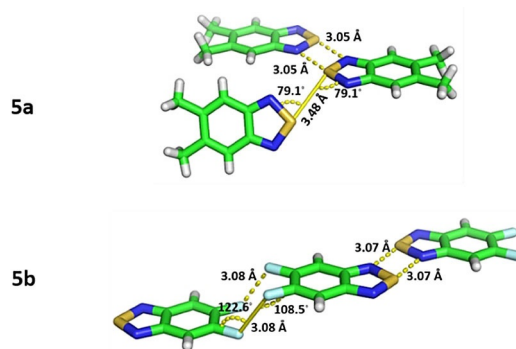


Figure 5. Crystal structures of **5a–5b**, featuring complementary interactions with squares. Atom coloring: C green, N blue, S yellow, F cyan.

5b (Figure 5), each having 5,6-substitution, form squares nearly identical to the dimers having asymmetric 4- or 5-substitution in **2a** and **4a** (Figure 6).

In **5a** and **5b**, there are also tail–tail interactions that allow for apolar Me...Me or Teflon-like F...F ribbons to form (Figure 5). In **5b**, the squares are further stabilized by close F...H contacts^[89] (not shown) similar to those reported for di-thieno-2,1,3-benzothiadiazoles.^[90]

Twelve of the fourteen asymmetric monomers align to orient their largest substituent *anti*- relative to each other, regardless of the substituent being electron withdrawing or donating (Figure 6).^[91] For instance, in **2d**^[92] and **2e**^[92] the 4-NH₂ and 4-NO₂ groups differ dramatically in their electronic properties but **2d** and **2e** contain nearly identical squares (**2d**; **2e**, respectively: $CB_{ave} = 3.12 \text{ \AA}$; $3.09 \text{ \AA}$, $\theta_{ave} = 72.7^\circ$; 74.9° , $\phi_{ave} = 0.0^\circ$; 0.0° , $\Phi_{ave} = 177.0^\circ$; 177.2°).

The electronic characteristics of -CH₃ versus -NO₂ also differ profoundly, yet the dimers of **4a** and **4e**^[93] are nearly equivalent as well (**4a**; **4e**, respectively: $CB_{ave} = 3.09 \text{ \AA}$; $3.14 \text{ \AA}$, $\theta_{ave} = 78.6^\circ$; 71.7° , $\phi_{ave} = 0.0^\circ$; 0.0° , $\Phi_{ave} = 177.6^\circ$; 173.3°). The only two asymmetric structures that display dimerization with their substituents in *syn*-orientation are **2c** and **8**^[94] (Figure 7). These represent rare examples of benzothiadiazole square-ribbon complexes^[95] that have repeating square interactions on both

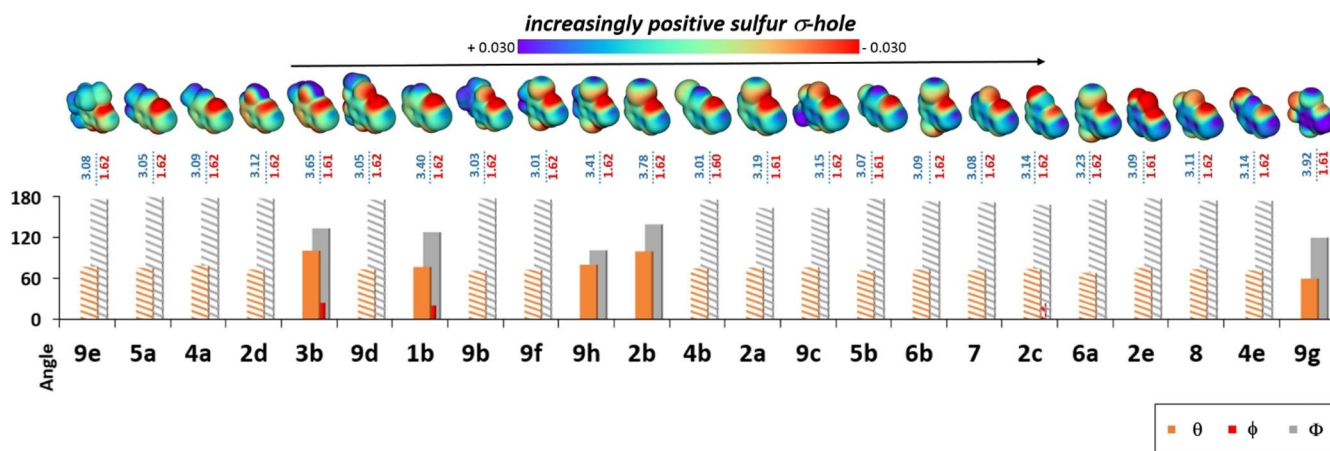


Figure 4. Compounds **1–9** having $CB_{ave} \leq 4.0 \text{ \AA}$ (blue values), plotted in the order of increasing sulfur σ -hole electrostatic potential.^[80] For compounds having more than one 2S–2N square interaction, only the shortest CB_{ave} contact is plotted. Striped bars represent dimers having $CB_{ave} \leq 3.35 \text{ \AA}$. The S–N covalent bond length of each monomer is presented in red (Å).

