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Participation of S and Se in hydrogen and chalcogen bonds

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This article reviews the history and the current state of knowledge concerning the ability of the heavy chalcogen atoms S and Se, and to some extent Te, to participate in a H-bond as either proton donor or acceptor. These atoms are nearly as effective proton acceptors as O, and only slightly weaker as donor. They can also participate in chalcogen bonds where they act as electron acceptors from a nucleophile. These bonds rapidly strengthen as the chalcogen atom becomes larger: S < Se < Te, or if they are surrounded by electron-withdrawing substituents, and can exceed that of many types of H-bonds. Experimental and computational evidence indicates that both H-bonds and chalcogen bonds involving S and Se occur widely in chemical and biological systems, and play an active role in structure and function.

Introduction

The past few years have witnessed a dramatic expansion in the scope of the hydrogen bond (HB). After its early conception as an interaction where H bridges a pair of highly electronegative atoms O, N, and F, this criterion has been relaxed to encompass a score of other atoms, coming from other rows and columns of the periodic table. This expansion has generated a rethinking of the original concept, even motivating a redefinition of this bond by the IUPAC.[1] Among the atoms added to this listing are the heavier chalcogens S, Se, and Te. Despite this progress, the participation of these atoms in HBs has not yet been fully appreciated.

At the same time, an entirely new family of noncovalent bonds has been rediscovered. These bonds are closely related to the HB, but the central proton is replaced by any of a set of more electronegative atoms. Among these are the chalcogen atoms, which provide this interaction with its eponymous appellation as the chalcogen bond (ChB). Perhaps because of the relative newness of this idea, coupled with what might appear at first blush to be its counterintuitive nature, the ChB has not yet enjoyed the same widespread acceptance and understanding as has the HB, even though it has also been defined by IUPAC.[2] The narrative below represents an attempt to summarize the development and current state of knowledge concerning the participation of the heavier chalcogen atoms in both HBs and ChBs, and how such bonds impact structure and function in chemistry.

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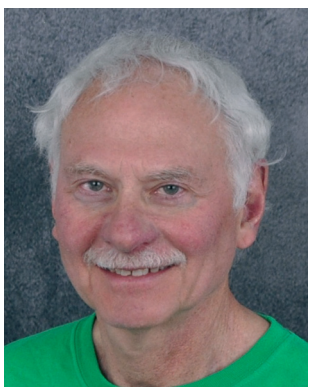
Hydrogen bonds

Perhaps the first attempt to quantitatively evaluate S as a H-bond participant arose in the context of an early and understandably fairly primitive CNDO calculation[3] of the H_2S dimer. This semiempirical method vastly overestimated the interaction energy of the linear dimer at more than 20 kcal mol^{-1}. *Ab initio* results were more reasonable, at less than 1 kcal mol^{-1}, but still an underestimate as no electron correlation was considered. These results led to forgoing the



After attaining his BS degree in chemistry at City College of New York in 1972, Steve Scheiner conducted molecular orbital studies of enzyme activity under the supervision of William N. Lipscomb at Harvard University, completing his PhD in 1976. Following a two-year Weizmann Postdoctoral Fellowship at Ohio State University, he began his independent career on the faculty of Southern Illinois University, where his research focused on H-bonds and the proton transfers that occur within, in both the ground and excited states. In 2000, he moved to his current position at Utah State University, where his interests broadened into noncovalent bonds in a more general sense, including the full spectrum of halogen, chalcogen, pnicogen, tetrel, triel, and aerogen bonds.

use of semiempirical methods in favor of those of *ab initio* type in later calculations of this issue. An early set of such computations considered SH_2 as proton acceptor from FH[4,5] and found its structure to be much like that in $FH\cdots OH_2$. SH_2 could also accept a proton from cations H_3O^+ or NH_4^+ in what might be categorized as a strong H-bond[6] of more than 20 kcal mol^{-1}, or from another S in the case of SH_3^+ (ref. 7) which is only slightly weaker. A set of calculations in 1996 (ref. 8) found S to be a weaker proton acceptor than analogous O bases. This particular question as to the relative strength of S as compared to O as proton acceptors has been a recurring theme over the years.

The following overview takes account of the fact that S, as well as Se and Te, can serve as both proton acceptor and donor in HBs. In so much as these two roles can be separated, the first section focuses on its accepting ability, followed by YH as donor. The narrative below is organized in an approximate chronological time frame to provide the reader a picture as to how our understanding of S and Se as H-bond participants has evolved over time. Most of the results described below are taken from papers published since 2000 or thereabouts.

Proton acceptor

The turn of the millennium saw extensive study of S as proton acceptor *via* quantum chemistry. S engages in a strong HB[9] with a NH group of $(\mu\text{-}\eta^1\text{-}S_2)_3$(triazacyclononane)$_2Fe_2S_6$, observations supported by DFT calculations. Methanethiol formed dimers and trimers through the intermediacy of $SH\cdots S$ H-bonds[10] with trimer interaction energies of some 7 kcal mol^{-1}. The computed S–H red shifts bolster the contention that these sorts of interactions are indeed HB. The binding energy of the $OH\cdots S$ H-bond in methanol–dimethylsulfide was computed to be 5.5 kcal mol^{-1}, only slightly lower than 6.0 for the $OH\cdots O$ bond.[11] Wennmohs *et al.*[12] considered the ability of the S atom of dimethylsulfide to accept a proton from an OH group. The binding energies were reasonably high, as much as 5.5 kcal mol^{-1} for methanol, which was only slightly smaller than the same quantity for the $OH\cdots O$ analog. When paired with HNO_3 as proton donor, dimethyl sulfide was only slightly weaker as proton acceptor than dimethylether, 7.4 *vs.* 8.9 kcal mol^{-1}, both inducing very similar red shifts to the O–H stretching frequency.[13]

Calculations by Freitas and Galembeck suggested that S could accept a proton even from as weak a donor as a C–H bond,[14] with their presence verified by both NBO and AIM analyses. S can function in place of O in terms of proton acceptor within the context of an intramolecular H-bond.[15] Dimethyl sulfide and ether were the point of comparison for S *vs.* O as proton acceptor[16] with a series of different proton donors. The former engages in complexes only marginally weaker than the latter. In both cases, it is the electrostatic component that plays the largest role, supplemented by induction and dispersion, providing another indicator of similarity. Other points of similarity arise in terms of AIM and NBO analyses. Calculations by the Chakraborty group[17] showed both SH_2 and SeH_2 can accept protons from a donor, whether the latter is neutral or positively charged, with a full range of HB induced perturbations such as O–H stretching and red shift within the donor. Biswal's group[18] has expanded the range of proton donors to M–H groups where M refers to a metal atom Mn, Fe, or Co, with HB energies up to 7 kcal mol^{-1}. These authors stressed the importance of the high polarizability of these chalcogen atoms and the enlarged dispersion attractive force to which that leads.

Of course, assessment of the ability of the S and Se atoms to participate in HBs has not been limited to quantum calculations. As one avenue, matrix isolation IR spectroscopy has provided a fruitful means of considering this question. An early application emerged in 1991 (ref. 19) which paired SO_2 with a series of dialkyl sulfides. A later example from 2000 (ref. 20) showed that both dimethyldisulfide and H_2S could interact with HNO_3 *via* sulfur HB. Biswal and Wategaonkar[21] evaluated the ability of the divalent S of dimethyl sulfide to accept a proton from indole by jet-cooled R2PI, RIDIRS, and FDIRS spectroscopy, with supplementary analysis from quantum calculations. They found that the HB could be attributed to both dispersion and electrostatic forces. They concluded that the $NH\cdots S$ interaction is stronger than $NH\cdots O$. Later measurements[22] focused on O and S within the tetrahydrofuran and tetrahydrothiophene molecules, respectively. FDIR spectra analyzed their complexes with a proton donor, and calculations provided interaction energies of 7.4 and 6.2 kcal mol^{-1} for the O and S accepting systems, respectively. Biswal, Mons, *et al.* used gas-phase IR/UV spectroscopy to assess the strength of $NH\cdots S$ H-bonds related to methionine[23] within two dipeptides. These $NH\cdots S$ HBs were competitive with the classic $NH\cdots O{=}C$ bonds that are so characteristic of proteins. Analysis of available protein structures found 24% of methionine groups participate in such bonds, when both chemical elements are present.

