Review Article

Unleashing the Potential of Machine Learning in Chalcogen Bonding Research

Humphrey Sam Samuel[1] | **Ugo Nweke-Maraizu[2]** | **Emmanuel Edet Etim[1,*]**

[1]*Department of Chemical Sciences, Federal University Wukari, Taraba State, Nigeria*
[2]*Department of Chemistry, Rivers State University, Nkpolu-Oroworukwo, Port Harcourt, Nigeria*

A B S T R A C T

Chalcogen bonding, a non-covalent interaction involving chalcogen atoms (e.g., sulfur, selenium, and tellurium), plays a crucial role in various chemical and biological processes. Understanding and characterizing chalcogen bonding interactions are essential for designing novel materials, medications, and catalysts. In recent years, machine learning has emerged as a powerful tool for studying molecular interactions, including chalcogen bonding. This study provides an overview of the application of machine learning in characterizing chalcogen bonding. Experimental techniques, such as infrared (IR), nuclear magnetic resonance (NMR) spectroscopy, and X-ray crystallography, have been used to study chalcogen bonding. However, these methods often suffer from inherent experimental challenges. On the other hand, computational approaches, including quantum mechanics (QM) and molecular dynamics (MD) simulations, offer valuable insights into the electronic structure and energetics of chalcogen bonding. Nonetheless, they can be computationally demanding and may not fully encompass the diversity of chalcogen bonding interactions. Machine learning, with its ability to identify patterns and relationships in vast datasets, presents a promising alternative for characterizing chalcogen bonding. The study explains how machine learning algorithms, such as supervised and unsupervised learning, can be employed to classify and predict chalcogen-bonded complexes using neural network potentials to assess the persistence of chalcogen bonds in solution and ML models to predict two key solid-state synthesis conditions that must be specified for chalcogenide glasses. By integrating experimental data and computational results, machine learning models offer a holistic approach to understanding chalcogen bonding in various molecular systems. It emphasizes the integration of experimental and computational data as a means to maximize the accuracy and applicability of machine learning models and envisions a promising future for machine learning in characterizing chalcogen bonding interactions.

---

*Corresponding Author: Emmanuel Edet Etim, emmaetim@gmail.com

Introduction

The structure, stability, and functionality of molecules and molecular systems are largely shaped by non-covalent interactions, a class of intermolecular forces. These exchanges take place between molecules or different atoms of the same molecule without the exchange of electrons that covalent bonds do. Instead, they are based on less powerful electrostatic forces that develop as a result of variations in electron distributions within atoms or molecules [1]. Because of differences in electron distributions, non-covalent interactions are dependent on electrostatic forces. A variant of Coulomb's Law can be used to explain these interactions, which are inherently electrostatic in nature. Positively charged organisms and negatively charged species interact to produce electrostatic interactions. Intermolecular interactions are the combination of attracting and repulsive forces, just like covalent and ionic bonds. Intermolecular contacts are crucial for solids and liquids because they have close-packed molecules with a high electrostatic interaction rate relative to their distance from one another. The Van der Waals forces, hydrogen bonds, and chalcogen bonds are only a few examples of non-covalent interactions. Because transient dipoles exist between molecules, Van der Waals forces, which are weak attractive forces, are generated. Chemistry, biology, materials science, and drug design are just a few of the scientific disciplines that depend on non-covalent interactions [1]. The behaviour and characteristics of molecules and materials are governed by non-covalent interactions, which represent a fundamental force. In numerous scientific fields, including drug design and materials research, understanding and describing these interactions is essential. Our understanding of non-covalent interactions is continually expanding thanks to experimental methodologies, computational tools, and machine learning strategies, which help us create molecular systems and materials that are more effective and precise [2]. Several types of non-covalent interactions include Van der Waals, hydrogen bonding, chalcogen bonding, etc. Molecules interact with one another through weak attractive interactions called van der Waals forces. Temporary dipoles are produced as a result of variations in the molecules' electron densities, which give birth to them. Because of the dipoles that these transient dipoles can create in nearby molecules, there is an attractive force between them. The strength of Van der Waals forces is often lower than that of other non-covalent interactions like hydrogen and chalcogen bonds. Between a hydrogen atom and an electronegative atom, such as oxygen, nitrogen, or fluorine, hydrogen bonds are a sort of non-covalent interaction that takes place. Although it can weakly link with another electronegative atom in a nearby molecule, the hydrogen atom is covalently bound to one electronegative atom in one molecule. While hydrogen bonding and chalcogen bonding are particular forms of dipole-dipole interactions, Van der Waals forces cover a wider spectrum of non-covalent interactions, including dispersion forces, dipole-dipole interactions, and dipole-induced dipole interactions. In contrast to chalcogen bonding, which involves chalcogen atoms (such as sulfur, selenium, or tellurium), hydrogen bonding is characterized by the presence of hydrogen atoms bound to strongly electronegative atoms (such as oxygen or nitrogen). Chalcogen bonds are stronger than ordinary Van der Waals forces, but hydrogen bonds are often stronger than chalcogen bonds. For example, as it is the case for other non-covalent interactions, the chalcogen bond strength rises with the polarizability of the participating atom (thus, as the atomic number of an atom of the 16th group increases, the strength of the bond rises), the basicity of interacting atom and the polarization of LA induced by the backbone [3].