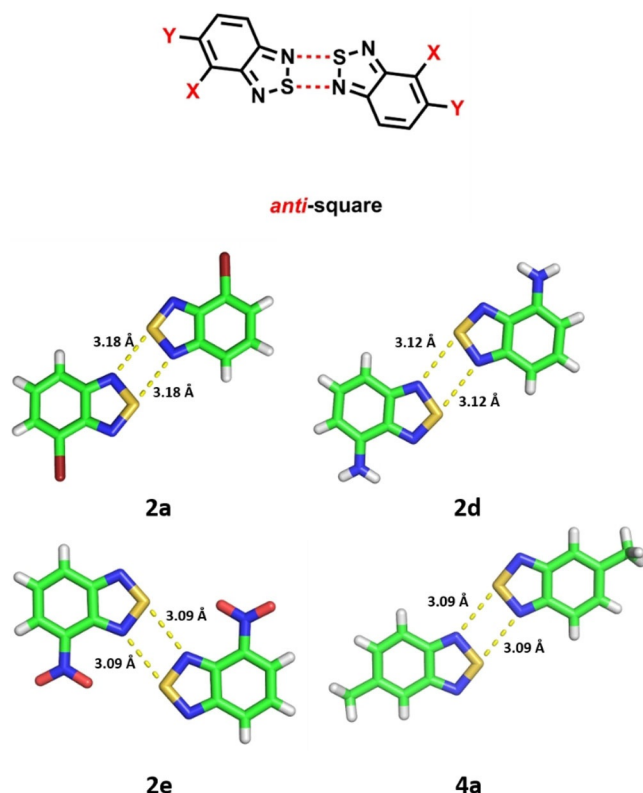


Figure 6. anti-Square orientation and crystal structures of **2a**, **2d**,^[92] **2e**, and **4a**. Atom coloring: C green, N blue, O red, S yellow, Br brown.

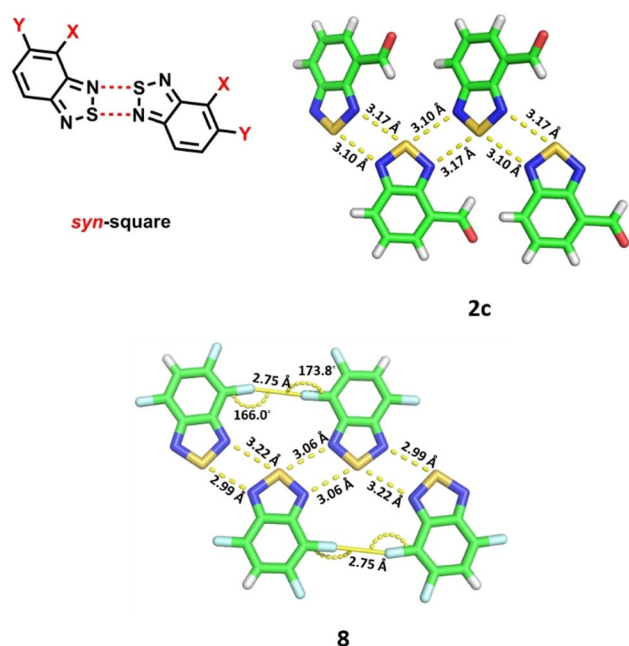


Figure 7. syn-Square orientation and crystal structures of **2c** and **8**. Atom coloring: C green, N blue, O red, S yellow, F cyan.

thiazole edges, and may be useful for supramolecular wiring applications.^[50, 96, 97]

To determine the role these small substituents play in sulfur's electronic environment and the resulting 2S–2N square in-

teractions, we further organized the square class according to the increasing molecular electrostatic potential (MESP) of the sulfur atom. Every sulfur in the set contains some degree of electropositive (δ^+) potential, known as the σ -hole region, located in the extension of the N–S bonds (Figures 1b and 4). In the case of 2,1,3-thiadiazole, which contains divalent sulfur,^[98] two σ -holes are generated that result in two angular distributions with respect to the N–S–N bonds (N–S– σ -hole angles 60–90° and 150–180°, Figure 1b).^[99, 100] The sulfur atoms in the 5-nitro derivative **4e** and 5,6-dimethyl derivative **5a** contain among the largest and smallest σ -holes, respectively. These two extremes nevertheless have virtually identically aligned dimers (**4e**; **5a**, respectively: $CB_{ave}=3.14$ Å; 3.05 Å, $\theta_{ave}=71.7^\circ$; 75.2° , $\phi_{ave}=0.0^\circ$; 0.0° , $\Phi_{ave}=173.3^\circ$; 179.1°).

While sulfur σ -holes do pervade the 2S–2N square class, we acknowledge that the extent of their influence on square interactions would likely be limited to cases when the δ^+ charge is very large. If they are the primary cause of dimerizations throughout the class, the preservation of highly aligned squares and contact distances for compounds like **5a**, where the sulfur σ -hole is significantly diminished in both size and magnitude, would not be observed (Figure S5). This is in agreement with the recent comprehensive CSD X-ray investigation of C=S...S=C interactions, where no meaningful correlation could be found between sulfur σ -hole magnitude and S...S contact distance, binding energy, or trajectory angle.^[101] Rather, attractive binding energies and close contacts were calculated to exist even for two δ^- charged S...S atoms in the dimers (H₂CS)₂ and [(OH)₂CS]₂. Furthermore, stabilizing contributions from $n \rightarrow \sigma^*$ orbital–orbital or electrostatic interactions of the N...S contacts could be evidenced by the lengthening of the accepting S–N bond.^[39, 102] However, the accepting S–N bond length of each structure does not follow this trend (Figure 4, Å in red). For instance, the unsubstituted **1b** has poor alignment ($CB_{ave}=3.40$ Å; $\theta_{ave}=76.4^\circ$; $\phi_{ave}=20.0^\circ$; $\Phi_{ave}=145.5^\circ$), yet its S–N bond length of 1.62 Å matches that of highly aligned squares such as **4a** (1.62 Å) and **2c** (1.62 Å).