Biswal's group later continued assessment of S as proton acceptor,[24] this time with amide NH as donor; the S atom was present on the methionine and cysteine side chains. The $NH\cdots S$ H-bonds were found to be as strong as those with O as acceptor, as measured by quantum calculations and gas-phase IR/UV double resonance spectra. Calculated $NH\cdots S$ binding energies lay in the 6.7–11.7 kcal mol^{-1} range. The authors concluded that one must look beyond simply acceptor atom electronegativity in predicting HB strengths. Contemporary work[25] focused on the $OH\cdots S$ H-bonds with H_2S pairing with a series of phenols, where the researchers were able to extract a dissociation energy from ZEKE-PE spectra. These quantities were equal to 3.1 and 3.2 kcal mol^{-1} for phenol and cresol, respectively, which compared nicely with 3.3 and 3.2 kcal mol^{-1} computed at the MP2/CBS level.

The Kjaergaard group[26] were able to demonstrate *via* Fourier transform infrared spectroscopic measurements, combined with quantum calculations, that in the gas phase

the NH···S H-bond is just as strong as NH···O. The systems considered utilized dimethylamine as acid, with bases dimethyl ether and dimethylsulfide. The binding energy for the NH···O bond is 3.2 kcal mol^{-1}, as compared to 3.8 kcal mol^{-1} for NH···S. Davydov *et al.* presented radiolytic cryoreduction, EPR, and electron-nuclear double resonance spectroscopic evidence[27] that the S atom on the Cys residue acts as proton acceptor from His which decreases the S→Fe donation and weakens the Fe(III)–S bond. As one result, this HB changes the primary catalytic product. Careful protein structure analysis documented that selenomethionine can accept protons from the amide group within proteins,[28] and are as strong as the conventional NH···O bonds. The authors attributed this strong binding to a combination of electronegativity, atomic charge, and polarizability. Concurrent work by this group[29] showed thioamides to be comparable to amides as proton acceptors. Experimental measurements arrived at a NH···S=C bond binding enthalpy of 7 kcal mol^{-1}. These authors went so far as to suggest that bonds of this type be added to biomolecular force fields.

Combining gas phase spectroscopy with high-level calculations Mishra *et al.*[30] reiterated the proton-accepting ability of S and Se to be comparable to that of O. Focusing on the interaction between phenol and indole with dimethyl selenide, they attributed this strength to a balance between electrostatics, polarization, and charge transfer. Laser-induced fluorescence, 2-color resonant 2-photon ionization, and fluorescence depletion by IR measurements by Wategaonkar and Bhattacherjee[31] on NH···S HBs of benzimidazole and thioethers led the authors to echo the conclusion that these bonds are comparable to their O-analogues.

Minkov and Boldyreva[32] examined the effect of high pressure on interactions involving *N*-acetyl-L-cysteine in a series of crystals where the thiol group is involved as both donor and acceptor. Unlike certain other systems where pressure induces a phase transition that switches from SH···O to SH···S, no such transition was observed here. On the other hand, increased pressure does promote a shift of acceptor from carboxyl to carbonyl. These same authors[33] looked at the effect of temperature on the SH···O H-bonds in homocysteine. Whereas cysteine crystals contain SH···S H-bonds, homocysteine is characterized by a bifurcated SH···O arrangement with two carboxylate groups.

In perhaps the simplest model of such interactions, microwave spectra of the H_2S dimer by the Arunan group[34] recently confirmed this species to be bound by a HB, with a structure much like that of the water dimer. Moreover, these authors verified the ability of quantum calculations to reproduce this sort of bond.

Proton donor

One of the earlier examinations of SH as a proton donor arose in the context of thiols in combination with aromatic π-electron donors.[35] Quantum calculations estimated HB energies of some 2.6 kcal mol^{-1}, stronger than those arising from OH or NH donors. A survey of 609 protein structures yielded 14 categories of interactions of this type, totaling 268 individual contacts. Shortly thereafter, Sherrill's group[36] pinned down the HSH–benzene interaction energy more accurately to 2.74 kcal mol^{-1} *via* CCSD(T) computations applied to a large quadruple-ζ basis set, quite similar to the same quantity for HOH as proton donor. This group went on to show[37] the similarity of the computed structure to the cysteine configurations most frequently found in crystal structures of the PDB. This sort of contact with an aromatic ring was extended shortly thereafter[38] to small clusters of H_2S with benzene, where the additional H_2S units formed chains with one another, amplifying the HB strength with the benzene by cooperativity. The enlargement of the π-system to naphthalene[39] reiterated the near identical HB energies of OH and SH as proton donor, suggesting the SH depends more on dispersion than does OH. Later work extended these analyses to other aromatic electron donors such as azulene[40] and indole-like systems.[41,42] High-level calculations in 2009 (ref. 43) echoed the earlier findings that the SH group can donate a proton to an aromatic π-system with an interaction energy on the order of 3 kcal mol^{-1}. The ability of an SH group to serve simultaneously as both proton donor and acceptor was demonstrated in 2009 (ref. 44) when H_2S was paired with SSH. Total binding energies were fairly small, only about 3 kcal mol^{-1}.

Biswal and Wategaonkar showed SH to be quite competitive with first-row OH, NH, and CH, through the auspices of LIF, R2PI, and FDIRS spectroscopy, attributed in part to the greater contribution of dispersion to second-row S molecules.[41] Recently, the proton of HSN was found capable of participating in a H-bond to various amines[45] which induce a blue shift of the S–H stretching frequency, rather unusual in the context of HBs. Both SH_2 and the SH radical can also pair with amines,[46] with SH shifting to the red as is the usual case. The radical is a slightly more potent proton donor, with binding energies as large as 5 kcal mol^{-1}. Mintz and Parks[47] applied high-level CCSD(T) calculations on a basis set extrapolated to completeness to a series of small molecules containing S in both proton donating and accepting scenarios. Interaction energies lay in the 2–3 kcal mol^{-1} range for the most part, but were as high as 6.2 kcal mol^{-1} when dimethylsulfide accepted a proton from formamide. The general pattern did not show a dramatic difference between S as proton donor *vs.* acceptor.

Grzechnik *et al.*[48] compared SH with OH specifically in terms of their proton donation to NH_3, applying both matrix isolation spectroscopy and *ab initio* calculations. Their calculated SH/OH stretching red shifts correlated quite well between these two approaches, as the calculations suggested OH to be a considerably stronger donor. The interaction energies for the OH···N and SH···N complexes were computed to be 4.5 *vs.* 1.7 kcal mol^{-1}, respectively. As further evidence of HBs in both cases, this group noted large intensifications of the OH/SH stretching band.

The ability of the H_2S molecule to donate a proton was assessed by combining this unit with both a second H_2S and a methanol molecule[49] *via* VUV ionization-detected IR-predissociation spectroscopy. The SH stretch is shifted to the red by 31 cm^{-1} in the H_2S dimer. Its complex with MeOH could in principle yield either a OH···S or SH···O configuration, but the data indicate it is the latter that is present, suggesting S to be a stronger donor than acceptor. Quantum calculations support this distinction, with computed binding energies of 1.97 *vs.* 1.61 kcal mol^{-1} for these two structures, which is admittedly a small margin. The combination where S serves as both proton donor and acceptor in the H_2S dimer is only weakly bound at 0.5 kcal mol^{-1}. This group continued this line of work,[50] pairing H_2S with diethyl ether, dibutyl ether, and 1,4-dioxane in a supersonic jet. All dimers contained a SH···O H-bond, with a red-shifted S–H stretching frequency. Computed interaction energies were between 3 and 4 kcal mol^{-1}, along with AIM and NBO evidence of the purported H-bond.

An interesting twist on SH donors arises in the context of carboxylic acids. Replacement of the OH group by SH[51] maintains the same sort of H-bond patterns in the resulting homodimers as arise in the unsubstituted systems, albeit somewhat weaker. Similar conclusions were reached in regard to salicylic acid and salicylamide and their thiol counterparts,[52] not only for intermolecular but also internal SH···O HBs. In connection with the SH···S H-bond, Mishra *et al.*[53] have examined the strength of this bond through the window of the red shift incurred by the S–H bond stretching frequency. The evaluation of 150 cm^{-1} for this quantity in a model dimer pairing 2-chlorophenol with dimethyl sulfide was attributed to this bond, and in particular to the charge transfer within it. Their survey of the PDB yielded 750 such SH···S bonds within 642 proteins considered.

