Supramolecular Chemistry

Resonance Assisted Chalcogen Bonding as a New Synthon in the Design of Dyes

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Dedicated to Professor Roberta Bertani on the occasion of her 65th birthday

Abstract: ■■please provide academic title for each author■■Intramolecular chalcogen bonding in arylhydrazones of sulfamethizole is strengthened by conjugation in the π-system of a noncovalent five-membered ring. The S···O distance in the sulfamethizole moiety of these compounds ranges from 2.698(3) to 2.806(15) Å, which indicates its strong dependence on the attached arylhydrazone fragments. Information on the nature of the intramolecular chalcogen bond was afforded by DFT calculations.

Inter- and intramolecular noncovalent interactions (hydrogen, halogen, chalcogen, pnictogen, and tetrel bonds, as well as cation–π, anion–π, π–π stacking, n–π*, agostic, anagostic, dispersion-driven interactions etc.) play a crucial role in synthesis and catalysis, crystal engineering, molecular recognition, drug delivery and structural organization of biomolecules, design/decoration of materials, and many other phenomena.[1–11] In the palette of weak bonds, the recently explored chalcogen bonding (ChB)[11–17] has received a particular attention in view of its *directionality, hydrophobicity, tunability, and multiplicity.* These properties have successfully been utilized in catalysis,[2b,18–21] crystal engineering,[13] anion binding and transport, capsule formation.[22–25] Similar to the hydrogen bonds,[5,6] the ChBs can be classified into some subclasses. Other than the conventional (and neutral) chalcogen bond (Ch···D, D = donor of electron density), evidences have been reported of negative charge-assisted chalcogen bond (Ch···D$^-$), positive charge-assisted chalcogen bond (Element$^+$–Ch···D), and resonance assisted chalcogen bond (**RAChB**).[11,26] Following the concept of resonance assisted hydrogen bond,[5] RAChB is usually treated as a chalcogen bond strengthened by conjugation in a π-system due to electron (charge) delocalization or favorable rearrangement of charge distribution in the molecular system. Despite the contribution of resonance in H-bond energy and the nature and mechanism of the bonding in these systems are under intensive debates,[27] this general concept (applying also to other noncovalent interactions) is a useful tool for the description of the bonding of this type. Intramolecular RAChB was only theoretically highlighted,[28] in contrast to other ChB subclasses. But an analyses of the Cambridge Structural Database (CSD)[29] shows that intramolecular S···O ChBs forming 5-membered arrangements are particularly short and directional when a conjugated π-system bridges the sulfur and oxygen atoms (the ChB donor and acceptor sites). Compounds with Refcodes BPTSTZ, BISGIT, BESNUI are prototype examples of this situation in sulfur systems (Scheme 1). The neutral and zwitterionic limit forms (**N-LF** and **Z-LF**) of the resonating π-system bridging sulfur and oxygen are represented for BPTSTZ in order to point out an elementary explanation of the short S···O ChBs in these compounds. The attraction between the ChB donor and acceptor sites in **Z-LF** is much stronger than in **N-LF** and the contribution of **Z-LF** to the real structure of this compound may be the cause of the presence of a short S···O ChB in its crystal. A remarkably short S···O separation is similarly observed also in BISGIT and BESNUI and can be considered a fingerprint of any RAChBs. If no zwitterionic limit form can be written for a compound, the intramolecular S···O ChB that it forms becomes longer, sometimes even longer than the sum of van der Waals radii of oxygen and sulfur (3.32 Å)[30] (and it can be assumed that no ChB is present). This is the case when the N(sp^2) atoms enabling for conjugation in the π-systems of the chalcogen bonded five-membered arrangements is substituted by an N(sp^3) atom (e.g., AJULUM, IPAQUN, POXYUY in Scheme 1), an S atom (e.g., SAPHUN), or a CH_2 group (e.g., NUDSEL and NIXHIL).