In addition to the interatomic electrostatic considerations between thiadiazoles, the influence of multipole expansion of the electrostatics within each thiadiazole structure may cause favorable dipole–dipole alignments to play a role in forming the 2S–2N square geometries. We estimated the dipole and quadrupole moments of compounds **2a–9h** by performing DFT calculations at the B97D3/aug-cc-pvtz level of theory (Supporting Information).^[103] For most monomers, the dipole vector lies within the flat plane of the benzothiadiazole scaffold. Arranging the class in accordance with the (+) and (–) poles of each monomer's vector (Figure S7) reveals that, for most monomers, the vector pole is unfavorably positioned toward its contact partner.^[104] For instance, the top seven structures containing the strongest dipole moments ($\mu > 3.0$ D) position their monomer vector poles in (+,+) or (–,–) orientations. Most notable is compound **2e**, which has among the strongest dipole moment in the series (4.53 D), yet positions its vector unfavorably with its contact partner to achieve highly aligned square interactions.

Favorable quadrupole interactions would not result in square contacts and would instead reveal themselves as T-shaped dipole-quadrupole configurations between partners.^[105,106] A significant contribution of the quadrupole moment is only expected in the case of small dipole moments, which otherwise would be dominant. The calculated molecular quadrupole moment Q_{zz} values^[103] were used to interpret stacking interactions, while the dipole values are provided in Figure S7.

The Halogenated Class: Halogen Bonding Outcompetes Chalcogen Bonding in the Assembly of 2,1,3-Thiadiazoles Bearing Multiple Higher Halogens

For the halogenated compounds in Figure 2, a wide variety of XB contacts appear to out-compete the square class, since the thiadiazole moiety itself contains exposed nitrogen and sulfur lone pair electrons that provide convenient acceptor points to halogens.^[107] Additionally, the nonbonded electrons of halogens also serve as convenient acceptors to halogen or sulfur donors. We have summarized the XB contacts that are structure-determining into four categories, as follows.

4-Halogenation: A halogen in the 4-position serves as a natural handle for $X\cdots N$ intermolecular contacts and attenuates 2S–2N square alignments. For instance, brominated **2a** has closer and higher-ordered 2S–2N squares ($CB_{ave}=3.19\text{ Å}$, $\theta_{ave}=75.5^\circ$, $\phi_{ave}=0.0^\circ$, $\Phi_{ave}=163.1^\circ$) compared to **1b**, and contains a long-range $Br\cdots N$ donor–acceptor contact at 4.0 Å and angles of $149.5/156.0^\circ$ (Figure 8). The $I\cdots N$ contact in **2b** is closer (3.29 Å) and now has an in-plane, near ideal XB at an angle of interaction at 177.8° that appears to weaken its neighboring square dimer interactions in the lattice ($CB_{ave}=3.78\text{ Å}$, $\theta_{ave}=99.5^\circ$, $\phi_{ave}=0.0^\circ$, $\Phi_{ave}=139.0^\circ$). Polarizing the iodine with the addi-

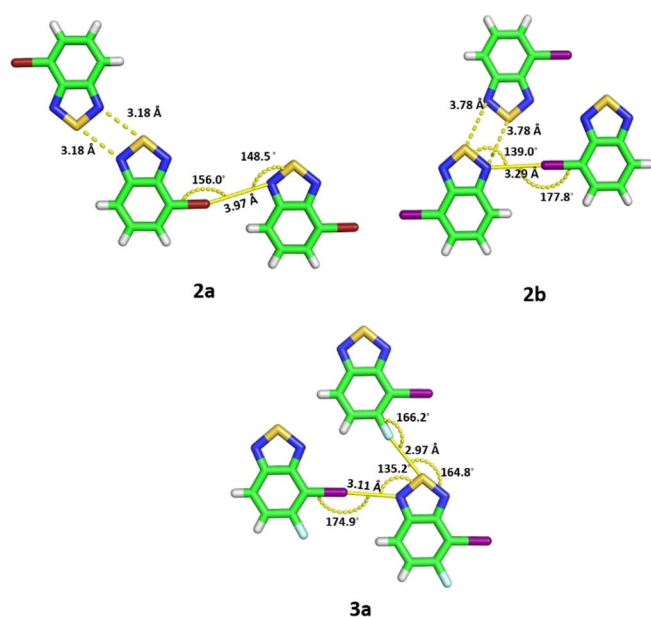


Figure 8. Crystal structures of **2a–2b** and **3a** featuring co-existing and competing XB and CB interactions. Atom coloring: C green, N blue, S yellow, Br brown, F cyan, I purple.

tion of a 5-fluoro atom (**3a**)^[108] causes the $I\cdots N$ distance to shorten further to 3.11 Å , far below the van der Waals radii sum of 3.53 Å . The square interactions are suppressed, and a complementary CB-type $F\cdots S$ contact exists at 2.97 Å with a $N\cdots F$ angle of 164.8° ($F+S$ sum of van der Waals radii: 3.27 Å). **5,6-Halogenation:** While the parent scaffold **1b** shows poorly aligned 2S–2N squares that become highly aligned in the 5,6-difluoro derivative **5b** (Figure 5), the squares cannot compete with heavier halogens in this position. For **5c–5e**, square CB interactions are replaced by XB interactions, as shown in Figure 9. Replacing just one fluorine in **5b** with bromine (**5e**)