Dipole-dipole interactions between electronegative atoms, chalcogen bonding and hydrogen bonding are similar, but they differ in the particular involved atoms.

The recognition and understanding of chalcogen bonding, a relatively recent addition to the family of non-covalent interactions, have

increased dramatically during the past few decades. While the exact timeframe is not specified, recent research in the area of chalcogen bonding has been booming in the last 10 years [4]. Chalcogen bonding has evolved as a distinct and significant non-covalent contact with its own special features and uses, in contrast to hydrogen bonding, which has been extensively investigated and acknowledged for its role in molecular recognition and self-assembly. A Lewis base and a chalcogen atom (O, S, Se, or Te) engage electrostatically to form a chalcogen bond. An electron-rich species called a Lewis base is one that can give up a single pair of electrons to create a bond. Dependence on the polarizability of the chalcogen atom is one of the distinctive features of chalcogen bonding. The strength of the chalcogen bond typically increases from oxygen, which is the least polarizable element, to tellurium, which is the most polarizable element [5]. This is because higher attractive forces are produced as a result of the enhanced ability of more polarizable chalcogen atoms to react to variations in electron density. Chalcogen bonding's geometry can vary and is influenced by steric and electrical variables, as well as the strength of the bonding. Linear, branched, and t-shaped configurations are typical geometries [6]. Chalcogen bonding is an intermediate force that can have a major impact on molecular structures and supramolecular assemblies. Its strength is typically smaller than Van der Waals contacts but greater than covalent bonds. Chalcogen bonding has come under the spotlight in the study of biochemistry due to its significance in a number of biological processes. In the stability of protein structures, such as the secondary structural components (such as -helices and -sheets), and in ligand-receptor interactions, for instance, chalcogen bonding interactions are essential. Chalcogen bonding is also being investigated in medicinal chemistry and drug design. Drug compounds' binding affinity and selectivity for particular protein targets can be improved by including chalcogen-bonding interactions. This might enhance the medications effectiveness and lessen their negative effects. Chalcogen bonding has uses in supramolecular chemistry, where it is exploited to create self-assembling structures

and useful substances. Chalcogen bonding has been used in supramolecular chemistry to design and synthesize new materials. For example, a study published in Nature Communications developed hybrid chalcogen bonds (-STeS- and -SSeS-) bridged HPNAs using docetaxel (DTX) as the model drug. The effects of hybrid chalcogen bonds on the self-assembly, bioactivation, pharmacokinetic behaviour, bio-distribution, and HPNAs pharmacodynamics were investigated in detail. Multiple non-covalent molecular forces drove self-assembly, including π–π stacking among DTX molecules, alkyl-alkyl interaction among alkyl part, hydrogen bonding among hydroxyl structure, and chalcogen bonding among linkers. Chalcogen bonding has also been used in drug design. A study published in the Journal of the American Chemical Society reported that chalcogen bonding can be used to assemble discrete molecules. The study used chalcogen-chalcogen bonding catalysis to assemble a series of discrete molecules. Another study published in PMC reported that chalcogen bond-guided conformational isomerization enables catalytic dynamic kinetic resolution of sulfoxides. Chalcogen bonding has been used in materials science to design new materials with specific properties. For example, a study published in the Journal of the American Chemical Society reported that chalcogen bonding can be used to activate ethers in supramolecular catalysis. The study used dual chalcogen bonding activation to catalyze the ethers activation. Another study published in PMC reported that cooperative chalcogen bonding interactions in confined sites activate aziridines. Anion recognition has been accomplished using chalcogen-based receptors, enabling the selective binding [7].