Herein, we report experimental and theoretical evidences that a RAChB similar to those described above is present in sulfamethizole (**SU**) (Scheme 2a), a sulfonamide antibiotic. The solubility and other properties of **SU** derivatives are strongly

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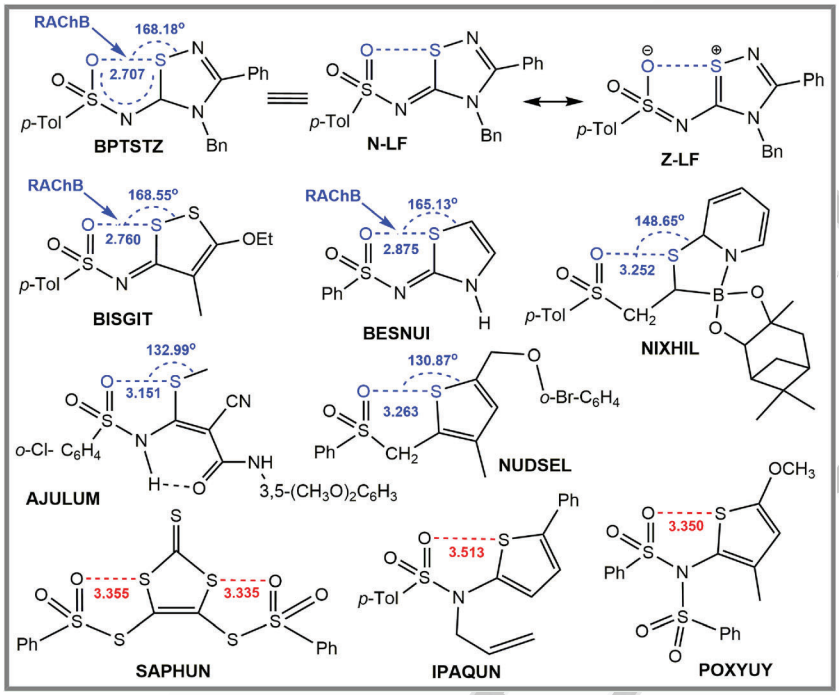
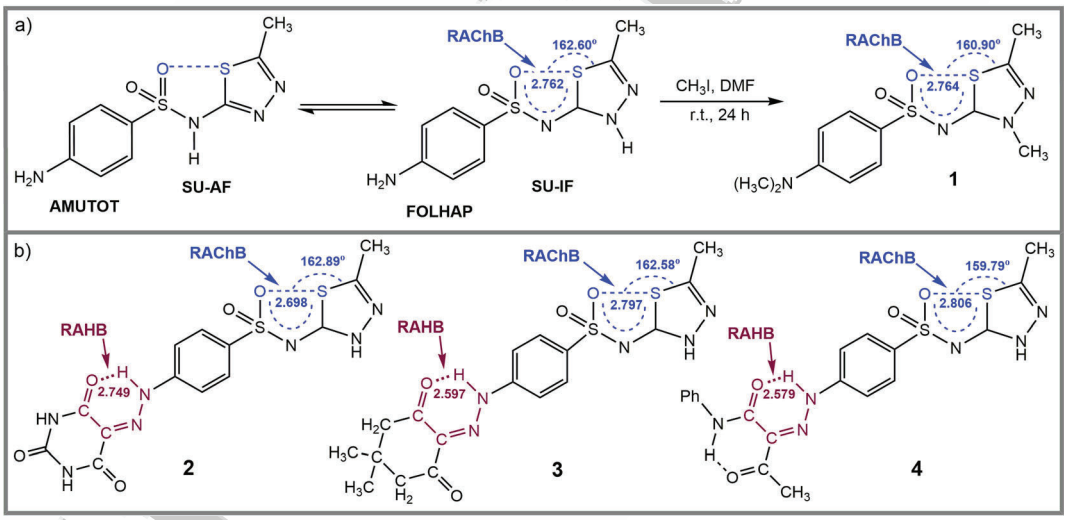


Scheme 1. Structurally related compounds from CSD where a sulfur atom may act as ChB donor. S···O separations (in Å) and C/S/N–S···O angles are in blue for RAChBs and other ChBs, in red when S···O distances are longer than the sum of van der Waals radii of sulfur and oxygen. Refcodes are also reported.