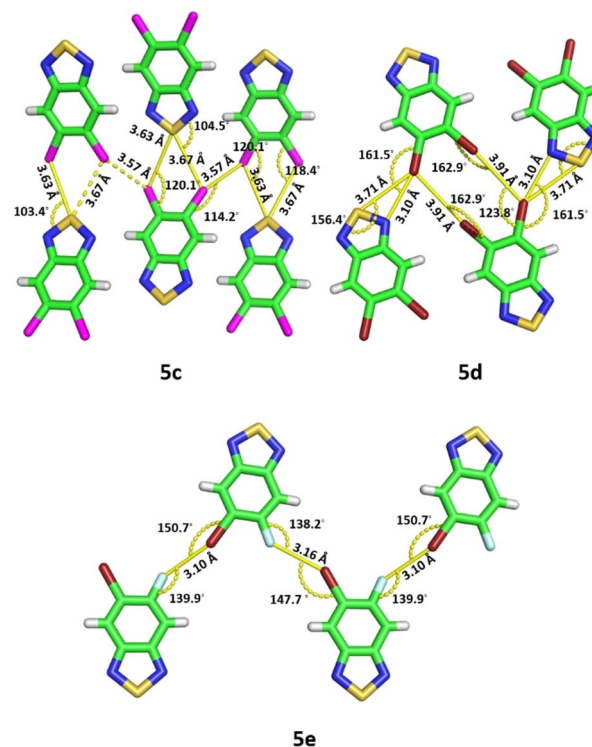


Figure 9. Crystal structures of **5c–5e** with XB interactions that attenuate CB. Atom coloring: C green, N blue, S yellow, Br brown, Cl magenta, F cyan.

results in repeating close XB-type $F\cdots Br$ contacts that are at or slightly below the sum of the van der Waals radii (3.32 Å) and at angles of 150.7° 147.7° respectively. Brominating both 5,6-positions (**5d**) results in a triangular $N\cdots Br\cdots S$ XB/CB-type contact ($N\cdots Br$: 3.10 Å , angles 154.9° and 161.5° ; $Br\cdots S$: 3.71 Å , angle 156.4°) near or slightly below the sums of the van der Waals radii (3.40 Å ($N+Br$) and 3.65 Å ($Br+S$)). These are additionally stabilized by weak XB-type $Br\cdots Br$ contacts (3.91 Å) between the monomer tails at a favorable angle of 162.9° . The tail–tail contacts are maintained in the dichloro-derivative **5c**, where the $Cl\cdots Cl$ distance is 3.57 Å (sum of van der Waals radii for ($Cl+Cl$): 3.50 Å). Interestingly, the monomers further arrange to position the sulfur between the two chlorines of the next monomer's tail at $3.63/3.67\text{ Å}$. Sulfur can similarly interact between two oxygen atoms at close range (3.15 Å), as observed in **9a** (Figure S12).^[109]

4,7-Halogenation: Prominent XB-type $X\cdots X$ networks, with $\text{Br}\cdots\text{Br}$ distances below the sum of the van der Waals radii and $\text{C-Br}\cdots\text{Br}$ angles between 163° and 172° are observed when the 4,7-positions are substituted by the heavier halogens bromine or iodine, as seen for **6a**,^[110] **6b**,^[111] and **9f-h** (Figure 10). In contrast the 2S–2N squares completely vanish. It becomes clear that the doubly CB-bridged squares cannot compete with two strong XB interactions. Past reports have noted the $X\cdots X$ networks without highlighting their recognition significance.^[110–113]

In each crystal shown in Figure 10, there are at least two $\text{Br}\cdots\text{Br}$ or $\text{I}\cdots\text{I}$ contacts for each monomer that are at or below the respective van der Waals radii sum of $3.70 \text{ \AA}$ for $(\text{Br}+\text{Br})$