A great deal of analysis of S or Se to participate in HBs has been deduced from the structures emanating from crystal diffraction studies. A 1997 survey of crystal structures[54] suggested that divalent S was a poor proton acceptor (PA). When OH and NH donors are present, less than 5% of divalent S atoms engaged in structures consistent with a HB. On the other hand, 70% of SH donors seemed capable of donating a proton, particularly to carbonyl groups. A survey in 2009 (ref. 55) detailed sulfur HBs within the context of proteins. The geometric structures of these bonds within 500 crystal structures suggested S to be a poor proton acceptor, but a better donor with a ratio of 5 : 1 for these two types. The authors believed these bonds to be integral to protein structure and regulation. Also in a biological context, Ranaghan *et al.* demonstrated experimentally that the sidechain of a Met residue has a catalytic role,[56] deduced from calculations to act by stabilizing the transition state for hydride transfer, through the intermediacy of a sulfur H-bond. *Via* analysis of the PDB, coupled with high-resolution crystallography, two-dimensional NMR, and gas-phase spectroscopy, Mishra *et al.*[57] recently observed that water molecules frequently mediate H-bonds to Se within proteins.

Chand and Biswal[58,59] have recently reviewed a good deal of data concerning numerous S and Se HBs that have appeared in the literature. They stress their importance in biological systems, and suggest means of exploiting them in other areas such as crystal engineering and superconductivity. The literature concerning the participation of S in HBs was thoroughly surveyed by Biswal in 2015 (ref. 60) who provided a compelling case for S as both proton donor and acceptor.

In summary, there would appear to be an overwhelming body of evidence, drawn from quantum calculations, crystal structures, spectroscopic data and various other sources, that Se, and particularly S, can and do involve themselves in HBs.

Chalcogen bonds

If the bridging proton of a HB is replaced by any of a series of nominally electronegative atoms, one has instead a halogen, chalcogen, pnicogen, or tetrel bond, depending upon which family of the periodic table this replacement atom falls in. The chalcogen bond (ChB) has become a staple in the list of these noncovalent interactions, to the point where it has achieved formal recognition and definition by IUPAC.[2] In a general sense, the Y chalcogen atom is typically covalently bonded to one or more electron-withdrawing substituents R. A basic atom from a nucleophile positions itself roughly along the extension of one of the R–Y covalent bonds. This basic atom approaches Y to a distance that is typically shorter than the sum of their vdW radii. It was this structural framework that was taken as a general formula by which to detect the presence of ChBs in early studies.

Crystallographic findings

The bulk of the earliest work dealing with chalcogen bonding was derived from detailed scrutiny of the structures emerging from X-ray diffraction of crystals. One such early analysis in 1977 (ref. 61) found a distinction between the approach of electrophiles and nucleophiles to S atoms in a divalent bonding environment. Whereas electrophiles approach the S some 20° from the perpendicular to the X–S-*X* plane, nucleophiles tended to approach along an extension of one of the two S–X covalent bonds. The authors applied a frontier orbital model which would have the nucleophiles interact with the LUMO of the S-molecule which can be thought of as a σ*(S–X) antibonding orbital. This idea laid the groundwork for much of the conceptual understanding of these bonds that were to come.

Another survey of crystal structures several years later[62] focused on interactions between pairs of S atoms, again using the directionality of the σ*(S–X) orbital to understand the geometric patterns. A decade later Desiraju and Nalini[63] considered 926 structures from the CSD that included a divalent S atom. The authors identified 77 structures wherein the distances were appropriately short, and angles correct for the presence of a ChB. A later crystal structure suggested Te was also capable of engaging in a ChB (ref. 64) in the context

of a four-membered $(TeN)_2$ ring. In a very recent example of this same motif, a TeNTeN rectangular arrangement is capable of forming a ChB to an alkyne π-electron donor,[65] rather than the more common lone pair. Further expanding the database, Nagao *et al.*[66] observed S···O/N ChBs in a large number of organosulfur compounds in 1998, which were partly responsible for the structures adopted by the molecule. The S atom can serve as not only electron acceptor but as donor as well, with several examples involving Cys noted the following year.[67]

This S donor was added to a growing list of carboxylate and aromatics in the next millennium[68] which witnessed an expanding body of surveys of crystal structures. One example is the influential work by Iwaoka *et al.*[69] who found an O atom had a strong predilection to approach along the backside of the C–S bond, where it could best donate charge to the σ*(SC) antibond. Later computations by this group[70] also invoked NMR to demonstrate the presence of Se···O ChBs, which help decide on a preferred conformation.

The Cozzolino group focused on organochalcogen–nitrogen heterocycles[71] in the solid state, establishing ChBs to S, Se, and Te, and then studying these systems *via* relativistic quantum chemistry. They proposed it is orbital mixing that plays a dominant role, especially the charge transfer into the chalcogen-centered antibonding orbitals. The particularly high strength of the Te ChBs places them on a par with HBs. Later work by this group[72] suggested Te ChBs could function as a promising synthon unit, echoed later by Thomas *et al.*[73] Faoro *et al.*[74] echoed the ability of Te to engage in ChBs, even with another Te as partner.

A recent search of the CSD[75] turned up a very large number of C–S···O═S/C ChBs, suggesting they are really rather common. Fanfrlík *et al.*[76] provided evidence that ChBs are not only present, but play a dominant role in the crystal packing of 2D and 3D aromatics. Nitrophenyl selenocyanate crystals studied by the Wang group[77] were stabilized by strong C–Se···O/N ChBs, as verified by thermogravimetric and differential scanning calorimetry thermogram analyses, and quantum calculations. In related applications, ChBs can be used to construct chain-like structures within a crystal as in the case of Se···N≡C bonds within organic selenocyanates[78] where as many as 15 such systems have been detailed. The S···O ChB was considered a synthon,[73] where this group of researchers evaluated its contribution to the lattice energies of a series of different crystals.

In very recent work, Dhaka *et al.*[79] focused on Se···N chalcogen bonds within cocrystals pairing a ditopic bipyridine with a ditopic Lewis acid on which each Se is connected to one or more perfluorosubstituted phenyl rings through an alkynyl group. The results indicated that adding more such phenyl groups amplifies the chalcogen bond strength. Adding to the idea that ChBs are commonplace, the S atom of the frequently used solvent DMSO engages in a chalcogen bond[80] with an oxygen of a benzoate of a dinuclear Cu(II) complex. The Aakeröy group[81] has recently demonstrated how the change from S to the larger Se can strengthen a ChB and thereby shift its balance with a HB, and thereby alter crystal structure.

Intramolecular ChBs

Observations of ChBs are not limited to those between pairs of discrete molecules, but are a common occurrence within the framework of a single molecule. One example of such an intramolecular contact arises within the structure of *N*-acetylglycine ethyl dithioester[82] where the N atom comes quite close to the S, 0.45 Å shorter than the sum of their vdW radii. The θ(CS···N) angle is within 19° of linearity, consistent again with the orientation of the antibonding σ(CS) orbital. Another intramolecular chalcogen bond was observed by Akiba *et al.*[83] who considered the attractive force to be the main factor in the conformation adopted.

Se was the focus of a study in 2002,[84] specifically with F as the electron donor. The temperature dependence of the nuclear spin coupling between Se and F was evaluated in 2-(fluoromethyl)phenylselenenyl cyanate and bis[2-(fluoromethyl)phenyl] in both CD_2Cl_2 and CD_3CN. Analysis of the data suggested the Se···F ChB might contribute on the order of 1 kcal mol^{-1}, with a strong component arising from the $n_F \rightarrow \sigma^*_{Se-X}$ orbital interaction, as determined by NBO. Other intramolecular ChBs, this time involving both S···O and S···S,[85] were instrumental in the preferred conformation of acyl(or thioacyl)aminothiadiazoles, acyl(or thioacyl)-aminooxadiazoles and related molecules.