Scheme 2. a) Sulfamethizole (**SU**) and its methylation product at the thiaciazole ring **1**. S···O separation (in Å) and C–S···O angles of the RAChBs are indicated. b) Arylhydrazone derivatives **2**–**4** of sulfamethizole (**SU**). Some geometrical features of RAChBs (blue) and RAHBs (violet) are indicated.

dependent on the attached functional group(s),[31–33] which typically provide multiple noncovalent bond donor or acceptor sites. Thus, decorating **SU** structure with tailored functionalities (containing noncovalent bond donor or acceptor centers) can be a pivotal strategy to control and tune its properties. Here, we describe also that on **SU** functionalization with active methylene compounds, arylhydrazone **2**–**4** are obtained and these derivatives show the presence of RAChB as well as a resonance assisted hydrogen bonding (RAHB) (Scheme 2b). The relationship between S···O and N···O distances in chalcogen bonded and hydrogen bonded arrangements of **2**–**4** are discussed.

In [D_6]DMSO and in CD_3CN ^1H and ^{13}C spectra of **SU** show the presence (at 10, 25 and 40 °C) of only one set of peaks, namely one tautomeric form or an equilibrium between different forms which is rapid at the NMR timescale (Figures S1–S4 in the Supporting Information). Differently, crystal structures of both *amido* (AMUTOT)[34] and *imido* (FOLHAP)[35] forms have been claimed (Scheme 2a, **SU-AF** and **SU-IF**). The S···O separation is shorter and the C–S···O angle is closer to linearity in the

imido form than in the amido form, consistent with the presence of a RAChB in the former one, namely with the importance of π-system conjugation in determining the geometric features of ChB in 5-membered arrangements. Theoretical calculations confirm a conjugated π-system in the imido form (see below).

It may be worth observing that while the structural parameters of AMUTOT and FOLHAP are quite similar and their undoubted assignment to different prototropic forms might be questioned, the differences in the geometric features of the C–S···O supramolecular synthon are consistent with the claimed tautomeric forms. The relevance of π-system conjugation in **SU-IF** was confirmed by methylation with CH_3I (Scheme 2a). Both $^1H/^{13}C$ NMR (Figure S5 in the Supporting Information) and X-ray analysis prove that methylation occurs at the thiadiazole ring and the (*Z*)-*N*-(3,5-dimethyl-1,3,4-thiadiazol-2(3*H*)-ylidene)-4-(dimethylamino)benzenesulfonamide (**1**) is formed. Also in this compound a RAChB is present, as indicated by the length and directionality of the C–S···O contact (Scheme 2a).

Our interest in developing hydrazone dyes with diverse properties such as coordination ability, sensing, biological activity, and so on,[6,8] led us to synthesize arylhydrazones **2**–**4** of **SU** (see the Supporting Information for their synthesis and characterization). An interesting and unique feature in these systems is that they possess not only the resonance assisted hydrogen bonding (RAHB) synthon HN–N=C–C=O,[6] but, in the *imido* tautomeric form, they possess also a five-membered RAChB synthon (SC=*N*-S=O) (Scheme 2b). As in already reported hydrazones,[6] the NH protons of **2**–**4** involved in RAHB were observed at low field chemical shift (14.10, 14.64 and 13.31 ppm, respectively, see Figures S6–S8 in the Supporting Information). There is no trend between δ_{NH} and the N···O distance (Scheme 2b).

Depending on the electron donor character of the attached arylhydrazone moiety, the S···O ChB distance in the sulfamethizole fragment of **2**–**4** can decrease (in **2**) or increase (in **3** and **4**) with respect to **SU**. As can be seen from Scheme 2b, the N···O distance in RAHB decreases from 2.749(4) to 2.579(2) Å as the S···O distance increases from 2.698(3) to 2.806(15) Å in the RAChB synthon (Scheme 2b, Figure S9). This trend demonstrates that the RAChB becomes weaker as we move from a stronger electron donor arylhydrazone moiety to a weaker one.