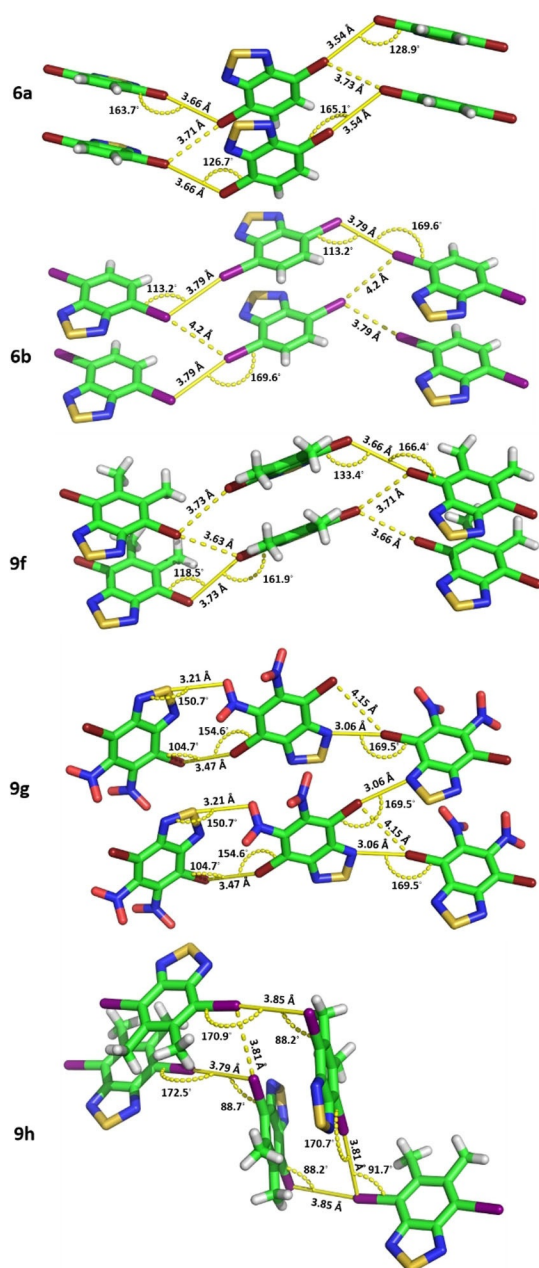


Figure 10. Crystal structures of **6a–6b** and **9f–9h**. Atom coloring: C green, N blue, S yellow, O red, Br brown, I purple.

and $3.96 \text{ \AA}$ for $(\text{I}+\text{I})$. We note that the addition of polarizing nitro groups tightens the XB interactions even further, as observed in **9g**,^[113] which now includes near linear $\text{Br}\cdots\text{Br}/\text{N}$ contacts at 3.47 and $3.06 \text{ \AA}$, respectively. A new $\text{O}\cdots\text{S}$ donor–acceptor contact at $3.21 \text{ \AA}$ also emerges, which is below the sum of the van der Waals radii of $(\text{O}+\text{S})=3.32 \text{ \AA}$.

Fluorination: Distinct from the derivatives bearing higher halogen substituents, highly aligned squares are abundant for most of the fluoro-benzothiadiazoles (**5b**, **7**, **8**, **9b–9e**).^[109] These interactions coexist with the congregation of tightly-packed $\text{F}\cdots\text{F}$ bands,^[114] as described for **5b** above (Figure 5), which are often at sub-van der Waals distance (Table S5). Structure **4c** is the exception, which has a 5-trifluoromethyl group instead of benzo-fluorination, and undergoes head-tail monomer orientation to gain $\text{F}\cdots\text{F}$ ($\geq 3.09 \text{ \AA}$), $\text{N}\cdots\text{H}$ ($3.44 \text{ \AA}$),^[115] and $\text{F}\cdots\text{S}$ ($3.15 \text{ \AA}$) contacts (Figure S11).

The $\text{S}\cdots\text{S}$ Interaction Class: Secondary Interactions Having Biological Significance

The $\text{S}\cdots\text{S}$ interaction is rare in **1–9**, but notable exceptions do appear in the X-ray structures of **5a** (Figure 5) and **3b**, **4d**, **5d**, and **6c** (Figure 11). We classify this subset as the $\text{S}\cdots\text{S}$ class to make note of the observed contact distances, near the $(\text{S}+\text{S})$ sum of the van der Waals radii, of $3.60 \text{ \AA}$ (**3b** ($3.71 \text{ \AA}$), **4d** ($3.83 \text{ \AA}$), **5a** ($3.48 \text{ \AA}$), **5d** ($3.62 \text{ \AA}$), and **6c** ($3.48 \text{ \AA}$)). Dispersion is presumed to be the major attractive force in these contacts,^[5,51,116] which is reflected in the varying interaction geometries. Nevertheless, the case of **4d** illustrates a nice example, where one sulfur accepts a chalcogen bond from a second thiadiazole moiety.

While the $\text{S}\cdots\text{S}$ contacts in Figure 11 appear attractive, they are not expected to control their lattice interactions. For instance, the CCSD(T) calculated $E_{\text{interaction}}$ for the electron-rich sulfurs in the $\text{SMe}_2\cdots\text{SMe}_2$ dimer is $-2.79 \text{ kcal mol}^{-1}$, and increases to $-3.85 \text{ kcal mol}^{-1}$ for the heterodimer pair $\text{SMe}_2\cdots\text{MeSCN}$.^[5,6] These strengths are weaker than the competing hydrogen

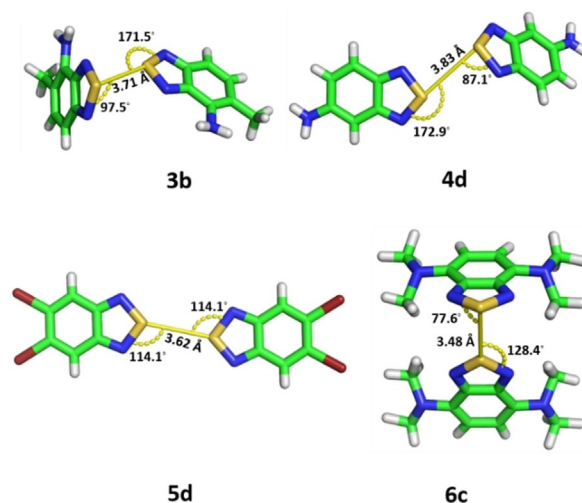


Figure 11. $\text{S}\cdots\text{S}$ motif in the crystal structures of **3b**, **4d**, **5d** and **6c**. Atom coloring: C green, N blue, S yellow, Br brown.

bonding observed in the X-ray structures of **3b**, **4d**, and **6c**,^[86] the square interaction in **5a** (≈ -3.14 kcal mol⁻¹),^[51] or the bromine XB contacts in **5d**.