Machine learning and chalcogen bonding are two fascinating and developing fields of science that have received a lot of attention recently. The non-covalent interaction known as chalcogen bonding, which involves the chalcogen elements oxygen, sulfur, selenium, and tellurium, has become recognized as a separate and significant force in molecular contacts that has a significant impact on a variety of chemical and biological processes [8].

Contrarily, machine learning, a branch of artificial intelligence, has fundamentally changed how scientists across fields of study examine complex data, spot patterns, and makes predictions. A Lewis base and a chalcogen atom interact electrostatically to form chalcogen bonds, which are similar to hydrogen bonds. The development of drugs, supramolecular assemblages, and molecular recognition all depend on this particular non-covalent interaction. Designing innovative materials, enhancing drug-target interactions, and modifying the characteristics of molecular systems all depend on an understanding of and characterization of chalcogen bonding interactions [9]. Machine learning has shown to be an effective method in molecular interactions, particularly chalcogen bonding. Machine learning techniques can recognize patterns, categorize interactions, and forecast molecular behaviour using algorithms that learn from data. Machine learning has the ability to speed up our understanding of this non-covalent interaction in the context of chalcogen bonding by evaluating massive datasets and forecasting the strengths of chalcogen bonds [10]. A significant force in molecular contacts having several applications in chemistry, biology, and materials science is chalcogen bonding, a sort of non-covalent interaction involving chalcogen atoms (oxygen, sulfur, selenium, and tellurium). The combination of machine learning and chalcogen bonding research in recent years has offered a potent and ground-breaking strategy to address the complexity of these non-covalent interactions [11].

A branch of artificial intelligence called machine learning focuses on creating algorithms that let computers learn from data and make predictions or judgments without having to be explicitly programmed. It has revolutionized with its ability to analyze huge and complicated datasets, find patterns, and make precise predictions. Machine learning has great prospects to improve our comprehension of these interactions and assist in the development of new materials and medications in the context of chalcogen bonding. Chalcogen bonding benefits greatly from machine learning. Initially, it can help with the categorization and prediction of chalcogen bonding interactions, allowing for the discovery of novel chalcogen-bonded complexes and the investigation of bonding patterns in substantial datasets. On the basis of known chalcogen bonding complexes, machine learning models can be trained to identify important characteristics that contribute to the potency and specificity of chalcogen bonding [12].

In addition, machine learning makes it easier to combine experimental and computational data, giving chalcogen bonding interactions a thorough and multidimensional perspective. Combining experimental and computational data has improved our understanding of chalcogen bonding in various ways, including understanding the properties of chalcogen-bonding transporters, the halogen bond, and materials discovery. It has also been used to generate high-quality datasets for training machine learning potentials. To better understand the electronic structure, energetics, and dynamics of chalcogen bonding, researchers can combine information from spectroscopic methods, X-ray crystallography, computational simulations, and machine learning models. Our comprehension of these non-covalent interactions can be advanced by the combination of machine learning and studies on chalcogen bonds. Researchers can unravel the complex nature of chalcogen bonding by fusing the power of machine learning with experimental and computational methods. This will enable the development of innovative materials, medications, and molecular systems with specialized capabilities. The topic of chalcogen bonding is poised to be opened up in exciting new ways by this interdisciplinary approach, opening the door for future ground-breaking research [13-15]. The aim of the article is to explore the various machine learning models in characterizing chalcogen bonding. The scope of the article is to examine the distinctive properties of chalcogen bonding and the significance of this bonding in many chemical and biological processes. Along with that, we highlight new uses of machine learning for describing chalcogen bonding interactions.