With the aim of understanding the nature of the ChBs in the compounds under study, we performed theoretical DFT calculations of **2**–**4** as well as of **SU-AF** and **SU-IF** (see Supporting Information for the computational details). The S···O distances calculated for the isolated molecules of **SU-IF**, **3** and **4** in the gas phase (M06-2X/Def2-TZVP) are significantly shorter than the experimental X-ray values (Table 1). This suggests that intermolecular interactions existing in the solid state and overall crystal packing requirements of these species play a significant role in determining the length of S···O bonding. Sensitivity of the S···O distance to the crystal packing is evidenced by the significantly different *d*(S···O) values for two non-equivalent units in (**SU**·H)$_2$·SO_4 (2.816 and 2.753 Å).[36,37] The calculated and experimental values for **2** are similar.

Table 1. The calculated parameters of **SU-AF**, **SU-IF** and **2**–**4**.

	SU-AF	SU-IF	2	3	4
$d(S\cdots O)_{exp}$ [a]		2.762[b]	2.698	2.797	2.806
$d(S\cdots O)_{theor}$ [a]	2.975	2.725	2.712	2.718	2.716
ρ_b [c]	0.013	0.020	0.021	0.020	0.021
$\nabla^2\rho_b$ [d]	0.051	0.077	0.079	0.078	0.078
H_b [e]	0.002	0.002	0.002	0.002	0.002
λ_2 [f]	−0.005	−0.014	−0.015	−0.014	−0.014
E_{id} [g]	−1.3	5.2	5.9	5.6	5.5
$E_{E/Vb}$ [h]	2.6	4.2	4.3	4.3	4.3
E_{od}**II**−E_{od}**I** [i]	1.83	1.83			
$E(2)$ [j] LP(O)→σ*(S–C)	1.15	4.08	4.43	3.91	3.93

[a] Experimental and calculated internuclear S···O distance (in Å). [b] Ref. [33]. [c] Electron density at $BCP_{S\cdots O}$ (in au). [d] Laplacian at $BCP_{S\cdots O}$ (in au). [e] Total energy density at $BCP_{S\cdots O}$ (in au). [f] Second eigenvalue of the Hessian matrix at $BCP_{S\cdots O}$ (in au). [g] The S···O bond dissociation energy (in kcal mol^{-1}) estimated using the isodesmic reactions method. [h] The S···O bond dissociation energy (in kcal mol^{-1}) estimated using formula $E_{E/Vb} = -0.375V_b + 0.5$ derived for the selenium bonds[38] (V_b is potential energy density at $BCP_{S\cdots O}$). [i] Difference of the vertical dissociation energy of the oxygen atom for **SU-IF** and **SU-AF** (in kcal mol^{-1}). [j] Second order perturbation energy (in kcal mol^{-1}).

The S···O distance calculated for **SU-AF** is significantly longer than that for **SU-IF** and the corresponding calculated values for **2**–**4** are similar to **SU-IF**; all values being smaller than the sum of van der Waals radii of O and S (3.32 Å).[30] In agreement with the computational results, a comparison of experimental S···O distances in five membered arrangements containing imido and amido moieties (i.e., containing the O=S–N=C–S and O=S–N(X)–C–S fragments (X = H, C, S), respectively) reveal that the former separations are significantly shorter than the latter (2.698–2.875 Å vs. 3.151–3.513 Å, Scheme 1, Table 1).

The topological analysis of the electron density distribution showed the existence of a bond critical point (BCP) for the S···O contact in the isolated molecules of all structures (Figures 1A,B and S12 in Supporting Information). The low value of the electron density at the BCP (ρ_b), the positive values of the electron density Laplacian ($\nabla^2\rho_b$), and the total energy density (H_b) in **SU-AF** (Table 1) are typical for very weak noncovalent interactions. The $BCP_{S\cdots O}$ properties in **SU-IF** and **2**–**4** are similar and indicate a stronger interaction compared to **SU-AF**. The negative sign of the second eigenvalue of the Hessian matrix (λ_2) reveals the bonding nature of the S···O interaction in all structures and this is further illustrated by the non-covalent interaction (NCI) analysis (Figure 1C and Figure S13 in Supporting Information).