An intramolecular ChB between S and N within the geometrical constraints that arise since they are separated by only three bonds was examined by Fraga's group[86] in the *N*-acylhydrazone cardioactive prototype LASSBio-294. IR, Raman, UV and NMR spectroscopy verified computations that this internal bond is an important component of the preferred conformation. Other systems which contain an intramolecular ChB include tris(5-methyl-[1,3,5]-dithiazinan-2-yl)stibine.[87] Calculations have shown that the stronger ChBs formed by Se as compared to S enable it to more rigidly fix the conformation of certain molecules *via* an intramolecular ChB.[88]

A recent review of the many diverse manifestations of ChBs within crystal structures was recently published by the Resnati group,[89] where the authors draw on parallels with halogen and other related noncovalent bonds. Another comprehensive survey[90] focuses on Se in particular and its potential for crystal engineering and conducting materials.

Biological implications

The quest for yet more ChBs was expanded to proteins in 1985. Reid *et al.*[91] analyzed the crystallographic data derived from 36 proteins. About half of all S atoms from cysteine and methionine residues were within 6 Å from the centroid of the aromatic ring of phenylalanine, tyrosine or tryptophan. However, unlike O or N, S prefers the edge of these rings, which the authors attributed to electrostatic factors. Other proteins were probed as well in later years such as

glutathione peroxidase[92] which yielded to NMR evidence of a Se···N chalcogen bond. Viguera and Serrano[93] found contacts between aromatic residues and Cys and Met residues in α-helical segments of polyalanine-based peptides. They used this information to infer that the S···aromatic ChBs lead to the statistic that around 50% of the S atoms are in direct contact with aromatic rings. A 1999 survey,[94] on the other hand, disputed these ideas since the minimum energy conformations observed in small molecule crystals are not observed within the protein core. Other authors[95] were also dubious of the presence of Y···Y bonds, but were more favorable toward this idea when electron-withdrawing substituents enter the picture.

At the beginning of this century, Iwaoka *et al.*[69] provided statistical data that the geometries within proteins support the idea that divalent S can engage in a chalcogen bond with O atoms. That is, the O approached the S approximately along the extension of a R–S bond where one would anticipate a σ-hole. This crystal analysis was bolstered by *ab initio* calculations on model complexes between dimethyl sulfide and several carbonyl compounds where the subunits adopted a suitable orientation and the complexation energies were some 2–3 kcal mol^{-1}. This survey was extended to proteins and found similar trends. Another study by this group[96] focused specifically on Cys and Met in 604 high-resolution heterogeneous X-ray structures, and again concluded there are ChBs present between these S atoms and nearby polar atoms, particularly within the context of α-helices. *Ab initio* calculations suggested interaction energies of roughly 3 kcal mol^{-1}. Later crystal structure analyses,[97] were coupled with *ab initio* calculations, and verified S···O ChBs. Other examples of ChBs, this time with F as electron donor, were found in a search of the PDB,[98] in a study in which an approximate energy of 1.4 kcal mol^{-1} was assigned to this quantity. A more recent survey of protein–ligand interactions in the PDB[99] notes that 23% of complexes containing a S or Se ligand feature close contacts to a basic atom. Their follow-up computations verified the presence of ChBs in these contacts.

Another set of biological systems comprising thiazole and selenazole nucleosides[100] yielded evidence of true intramolecular interactions, supported by computational evidence of net positive charges on S and Se, leading to attractive electrostatic components. The S···O ChB was considered a synthon,[73] where this group of researchers evaluated its contribution to the lattice energies of a series of different crystals. Iwaoka and Isozumi reviewed the case for ChBs involving S in both organic and biological systems in 2012,[101] and this sort of ChB mediates AdoMet recognition in lysine methyltransferase.[102] In a very recent study that combined inspection of the PDB with careful computations[103] the authors found 28 different structures in which *S*-adenosyl methionine and adenosyl selenomethionine interacted with uracil bases of RNA through the intermediacy of S and Se ChBs, respectively. These bonds were particularly strong due to the overall positive charge on the Lewis acids.

Other assorted environments

ChBs arise in a large number of diverse situations, for example within nanotubes,[104] or in tubular structures[105] where they are responsible for zigzag or ladder-type arrangements. Their presence can be employed to assist reactivity, as for example a thiol exchange reaction.[106] These bonds are of mechanistic importance: Some examples are reversible cyclization,[107] selenoenzymes,[108] glutathione peroxidase mimics,[106,109,110] glucosidase inhibitors,[111] or Se redox.[112] Other assorted phenomena[95] in which they play an instrumental role include various sorts of catalysis.[113–119] S···S bonds seem capable to direct self-assembly of fused thiophane derivatives,[120] and container assemblies[121] that persist even in aqueous solution.

An especially short Se···O ChB[122,123] was observed by FTIR in both solution and the solid state. The authors proposed a potential role of this ChB in forming the intermediate supramolecular assembly that leads to a bond cleavage mechanism. Analysis of data for acetazolamide[124] indicated the presence of an intramolecular S···O ChB ring motif, incorporating a π-hole on the S atom. Other potential applications of ChBs lie in the area of selective anion binding and transport,[125–140] or to control conformation in a scaffold that disrupts islet amyloid polypeptide fibrillation.[141] ChBs have been used as a key component in the construction of supramolecular capsules[142] incorporating 2,1,3-benzotelluradiazole and 2,1,3-benzothiadiazole. The analysis showed Te engaged in much stronger bonding than S, allowing it to form a 2Te–2N square interaction in all solvents, as confirmed by native electrospray ionization mass spectrometry. This same group[143] later surveyed the CSD and PDB, finding additional models of this square interaction involving S.

Smaller systems

Small molecules furnished another avenue to study ChBs, principally by spectroscopic means. The simplicity of these systems enables more attention to focus on the ChB, with fewer complications arising from extraneous interactions or solvent effects. In 1985 Sass and Ault[144] studied both N and O bases in N_2 matrices along with S-bearing molecules SF_4, SOF_2, and SO_2F_2. The S–F stretching frequency underwent a red shift, whose magnitude was correlated with the strength of the base. This finding was attributed to a charge transfer from the base lone pair to the dπ* orbital of S. The data also suggested that the Lewis acidity of the three S-acids diminished in the order $SF_4 > SOF_2 > SO_2F_2$. Far IR measurements were coupled with DFT calculations to verify S···O ChBs,[145] and hypothesize that vibrational perturbations could be simulated by a point charge model. Caminati's group[146] examined the high resolution rotational spectrum of the 2,2,4,4-tetrafluoro-1,3-dithietane···water complex in the gas phase, where the S atom involved in the S···O ChB is part of a four-membered S–C–S–C ring. Their accompanying quantum calculations suggested an interaction energy of some 5 kcal mol^{-1}.

Solid state NMR is rapidly becoming an important tool in studying these interactions. Bryce's group[147] examined a series of seven chalcogen-bonded cocrystals by this technique, coupled with Raman and IR spectroscopy. Red shifts of the C–Se stretching frequency on the order of 10–20 cm^{-1} were taken as evidence of a ChB. The authors found a lack of a very strong correlation between experimental and computed ^{77}Se chemical shift tensors which led them to surmise that many structural features likely influence these quantities. They were optimistic after computations on model systems showed that the ChB produces consistent and predictable effects when left to its own devices. Other work[148] led to the finding that Se and Te could serve as double electron acceptors, utilizing both of their σ-holes, leading to the proposal of such an arrangement as a synthon for crystal engineering. A similar idea of utilizing both σ-holes occurred in cocrystals of 3,4-dicyano-1,2,5-selenodiazole and 3,4-dicyano-1,2,5-telluradiazole,[149] with ChBs which persist in solution.