There are currently no published studies that use X-ray analysis to systematically evaluate substituent effects on divalent S...S contacts in small molecules.^[92,98,101,117] Yet such effects are becoming increasingly relevant in the recognition of substrates, pharmaceuticals, and agrochemicals by protein receptors. The sulfur atoms of methionine^[118] and cysteine^[43,119] are strongly involved in protein conformation and stability,^[120,121] and Met frequently act as gatekeepers in kinases, controlling ATP binding. Boeckler et al. recently published the X-ray structure showing the "gatekeeper" residue Met146 in the c-Jun N-terminal kinase 3 (JNK3) interacting by CB with the neighboring sulfur of Met115 and by XB with an iodinated inhibitor (Figure 12a).^[122] For comparison, we superimposed the X-ray structures of **3b** and **5a** onto JNK3 and observed them to possess strong similarities to the I-S_{MET146}-S_{MET115} contacts (Figure 12b–12c).

A similar chalcogen bonding interaction is also observed for the 3-hydroxy-1,2,5-thiadiazoles present within the protein co-crystal structures with of PDB IDs 3BFT and 3BFU,^[123] which align the thiadiazole and methionine sulfur atoms at 3.91 Å (angle S...S-N 159.1°) and 3.53 Å (angle S...S-N 142.2°), respectively (Figure 12d–12e).

The HB Interaction Class: Competition between 2S–2N Square Interactions and Hydrogen Bonding

The extent to which the benzothiadiazole 2S–2N square interactions may compete with HB has not been addressed. We identified several examples within the CSD, as well as through our synthetic contributions, that provide insight toward the influence of hydrogen bonding in this context.

The selected series of amine derivatives in Scheme 1 demonstrates that highly aligned squares can in fact coexist while hydrogen bonding occurs directly on the thiadiazole (TDA) unit. Within the **2d** monomer, the 4-NH₂ group intramolecularly H-bonds to one N_{TDA} while the remaining N_{TDA} engages in close, highly aligned 2S–2N squares with a second **2d** partner. Replacing the 4-NH₂ with 4-NH-pyridyl (CSD reference code

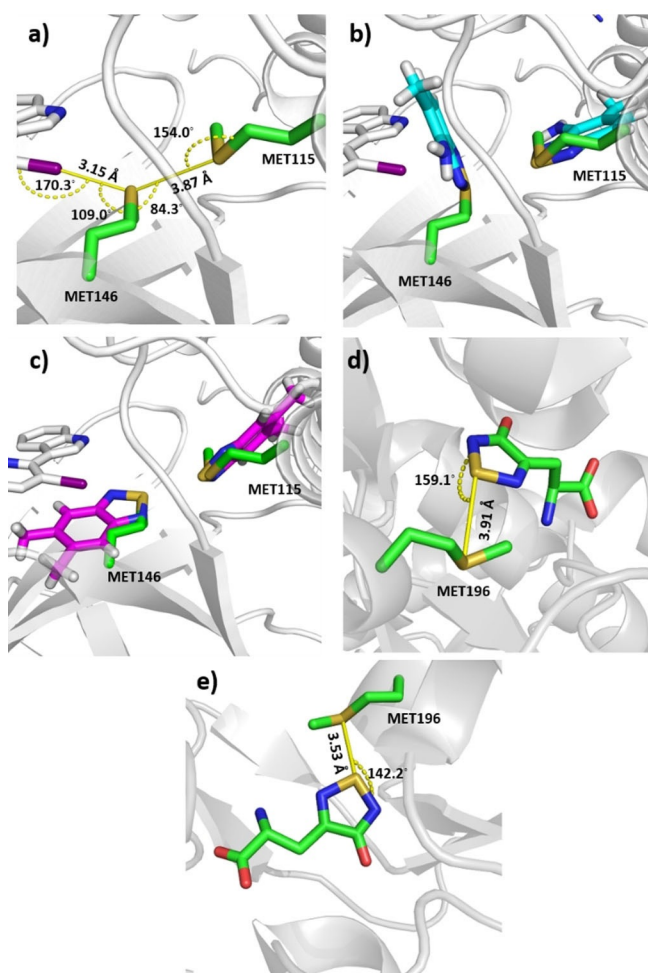
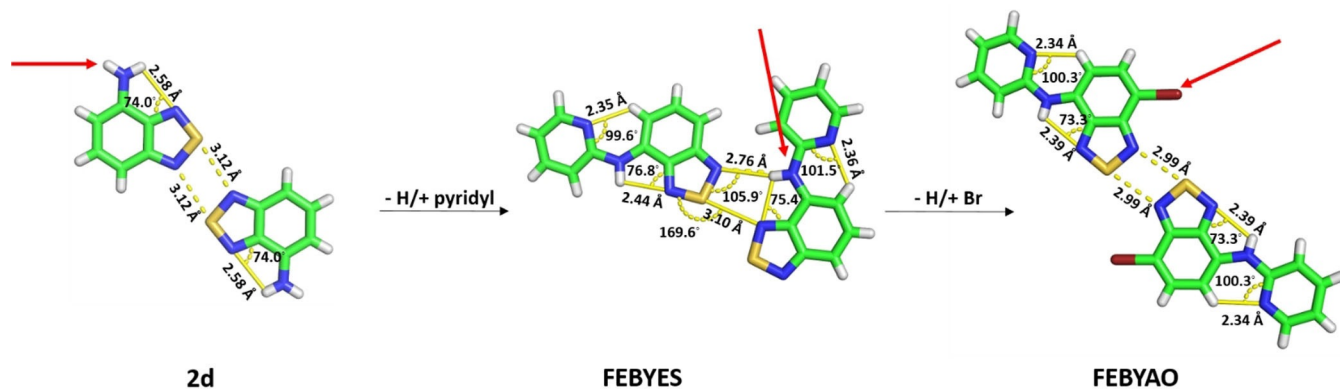
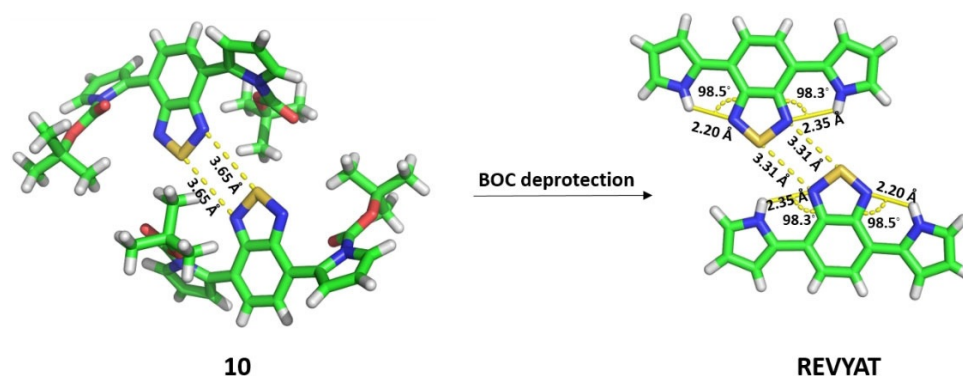