The ChB dissociation energy in **SU-AF**, estimated using the isodesmic reactions method (E_{id}, see Supporting Information for details), is slightly negative while that for **SU-IF** and **2**–**4** is clearly positive providing differences of E_{id} for **SU-AF** and **SU-IF** or **2**–**4** which span in the range 6.50–7.19 kcal mol^{-1} (Table 1). The difference of the vertical dissociation energy of the oxygen atom participating in the ChB (E_{od}) for **SU-IF** and **SU-AF** is positive (1.83 kcal mol^{-1}). All this clearly indicates a stronger interaction in **SU-IF** and **2**–**4** compared to **SU-AF** thanks to the effect of resonance assistance.

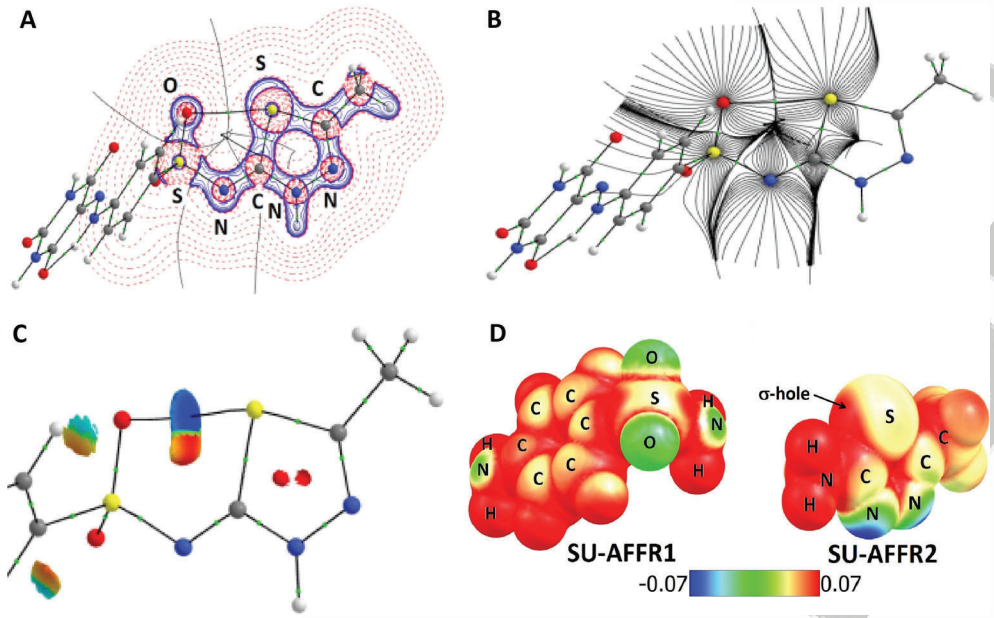


Figure 1. Contour line diagram of the Laplacian distribution $\nabla^2\rho(r)$, bond paths, zero flux surfaces (A), atomic basin paths projected on the OSNCS plane (B), the sign$(\lambda_2)\rho(r)$ function mapped on the reduced density gradient (s) isosurface with s = 0.5 a.u., cutoff of the maximum electron density 0.07 a.u. and blue-cyan-green-yellow-red color scale $-0.02 < \text{sign}(\lambda_2)\rho(r) < 0.02$ (C) and ESP distribution mapped on the 1× and 1.1× van der Waals surfaces for **SU-AFFR1** and **SU-AFFR2**, respectively (D).

The Natural Bond Orbitals (NBO) analysis demonstrates the existence of some charge transfer from the oxygen atom lone pair(s) to the σ*(S–C) orbital. The second order perturbation energy, E(2), for the LP(O)→σ*(S–C) transition is very low in **SU-AF** (1.15 kcal mol^{-1}) but it is 3.4–3.9 times higher in **SU-IF** and **2**–**4** (Table 1).