Within the framework of solution, the first intramolecular S···O ChB was observed by NMR data in 1995,[150] with some support arising from simple *ab initio* calculations. The next year Iwaoka and Tomoda[151] applied proton NMR to seven 2-selenobenzylamine derivatives and found evidence of Se···N ChBs. They estimated the ChB bond energies to lie in the neighborhood of 12–19 kcal mol^{-1}. Other intramolecular ChBs were noted later, this time as a Te···N type.[152] SF_4 engaged in a S···N interaction with diethylamine,[153] but it was only stable at low temperature. The binding energy was estimated by calculations to be some 3 kcal mol^{-1}. Benzotelluradiazoles are capable of engaging in a bifurcated ChB with a bidentate base, as can the S and Se analogues.[128] UV-vis, ^{1}H and ^{19}F NMR spectroscopy and nano-ESI mass spectrometry enabled estimates of the association constants of these complexes, as well as free energies in solution which were about 2 kcal mol^{-1} for a neutral base, but ranged up to as high as 7 kcal mol^{-1} for an anion like chloride. When placed in the context of the strain implicit within a 4-membered ring[154] as in 2,2,4,4-Tetrafluoro-1,3-dithiethane, the S atoms were able to maintain a ChB with a partner dimethyl ether, with a complexation energy of 3 kcal mol^{-1}.

Quantum calculations

Quantum calculations began to address the ChB issue explicitly in 1984 when Morokuma's group[155] considered $H_2NCH_2OCH_2SHX^+$ cations. Their calculations were at a low level, without inclusion of electron correlation, and led to the intriguing finding that the noncovalent intramolecular S···N attraction was enhanced by the presence of d-orbitals. The ability of S, or other atoms, to participate as electron acceptors is predicated on a σ-hole, which is in turn based on what is sometimes termed polar flattening wherein the electron density is reduced along the extension of a S–X bond. Ikuta demonstrated just this sort of polar flattening in the context of the SCH_2 molecule.[156] Additional calculations some years later[157] studied intramolecular ChBs involving S, Se, and Te, which were able to reproduce well the observed structural peculiarities of the interactions that stabilize the hypervalent T-shaped bond configuration. These interactions were found to increase in the order S < Se < Te.

Intramolecular ChBs were at the center of detailed quantum calculations[158] of β-chalcogenvinylaldehydes. The calculations suggested a strong linear correlation between the AIM bond critical point density and the strength of the bond. This relationship was important as it offers a tool by which to assess ChB strength in systems where it is inaccessible by standard quantum methods, *e.g.* intramolecular bonds. These authors considered intramolecular bonds further[159] where the ChB was found to be competitive in strength with a HB, and suggested further that resonance can play a role in ChB stabilization, just as is the case with HBs. Later calculations by the Ganguly group[160] demonstrated intramolecular ChBs from S to either O or S. S···O seemed to be marginally stronger than S···S, both in the neighborhood of 1.5 kcal mol^{-1}. Other intramolecular ChBs were studied in 2017 (ref. 161) wherein both a OR and YR group were placed proximate to one another on a naphthalene scaffold.

Other calculations considered the full range of Y atoms from O to Te,[162] partitioning the total interaction into its components *via* symmetry-adapted perturbation theory (SAPT). The authors found induction and dispersion to play key roles, while electrostatic contributions are variable. Other calculations the next year[163] expanded the scope to a larger number of systems, and at a high level of theory. The prevailing idea of lone pair → σ*(RY) charge transfer was able to qualitatively rationalize trends in many of these systems, but is not a universal factor, as both induction and dispersion are always present in large fractions.

Another set of computations in 2011 (ref. 164) compared ChBs with HBs in the context of homodimers of HYYH. The latter were generally the stronger of the two, but the former can take the lead for the heavier Se analogues. Another comparison was made[165] between ChBs and HBs as well as halogen bonds when SCS and SeCSe were paired with HOX. The calculations suggested the ChBs to be slightly weaker than the other types, and highlighted the importance of dispersion to all three. SHX, where X represents a halogen, can act either as proton donor in a HB, or as electron acceptor in a ChB. Calculations compared these two possibilities[166] and found the ChB to be preferred when X = F, equally stable for X = Cl, whereas it is the HB that is favored when X = Br.

Formaldehyde was taken as the common electron donor in a set of S···O ChBs[167] which displayed the characteristic geometric, energetic, charge transfer, and density topology features of noncovalent interactions. Sánchez-Sanz and coworkers[168] verified the greater strength of HBs, this time in the case of HTeYH dimers. Still another comparison[169] showed that substituents on the $R_2C{=}S$ molecule have opposite effects on the ChB and HB when this molecule is

paired with HCN. When compared with the tetrel bond,[170] the ChB is of the same general magnitude. CH_3SH is a molecule for which S can act as either proton donor or acceptor within a HB, but can also participate in a ChB. These various possibilities were explored by pairing this molecule with *N*-methylacetamide.[171] Most of the minima on the surface combined some of these possibilities such as the global minimum, in which S accepts a proton from a methyl group, while also accepting electrons from O in a ChB.

With SHF as the prototype electron acceptor, it was shown that this molecule could interact with either the lone pair of molecules such as H_2O or H_2CO, or with the π-systems of acetylene, ethylene, butadiene or benzene.[172] Li's group[173] examined the Se···N ChBs between F_2CSe and a series of nitrogen bases. The bond grew stronger as the base N atom changed its hybridization from sp to sp^3 and then to sp^2, not strictly along the order of basicity. The strongest such ChB paired F_2CSe with NMe_3, and amounted to 3.5 kcal mol^{-1}.

ChBs can occur in trimers as well.[174] Esrafili and Mohammadian-Sabet considered a range of SHR trimers, wherein R was one of various substituents, including halogen, cyano, C≡CH, amino, or OH.[175] The three S···S ChBs are cooperative in the sense that each S atom serves simultaneously as both electron donor and acceptor. These trimers have a cumulative interaction energy between 1 and 4 kcal mol^{-1}. This same pair of authors focused attention on bifurcated ChBs where S, Se, or Te could simultaneously interact with a pair of O donors on a bidentate donor molecule.[176] The entire dimerization energy displays the expected S < Se < Te trend, and varies up to as much as 7 kcal mol^{-1}. This same group evaluated other aspects of ChB cooperativity[177] in the context of XHS···NCHS···N(pyridine) trimers.

Other calculations delved into electron donors other than the usual lone pairs. One work showed that the π-system of an alkyne could serve as primary electron donor in a ChB to either S or Se,[178] with interaction energies as high as 5 kcal mol^{-1}. Other π-systems can serve a similar function,[179,180] such as benzene or its derivatives. The latter aromatic served as the electron source in a number of ChBs[181] with CH_2S and CH_2Se and their difluoro-, dichloro-, and dibromo-derivatives, which expanded the scope of ChBs to excited electronic states, and the way these excitations alter the electrostatic potential. A systematic set of calculations[182] of ChBs to various sorts of π-systems emphasized the influence of HOMO–LUMO energy gap and electronegativity difference within the Lewis acid upon the strength of its ChB, as well as noting the importance of orbital interactions. ChBs with π-electron donors are important for certain processes such as the control of stereoselectivity in a cycloaddition reaction.[183] The C atom of CS was shown by calculations[184] to be capable of acting as electron donor to S in a series of SHR molecules. In an unusual twist, the R–S bond of the Lewis acid elongates to the point where the SH group may be thought of as partially transferred to the CS, an issue which arose again later.

One of the salient characteristics of a HB is its directionality, in that the system is destabilized when the bridging H is moved off of the intermolecular axis. The same is true for ChBs,[185] and even more so. The calculations attributed this directionality to the angular extent of the electron density and the repulsive forces for which it is responsible. In terms of its distance dependence, the ChB dies off approximately as quickly as a HB upon being stretched.[186]

It has now come to be generally understood that the σ-hole on a chalcogen atom will be intensified by the presence of electron-withdrawing substituents on the Lewis acid. The effects of such substitutions has been demonstrated numerous times, including a systematic examination in 2012 (ref. 187) which showed the strength of the ChB formed by RHS with a base varies in the order R = CH_3 < NH_2 < CF_3 < OH < Cl < NO_2 < F. This span of R accounts for a range of interaction energies between 0.7 and 5.8 kcal mol^{-1}.