Overview of Experimental Techniques in Characterizing Chalcogen Bonding

For examining chalcogen bonding interactions, spectroscopic methods like infrared (IR), nuclear magnetic resonance (NMR), and Raman spectroscopy are invaluable resources. These techniques offer crucial details regarding the structural and dynamic characteristics of solid-state and solution-based chalcogen-bonded complexes [16]. Here is a thorough explanation of each spectroscopy method and how it relates to understanding chalcogen bonding:

i.   IR spectroscopy:Because it is sensitive to the vibrational modes of molecular bonds, IR spectroscopy is frequently employed to study chalcogen bonding. Stretching vibrations of the bonds between chalcogen atoms and Lewis base acceptors frequently occur in

chalcogen bonds. In contrast to free chalcogen-containing molecules, the creation of chalcogen bonds can cause distinctive shifts in the IR spectra. Specific IR bands' redshifts or blueshifts in wavenumbers reveal important details regarding the character and intensity of the chalcogen bond. For example, IR spectroscopy was utilized to examine the shifts in the stretching vibrations of the chalcogen-oxygen or chalcogen-nitrogen bonds in a study of chalcogen-bonded complexes between a ligand containing chalcogen and a Lewis base [17]. The establishment of chalcogen bonding connections was revealed by the redshifts seen in the IR spectra in Figure 1, supporting the stabilizing effects of these interactions in the complexes.
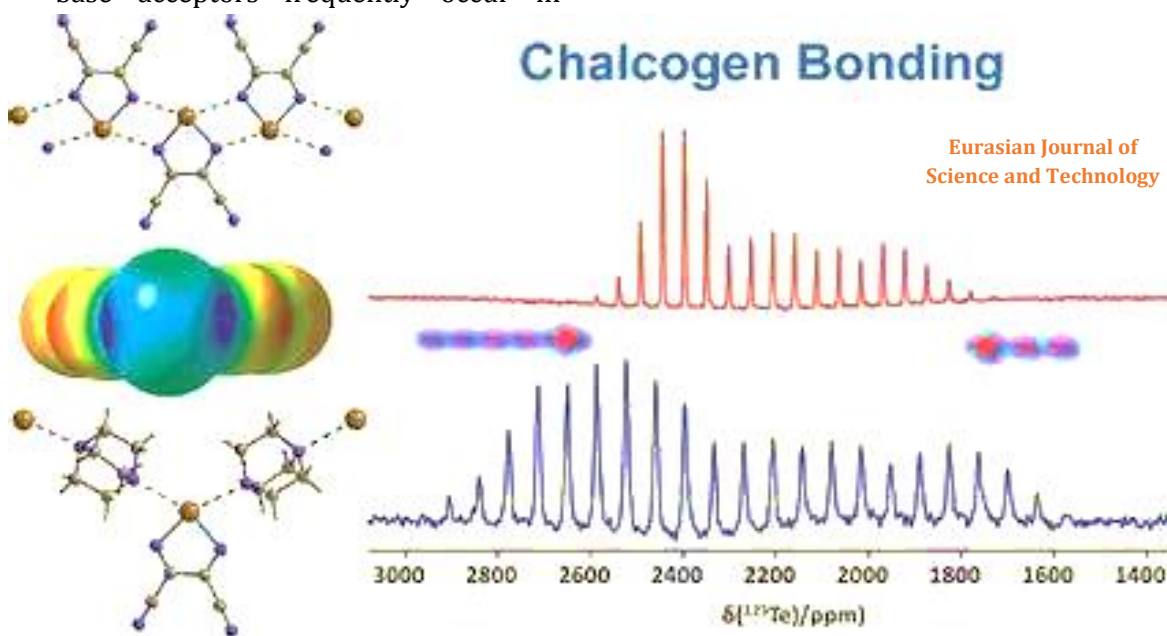
Figure 1 Chalcogen bonding in Infrared spectroscopy [17]