Analysis of the electrostatic potential (ESP) distribution for the optimized fragments **SU-AFFR1** and **AU-AFFR2** derived from **SU-AF** upon the C–N or S–N bond cleavage and with the exocyclic nitrogen atoms saturated by hydrogens reveals the σ-hole near the S atom at the extension of the C–S bond in **SU-AFFR2** and the region with negative ESP around the O atom in **SU-AFFR1** (Figure 1 D). A similar situation was found for fragments derived from the **SU-IF** structures and **2**–**4** (Figure S14 in the Supporting Information). Thus, it seems that both electrostatic and hypervalent mechanisms contribute to the formation of the ChB in the structures under investigation.

To analyze the effect of the ChB on electron delocalization, two model structures **M1** and **M2** with and without chalcogen bond (Figure 2) were calculated (see Supporting Information for details). The calculated bond lengths, Wiberg bond indices and delocalization indices indicate that the electron delocalization in the fragment O=S–N=C is higher in **M1** than in **M2**. The NBO atomic charges at the terminal O and S atoms of the fragment O=S–N=C–S are higher in absolute value in **M1** than in **M2** indicating the increase of polarization upon the S···O bond formation.

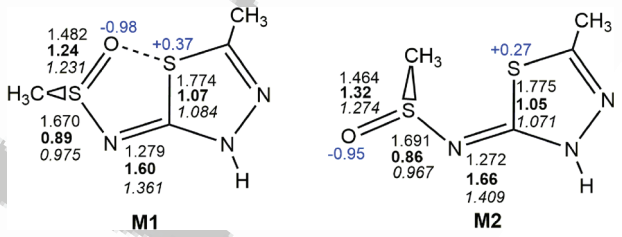


Figure 2. Calculated model structures with (**M1**) and without (**M2**) chalcogen bond. Bond lengths, NBO atomic charges (plain text), Wiberg bond indices (bold) and delocalization indices (italic) are indicated.

Finally, it is worth mentioning that the experimental intermolecular distances O(3)···O(5′) (in **2**) and O(3)···O(3′) (in **3**) (3.004(4) and 2.976(4) Å, respectively, Figure S10), are shorter than the sum of the van der Waals radii of the interacting atoms (3.04 Å).[30] However, these distances are forced to be relatively short due to strong intermolecular N–H···O H-bonds and probably they cannot be considered as ChBs resulting from attractive O···O interaction. This conclusion was confirmed by theoretical calculations (see Supporting Information for details).

In summary, we have synthesized and characterized by single-crystal X-ray analyses three new arylhydrazone dyes **2**–**4** in order to see the effect of attached substituents on the aromatic moiety of the molecule for highlighting the role of the RAChB synthon in the structural features of these dyes. A significant influence of substituents on the RAHB and RAChB is observed, that is, the N(H)···O distance decreases as the S···O distance increases in these synthons. The nature of the intramolecular ChB in **2**–**4** as well as in **SU-AF** and **SU-IF** was interpreted with theoretical DFT calculations, which revealed an effect of the resonance assistance on the strength of the ChB. This study is the first experimental report on a RAChB synthon and its relevance may be related to the fact it experimentally confirms similarities between hydrogen bond and chalcogen bond.[5,6,39,40]

Experimental Section

Crystallographic data: Deposition numbers 1893869, 1893870, 1893871 and 1978976 contain the supplementary crystallographic data for this paper. These data are provided free of charge by the joint Cambridge Crystallographic Data Centre and Fachinformationszentrum Karlsruhe Access Structures service.

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Conflict of interest

The authors declare no conflict of interest.

Keywords: chalcogen bonds · noncovalent interactions · synthesis

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COMMUNICATION

Supramolecular Chemistry

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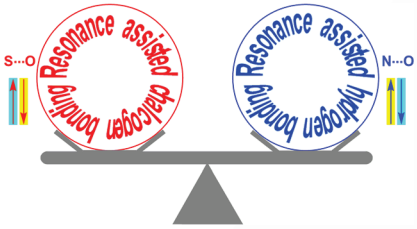
Resonance Assisted Chalcogen Bonding as a New Synthon in the Design of Dyes



A new synthon: Three new arylhydrazone dyes have been synthesized and characterized by single-crystal X-ray diffraction to investigate the effect of attached substituents on the aromatic moiety of the molecules, highlighting the role of the resonance assisted chalcogen bond synthon in the structural features of these dyes.■■ok?■■

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