As in the case of HBs and related noncovalent bonds, pairing a Lewis acid with an anionic electron donor ramps up the strength of any ChB. One set of calculations[188] found ChB energies of as much as 55 kcal mol^{-1}. Another[132] arrived at values even as high as 78 kcal mol^{-1} for a Te···F^- interaction. On the lower end of this spectrum is the C═S···X^- ChB with energies generally below 12 kcal mol^{-1}.[189] The converse is also true, in that a cationic Lewis acid is stronger than its neutral counterpart.[190] In another example, imparting a positive charge to the S-containing Lewis acid[191] multiplies the Y···N ChB strength by a factor of between 2 and 10. On the other end of the continuum, even weak bases like dimethyl sulfide and trimethylphosphine are capable of engaging in a ChB, as shown recently[192] by the Herrebout group *via* IR with 2,2,4,4-tetrafluoro-1,3-dithietane as the S-containing acid. Their measurements provided an estimate of the ChB energy of some 3 kcal mol^{-1}. A positive charge on a Te atom enhances its catalytic activity *via* a strengthened ChB.[193]

Murray *et al.* considered the various monomers that participate in ChBs in a systematic manner[194–197] with a particular focus on the σ-holes, and how they might account for the strengths and directionality of the ChBs in which they engage. The ChBs in which S engages was taken as a means to understand the strong solvent powers of $(CH_3)_2SO$, and $(CH_3)_2SO_2$.[198]

Hypervalent Y atoms and linear molecules

Of course, S does not always occur within the framework of a R–S–R divalent atom. The see-saw shape of hypervalent SF_4 is also conducive to formation of a ChB. Chaudhary *et al.*[199] demonstrated its ability to do so with a number of pyridine bases, forming solids that are stable below −45 C. A combination of Raman spectroscopy with DFT calculations placed the base N atom in an equatorial position. Its ChB with simple amines[200] varied between 6.6 and 14.4 kcal

mol^{-1}, while heterocyclic N-bases fell squarely in the middle of this range. As it contains more than one σ-hole, SF_4 can likewise engage in more than one ChB, as in the crystal of $C_6H_{12}N_4{\cdot}2SF_4$.[201] Indeed, ChBs involving tetravalent S are rather common, as outlined[202] in a combination of a CSD survey and quantum calculations. The authors noted an intriguing trend in that a nucleophile may sometimes prefer a site opposite the more polarizable substituent rather than the one that is more electron-withdrawing. Another hypervalent setting for S is within the context of phenyl-SF_3 which adopts a see-saw shape,[203] with the phenyl group at either an apical or equatorial site, the latter being favored. The S atom is capable of engaging in two separate S···O ChBs with $-CH_2OCH_3$ substituents on the phenyl ring, which directly influence the conformation adopted by this species. Both SF_2 and its hypervalent SF_4 analogue form ChBs with a π-system with strengths between 3.3 and 6.6 kcal mol^{-1}.[204] In most of these complexes it is the SF_2 that is the stronger electrophile.

Legon's broadband microwave spectra of the SF_6 molecule with octahedral coordination[205] showed that it can engage in a ChB with NH_3. The base is situated along a C_3 axis of SF_6, and the steric crowding reduces the gas-phase dissociation energy to less than 1 kcal mol^{-1}. YF_4 engages in fairly strong ChBs with NH_3, with binding energies between 8 and 22 kcal mol^{-1}, largest for Te.[206] However, the crowded octahedral geometry of YF_6 makes any such ChB quite weak, less than 2 kcal mol^{-1}, consistent with the earlier data.[205] On the other hand, replacement of some of these six F atoms by H[206] enables much stronger binding. SeF_3H_3, for example, binds NH_3 by 7 kcal mol^{-1}. Hypervalency at a S atom can also lead to as many as three concurrent ChBs, along with three coordination bonds.[111]

There are a range of small S-bearing molecules that are linear, and present interesting possibilities for ChB formation. In most of these cases, the S engages in a double bond with its neighbor. Linear systems such as OCS, SCS, and SCSe combine with various sorts of bases to form only rather weak ChBs, on the order of only 1–2 kcal mol^{-1}.[207–209] When OCS was paired with a variety of bases,[210] binding energies in the range of 1–4 kcal mol^{-1} were calculated. OSO behaves in a like manner.[211] This particular molecule is a more effective electron acceptor than a donor, at least within the context of interactions with organometallics.[212] Later calculations explored three YCY molecules, where Y = S, Se, Te,[213] allowing each to interact with pyridazine, pyrimidine, and pyrazine. The binding order was expectedly Te > Se > S, and binding energies were computed to vary between 2 and 5 kcal mol^{-1}. Direct interaction between the Y atom and the base N was preferred over that involving the π-system of the diazine. Chirped-pulse, broadband microwave spectroscopy provided details on the structure of the dimer pairing SCS with NH_3 in the gas phase,[214] demonstrating the geometry is consistent with a S···N ChB. One of the two Y atoms of linear YCY can interact with a pair of O electron donors in a bifurcated arrangement,[215] a bonding type that involves only a single σ-hole.

Hypervalency of S does not always involve single bonds, nor do all doubly bonded S atoms reside in a linear molecule. As one example, the bent O═S═O molecule engages in a π-hole ChB with pyridine[216] with a binding energy of some 9 kcal mol^{-1}. When combined with H_2CY, SO_2 engages in various dimer geometries,[217] the most stable of which include a ChB to the O or S atom of its partner. There are other carbonyl-bearing molecules that engage in a ChB with SO_2 as well,[218] including amides and esters, and $CH_3COOCOCH_3$ and $CH_3CONHCOCH_3$.

SO_3 likewise forms a ChB with ammonia,[219] as analyzed by DFT calculations and FTIR matrix isolation spectroscopy. Electrostatic attraction is a major factor, supplemented by a polarization contribution that is nearly as large. In fact, it is possible for the S atom to engage in two ChBs with a pair of NH_3 units, one on either side. This ability of SO_3 was mirrored by Esrafili and Nurazar,[220] when paired with both N and P bases, or with H_2CY.[221] The S of SO_3 also engages in a ChB with H_2CO, or with a second SO_3 unit[222] or with CO.[223] A related molecule that engages in such bonds, with Y = S or Se, is YO_2X_2.[224] Another is SOX_2 (X = F, Cl). Its most stable dimer with a set of N-bases includes a S···N ChB,[225] with interaction energies up to as high as 6.8 kcal mol^{-1}. Another molecule in this category is YF_4 (ref. 226) which engages two NH_3 bases simultaneously. The binding energy of these trimers grows along with the size of the central Y atom. While it is not the Y atom that is itself involved in two ChBs, the electron donor can do so[227] in the context of a four-membered YNYN intermolecular ring. The ability of Y atoms to involve themselves in more than one ChB has been recently reviewed[228] in the context of both σ and π-holes.

Comparison with other noncovalent bonds

The existence of ChBs, and their fundamental similarity to other noncovalent bonds like the HB, leads to the obvious question as to how a ChB compares in strength with its sisters. Esrafili and Akhgarpour[229] made a direct comparison with pnicogen bonds in the context of dimers of XHS and PH_2X. Interaction energies were quite similar for the two sorts of bonds, regardless of the nature of the X substituents. Another work compared ChBs with halogen bonds,[230] using YOX_4 as a testbed. The results indicated the energetic superiority of chalcogen bonds. A hydroxyl group was placed on a naphthalene skeleton alongside a neighboring YH (Y = S, Se) group[231] in such a way that the two chalcogen atoms could interact directly through a ChB or a HB could form between them if the H atoms were oriented correctly. The favored orientation comprised a OH···Y HB, followed in stability by the O···Y ChB. A later study again took advantage of the naphthalene scaffold,[232] with O, S, Se, and Te in neighboring α substituent positions, and verified the presence of intramolecular ChBs. Another set of computations[233] placed the strength of ChBs intermediate between halogen and pnicogen bonds, at least with regard to interactions with a chloride anion.