Figure 12. Co-crystal structure of JNK3 bound to an iodinated ligand (PDB ID: 2P33) (a),^[122] overlaid with the crystal structures of dimer **3b** (b) and **5a** (c). The protein co-crystal structure of a 3-hydroxy-1,2,5-thiadiazole ligand as CB donor interacting with a Met S-atom as acceptor (PDB IDs 3BFT (d) and 3BFU (e)).^[123] Atom coloring: C green (amino acids, ligands) or cyan and magenta (overlay), N blue, S yellow, O red, I purple.

FEBYES, Scheme 1)^[124] disrupts the square **2d**:**2d** dimer in favor of new intermolecular N_{TDA}...NH networks and close N_{TDA}...S-N CB contacts at 3.10 Å (angle N...S-N 169.6°). Adding



Scheme 1. Crystal structures **2d**, FEBYES^[124] and FEBYAO^[124] highlighting the co-existence of HB and CB interactions. The red arrows indicate the position of the substituent changes. Atom coloring: C green, N blue, S yellow, Br brown.



Scheme 2. Crystal structures of **10** and **REVYAT**^[126] highlighting the propensity for co-existence of HB and CB interactions revealed after deprotection. Atom coloring: C green, N blue, O red, S yellow.

bromine to the 7-position (FEBYAO,^[124] Scheme 1), or fluorine in the case of **9e**^[109] (Figure S12), evidently prevents the intermolecular $N_{TDA} \cdots NH$ networks and permits highly aligned squares to compete again ($CB_{ave} = 2.99 \text{ \AA}$, $\theta_{ave} = 74.2^\circ$, $\phi_{ave} = 0.0^\circ$, $\Phi_{ave} = 179.0^\circ$).

To determine whether the N_{TDA} atom participating *directly* in a square interaction can concurrently H-bond to neighbors, we synthesized the BOC-protected 4,7-pyrrole **10**^[125] and compared its crystal structure to the free amine **REVYAT**^[126] (Scheme 2). Both contain highly aligned squares (**10**; **REVYAT** respectively: $CB_{ave} = 3.65; 3.31 \text{ \AA}$, $\theta_{ave} = 118.0^\circ; 80.3^\circ$, $\phi_{ave} = 0.0^\circ; 0.0^\circ$, $\Phi_{ave} = 165.1^\circ; 176.0^\circ$), but **REVYAT** forms closer, sub-van der Waals CB contacts ($3.65 \text{ \AA}$ vs. $3.31 \text{ \AA}$) while the N_{TDA} simultaneously H-bonds to the flanking pyrrole (Scheme 2). This unexpected observation, which demonstrates that aligned squares can form even without the full electron donation of the participating N_{TDA} , lends additional support against orbital or electrostatically driven explanations for 2S–2N square interactions.

Conclusion

A detailed crystal structure investigation of the interactions of 2,1,3-benzothiadiazoles was performed to understand the nature of figurative 2S–2N square interactions and the inter-/intramolecular forces that compete with it. Our CSD study revealed 2S–2N square interactions in benzothiadiazole dimers with sub-van der Waals $N \cdots S$ distances for a wide array of derivatives. A model for the square geometry was created to characterize the angle variability of the dimer trajectory, showing a strong correlation between sub-van der Waals $N \cdots S$ distances and highly aligned square dimers (angles approaching $\phi \approx 0^\circ$, $\theta \approx 90^\circ$, and $\Phi \approx 180^\circ$).

To investigate substituent effects, library **1b–9h** containing 31 2,1,3-benzothiadiazole compounds with small, non-aromatic substituents was assembled and analyzed systematically. Four general interaction types were determined and are summarized as follows (see also Figure S13 for a visual summary):

- In the 2S–2N square dimer class, 71 % compounds of **1b–9h** have $N \cdots S$ contacts $< 4.0 \text{ \AA}$, with 18 dimers considered as $CB_{ave} \leq 3.35 \text{ \AA}$ and $\theta_{ave} = 68.1\text{--}78.6^\circ$, $\phi_{ave} = 0.0\text{--}23.4^\circ$, $\Phi_{ave} = 162.8\text{--}179.1^\circ$.