Theoretical calculations and NMR experiments[135] arrived at the interesting conclusion that when both types of bonding are possible, HBs are preferred for S and Se, whereas changing to the heavier Te makes the ChB favored. With specific regard to application as catalyst,[234] the ChB is intermediate between the halogen and pnicogen bonds. Another study placed ChBs third in strength when compared to halogen and pnicogen bonds[235] in the context of 6-OZF_2-fulvene (Z = As, Sb, Se, Te, Br, and I). In a systematic comparison[236] of bonds involving third-row atoms, ChBs were found to be competitive with halogen bonds, but stronger than tetrel or pnicogen bonds. The red shift of the internal A–F stretching frequency is greatest for halogen bonds, followed in order by chalcogen > tetrel > pnicogen;[237] in fact, there is a good correlation between bond strength and other spectroscopic parameters as well, such as NMR chemical shifts.[238]

Due to its low polarizability and high electronegativity, O is seldom considered as electron acceptor within a ChB. An early work[239] had suggested the possibility of a O···O ChB in the context of aggregates of CO_2 with H_2CO, CH_3CHO, and $(CH_3)_2CO$. Varadwaj *et al.*[240] pursued this issue further in the context of OF_2 as a potential participant, made possible by the two electron-withdrawing F substituents. The authors identified the necessary σ-holes on the O, albeit the potential at that site was slightly negative. The presence of the O ChBs was verified by various theoretical means of analysis, including NBO, AIM, and NCI, and the authors went on to argue against the use of electrostatic potential as the sole arbiter of the presence of such a bond. The White group reinforced this idea soon thereafter[241] in the context of two O atoms, both bonded covalently to N.

One should also remember that the chalcogen atoms typically bear a lone pair that can in principle be donated to an electrophile. So S, Se, and Te can in principle participate in noncovalent bonds in which they serve as electron donor. This proclivity has been well documented in the case of HBs (see above), but is just as true in the context of chalcogen, halogen, *etc.* bonds. Some examples arise in the context of halogen bonds[242] where the strength of the halogen bond varies in the order H_2S < $H_2C{=}S$ < $(CH_2)_2S$. Another example concerns the $F_3CX\cdots SMe_2$ series where X represents any of Cl, Br, or I.[243] The authors concluded that S was just as strong an electron donor as would be O or a halogen. Another study suggested such X···S halogen bonds might be used in molecular design.[244] A recent work documented the ability of S to act as electron donor in tetrel bonds to Sn.[245]

Some good summaries of chalcogen bonds, their history, manifestations, and origins, have appeared in the literature recently which a reader may wish to consult for further reading.[246–252]

Illustrative examples

It might be instructive to consider finally the various ways in which S can participate in and influence noncovalent interactions with a few specific examples. Due to its relevance as a model for a peptide group the carbonyl O atom of *N*-methylacetamide (NMA) was taken as the common electron donor in the various complexes described below.[253] MeSH was the first Lewis acid to be considered, which presents several sites for bonding to a nucleophile. The first of these, presented in Fig. 1a utilizes the SH group as a proton donor within a SH···O HB. Its binding energy is 4.1 kcal mol^{-1}, the strongest of the various interactions. As an atom with moderate electronegativity, S can draw density away from the C of the methyl group, developing a σ-hole on the C which in turn permits it to form a tetrel bond (not to be confused with a trifurcated HB). However, as indicated in Fig. 1b, this bond is much weaker than the HB in Fig. 1a. The methyl group may also serve as a direct proton donor, in a CH···O HB as illustrated in Fig. 1c. This direct CH···O bond is a bit weaker

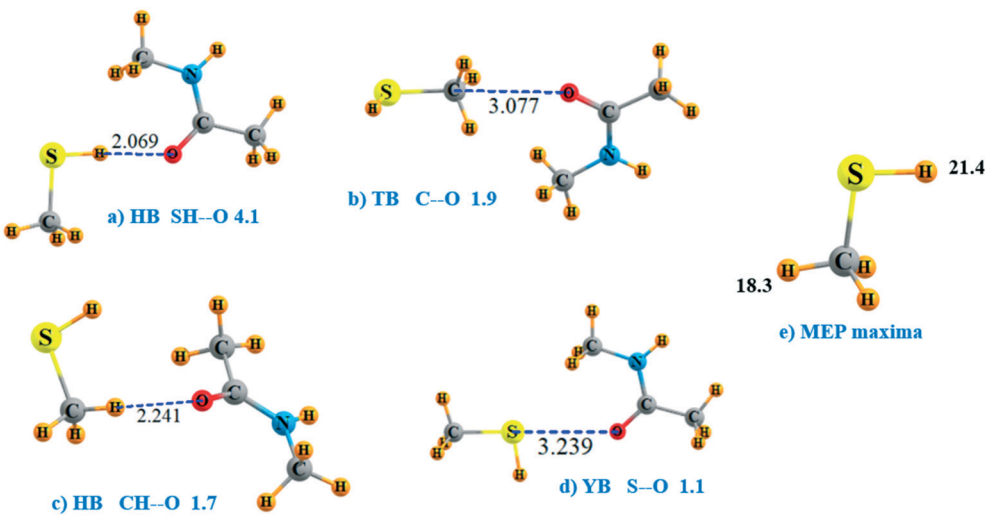


Fig. 1 Geometries of dimers between CH_3SH and NMA optimized at MP2/aug-cc-pVDZ level. Distances are in Å; the blue numbers indicate binding energies in kcal mol^{-1}. The magnitudes of the maxima in the MEP (kcal mol^{-1}) are indicated in e.

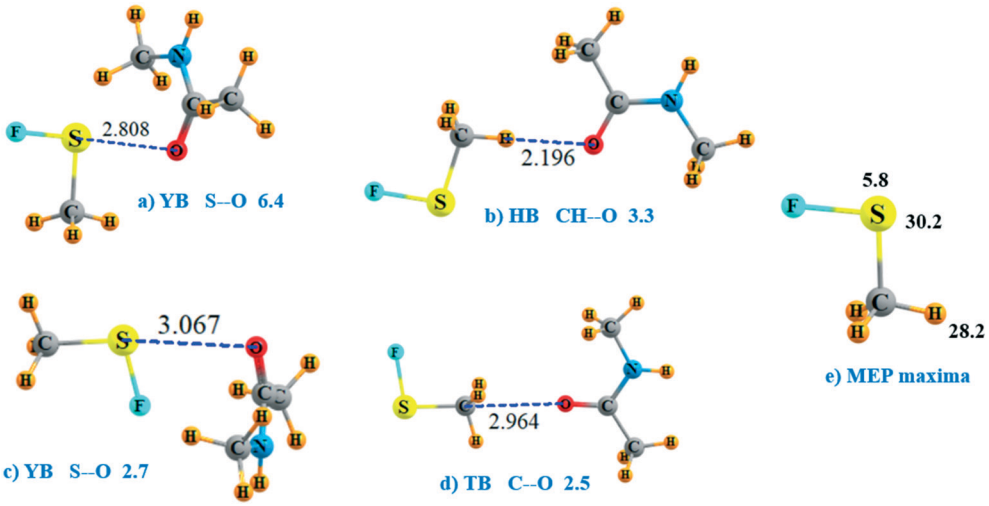


Fig. 2 Geometries of dimers between CH_3SF and NMA optimized at MP2/aug-cc-pVDZ level. Distances are in Å; the blue numbers indicate binding energies in kcal mol^{-1}. The magnitudes of the maxima in the MEP (kcal mol^{-1}) are indicated in e.

than the tetrel bond. The S can also participate directly in the context of a S···O ChB, as in Fig. 1d. But this interaction is the weakest of those considered. So this set of systems places the SH as the strongest electron acceptor group, more so than the S itself.

The molecular electrostatic potential (MEP) surrounding the MeSH monomer offers some guidance as to where a nucleophile is likely to bind. On the 0.001 au isodensity surface, the maxima are associated with the various H atoms, as indicated in Fig. 1e. The value of the MEP at the sulfhydryl H is 21.4 kcal mol^{-1}, slightly higher than the 18.3 kcal mol^{-1} associated with the methyl H, and consistent with the stronger SH···O as compared to CH···O. On the other hand, the MEP does not contain maxima that would be directly associated with either the tetrel bond in Fig. 1b or the ChB in Fig. 1d. Thus, while the MEP maxima offer some guidance, they do not provide a definitive listing of all complex geometries that might arise.

Replacing the sulfhydryl H by F would of course eliminate the possibility of a SH···O HB. On the other hand, the electron-withdrawing F wound intensify positive charge on the other atoms, especially the immediately neighboring S. And indeed, it is the FS···O ChB in Fig. 2a that represents the most stable dimer by a wide margin. The methyl H atoms are able to participate again as well, but as seen in Fig. 2b, the CH···O HB is considerably weaker. The S atom can form a second ChB, as noted in Fig. 2c where the nucleophile approaches opposite the methyl group. This option matches

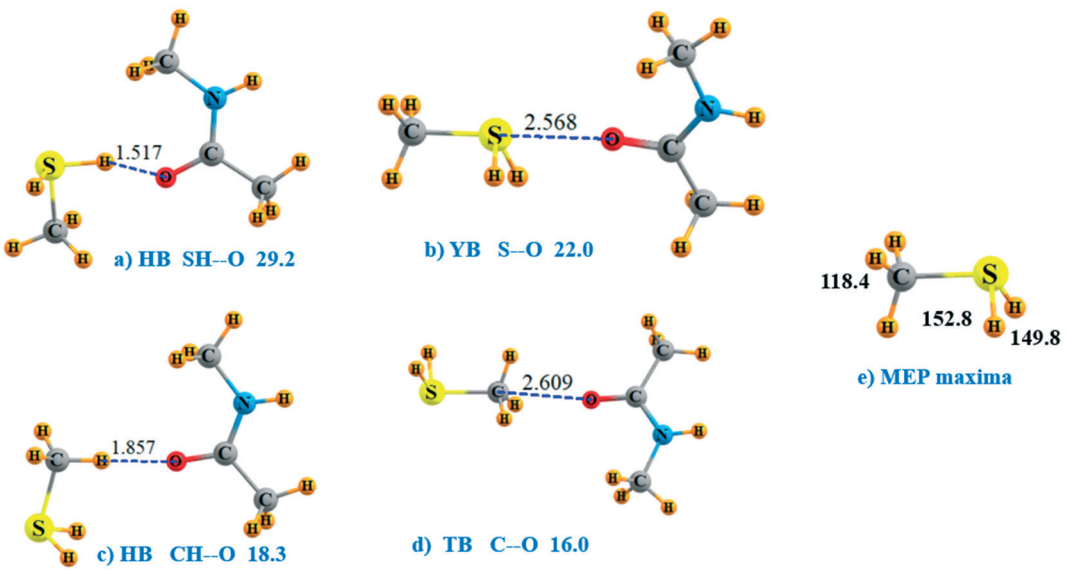


Fig. 3 Geometries of dimers between $CH_3SH_2^+$ and NMA optimized at MP2/aug-cc-pVDZ level. Distances are in Å; the blue numbers indicate binding energies in kcal mol^{-1}. The magnitudes of the maxima in the MEP (kcal mol^{-1}) are indicated in e.

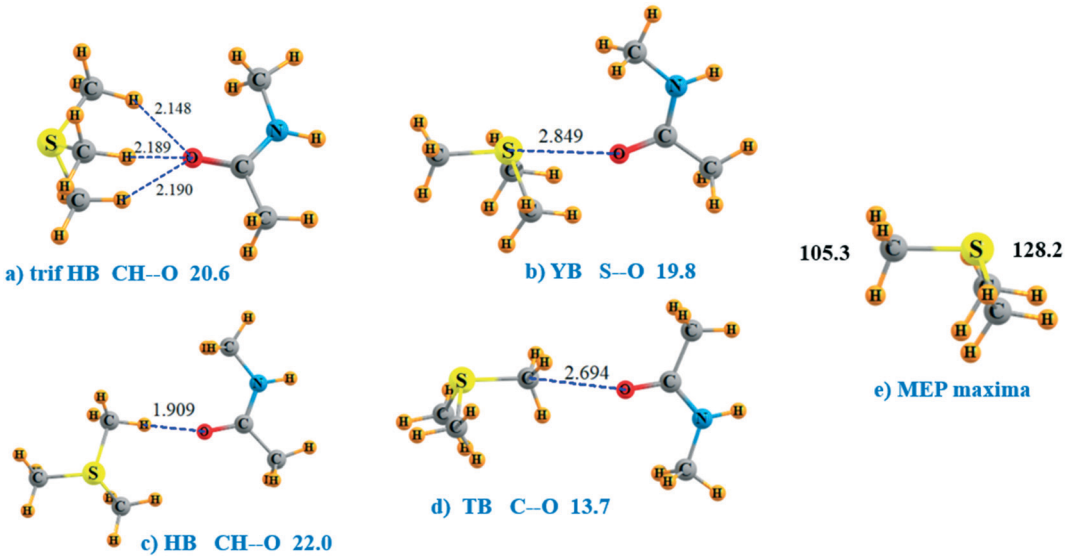


Fig. 4 Geometries of dimers between $(CH_3)_3S^+$ and NMA optimized at MP2/aug-cc-pVDZ level. Distances are in Å; the blue numbers indicate binding energies in kcal mol^{-1}. The magnitudes of the maxima in the MEP (kcal mol^{-1}) are indicated in e.

the ChB structure of Fig. 1d, and is considerably strengthened by the presence of the F. But at the same time, this alternate ChB is considerably weaker as CH_3 is not a good electron-withdrawing agent, especially when compared to F. The relative bonding strengths are consistent with the MEP maxima in Fig. 2e. A tetrel bond as in Fig. 2d is also possible, but is the least stable, nor is there a MEP maximum to match this geometry. The presence of the F, then, upgrades the strength of the ChB, allowing two such bonds as possibilities.

As noted earlier, adding a positive charge to the Lewis acid will amplify any of these bonds. This upgrade is obvious from the binding energies listed in Fig. 3 for $MeSH_2^+$. Of this set of complexes, the SH···O HB in Fig. 3a is strongest, followed by the S···O ChB, and then the CH···O HB and the C···O tetrel bond. Note that the addition of the positive charge has vaulted the CS···O ChB up to second place, when compared to the configurations in Fig. 1 where it was barely bound at all. The MEP maxima in Fig. 3e are all very large, expected in view of the overall positive charge. Removing the SH group, and making all three substituents on the S atom a methyl group leads to some interesting structures. This change of course eliminates the possibility of a SH···O HB. The most stable structure in Fig. 4a contains a trifurcated CH···O bond. Only very slightly less stable is the S···O ChB, again followed by the CH···O HB and the tetrel bond. Structures Fig. 4b and d are predicted by MEP maxima positions whereas the other two dimers are not.

Summary and perspectives

It is thus clear that S, as well as the heavier chalcogen atoms Se and Te, are active participants in noncovalent bonds. These chalcogen atoms appear to be comparable to the ubiquitous lighter chalcogen O as a proton acceptor in a HB. YH groups serve as proton donors, albeit not with the same vigor as a hydroxyl group. These atoms have the ability to act as electron acceptors in chalcogen bonds, something that O is typically unable to do. The strength of these bonds is comparable to, and even exceeds HBs in strength, particularly for the heavier Y atoms, or if electron-withdrawing substituents are placed on them. Indeed, as the chalcogen atom grows in size, its diminishing electronegativity and increasing polarizability makes it far more likely to participate in a ChB than in a HB.

There are a number of outstanding questions concerning these interactions. For example, there are numerous examples in the literature of S and Se engaging in HBs that are as strong as their O counterparts. Is this a universal parallel, or are there some important exceptions? As a second question, what is the upper limit on the strength of both HBs and ChBs? Under what conditions will a S or Se switch off its H-bonding capability in favor of a ChB, or *vice versa*? What is the maximum number of ChBs in which a single Y atom can engage, and under what conditions? Study of the effects of solvation or environment on these interactions remains in its infancy at this point.

The spectroscopic implications of HBs and ChBs to the heavier chalcogens are only beginning to be studied; much more remains to be learned. For example, do the trends observed in conventional HBs concerning Y–H red shift and NMR chemical shielding apply to S and Se HBs as well; under what circumstances might a YH proton donor shift its stretching frequency to the blue? The sensitivity of the ChB strength to the size of the Y atom may allow researchers to modulate a balance with other interactions such as the HB by simple substitutions. In that same vein, what sort of conditions must be met before an O atom will participate in a ChB? In what ways might these bonds be used to design large systems, as in crystal engineering, or within biological

systems? Applications of these bonds are now emerging, and new ideas, for example in the design of new catalysts, are sure to be forthcoming.

Conflicts of interest

The author declares no competing financial interest.

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