- In the halogenated compound class, new $X \cdots X/S/N$ motifs are abundant; they vary greatly depending on the halide position on the benzo ring and the nature of X. While squares coexist alongside 4-X interactions (**2a**), halogen-bonding type $X \cdots S/N$ motifs dominate for 5,6-halogenated systems (**5c–5e**), followed by $X \cdots X$ contacts for 4,7-halogenation (**6a–6b**, **9f**, **9h**). Good evidence is obtained to propose that halogen bonding interactions outcompete the chalcogen-bonding interactions in the 2S–2N squares. Fluorinated structures are exceptional as this hard halogen does not engage in halogen-bonding interactions. Here, close $F \cdots F$ contacts in unison with highly aligned squares (**5b**, **7**, **8**, **9b–9e**) dominate.
- In the $S \cdots S$ interaction class, a diversity of geometric alignments is observed, in agreement with the theoretically predicted predominance of dispersion interactions in these contacts. Five compounds (**3b**, **4d**, **5a**, **5d**, **6c**) contain sub-van der Waals $S \cdots S$, with the alignment of the S-atoms in the structures of **3b** and **5a** mimicking chalcogen-bonding type $Met \cdots Met$ interactions seen in kinases and in $Met_{protein-1,2,5}$ -thiazole complexes.
- With NH hydrogen-bond donor substituents on the benzothiadiazole, structural analysis revealed that highly aligned 2S–2N square interactions can compete with $NH \cdots N$ attractions (**2d**, FEBYAO, **REVYAT**, **9e**), and even occur simultaneously on the same N_{TDA} (**REVYAT**).

Though 2S–2N square dimers are the most abundant interaction motif, competing forces can disrupt or coexist with them. Though the complementary $N \cdots S$ dimer contacts are accepted as being weakly attractive,^[51] we found no correlation between purely electrostatic $N \cdots S$ contributions and contact distance or orientation angle. Structural evidence of $N \cdots S$ orbital delocalization effects ($n \rightarrow \sigma^*$) are also not clearly observed. Sub-van der Waals, highly aligned squares can form even when the donor N_{TDA} is occupied by hydrogen-bonding. Finally, no correlation is observed between favorably-aligned molecular dipoles and squares.

We express caution when attempting to generalize a singular, dominating attractive force for all sulfur interactions. In the absence of a high-level energy decomposition analysis of **1–9**, the chalcogenadiazole ab initio work by Tsuzuki et al.^[51] pro-

vides useful insights. In that study, the largest contribution energy for dimerization varies, depending on the chalcogen, being predominantly electrostatics for Te and Se, whereas dispersion for S. In all cases, the orbital-orbital contributions are repulsive. We anticipate a similar gradient of attractive contributions (E_{esr} , E_{indr} , E_{disr} etc.) in 1–9, depending on how substituents tune the local environment of sulfur.

Despite the complex energetic origin of the interaction, the 2S–2N square dimer presents a well-defined non-covalent interaction motif in the solid state. The studied set of compounds shows the scope of the interaction and can act as a design guideline for the use of the benzothiadiazole 2S–2N square motif in supramolecular chemistry and crystal engineering.

Experimental Section

General information: The crystallographic data for library 1a–9h and compound 10 were collected from various sources. Compounds 9f, 9h, and 10 are new compounds and their synthesis, characterization and crystallographic data are provided in the Supporting Information. Compounds 2a,^[127] 2b,^[128] 2c,^[129] 3b,^[130] 4a,^[131] 4b,^[132] 4c,^[133] 4d,^[134] 5a,^[64] 5b,^[60] 5c,^[68] 5d,^[135] 5e, and 7 were obtained commercially. These compounds were reported previously (except for 5e and 7), without crystallographic characterization. The crystals were grown or used as received, and reported for the first time in this report (see Supporting Information). Compounds 1a (BEOXAZ),^[85] 1b (BETHAZO1),^[86] 1c (BESEAZ),^[88] 1d (DEBHEY),^[81] 2d (KODXEI),^[92] 2e (KODXOS),^[92] 3a (IKUYUK),^[108] 4e (GINTII),^[93] 6a (ESUYEW),^[110] 6b (MOPHO),^[111] 6c (XOQBK),^[86] 8 (ZUFKIWI),^[94] 9a (NABRIU),^[109] 9b (NABROA),^[94] 9c (NABRAM),^[94] 9d (NABREQ),^[94] 9e (NABRUG),^[94] and 9g (JUYSONO1)^[113] are previously reported compounds and their crystallographic data are available free of charge from the Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/structures.^[136]

Computational details: Calculations were performed using Gaussian 09 on the Euler Cluster of ETH Zürich using the dispersion corrected B97D3/aug-cc-pvtz method.^[103,137] On iodine atoms, the LANL2DZ basis set was used. Basis sets from Gaussian internal library were used. Molecules were positioned in the XY-coordinate plane with the sulfur pointing in the +X direction. Optimized structures were used for the calculation of dipole, or quadrupole moments and for visualization. Further details are provided in the Supporting Information.

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Conflict of interest

The authors declare no conflict of interest.

Keywords: 2,1,3-benzothiadiazole • 2S–2N square • chalcogen bonding • sulfur • X-ray crystallography

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