IR spectra can be simplified by working at very low temperature in liquid krypton (120 K) and with a rigid ChB donor such as 2,2,4,4-tetrafluoro-1,3-dithiethane. Under these conditions, simplified spectra could be obtained in the presence of 1,2-dimethoxyethane (DME), with appearance of several new bands associated with the Ch-bonded DME 1,1 dimer, as confirmed by theoretical calculations, as depicted in Figure 2 [18].
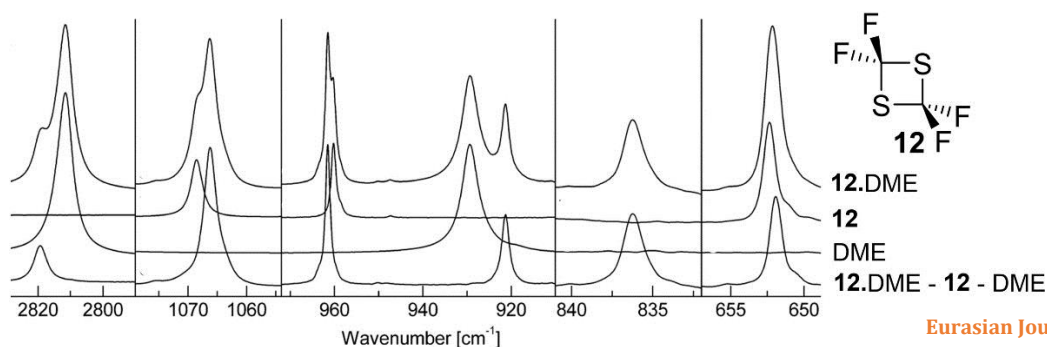
Figure 2 IR spectra of selected spectral regions for the mixtures of chalcogen with DME [18]

ii. NMR Spectroscopy:NMR spectroscopy is another effective method for examining chalcogen bonding interactions. In particular, in chalcogen-bonded complexes, the nuclei of chalcogen atoms like 17O, 33S, 77Se, and 125Te can show chemical shifts and spin-spin coupling patterns that are responsive to their local surroundings. The strength and geometry can be used to correlate changes in coupling constants and chemical shifts [20]. NMR spectroscopy was used to examine the chemical shifts of the chalcogen nuclei in a study of chalcogen-bonded complexes between a Lewis base and a ligand that contains chalcogen. The chalcogen atoms in the complexes' electronic surroundings were revealed by the observed chemical changes, which also revealed the existence and potency of chalcogen bonding interactions. For instance, consider a chalcogen-bonded complex between a tellurium atom and an aluminium, nitrogen and carbon atom, as demonstrated in Figure 3 [21].
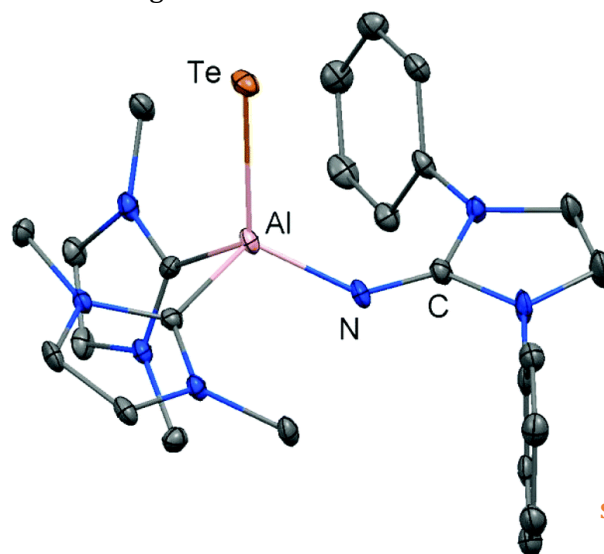
Figure 3 Chalcogen bond between tellurium and aluminium, nitrogen and carbon atom [21]

iii. Raman Spectroscopy:By examining the light scattering brought on by molecular vibrations, Raman spectroscopy is utilized to examine chalcogen bonds. Raman spectroscopy may identify vibrational modes linked to chalcogen bonding interactions, just like IR spectroscopy [22]. To supplement the information acquired from other spectroscopic methods, the shifts in

Raman bands reveal details about the geometry and strength of the chalcogen bond. Raman spectroscopy was used to examine the changes in vibrational modes linked to the chalcogen-oxygen or chalcogen-nitrogen bonds in a study of chalcogen-bonded complexes between a chalcogen-containing ligand and a Lewis base. The presence of chalcogen bonding contacts was indicated by shifts in Raman bands, further supporting the complexes' stability [22].

iv. X-ray Crystallography for Chalcogen-Bonded Complexes:A potent method for figuring out the three-dimensional structures of chalcogen-bonded complexes in solids is X-ray crystallography [23]. In this method, single crystals of chalcogen-bonded

complexes' X-ray diffraction patterns are analyzed. Researchers may calculate the bond lengths, bond angles, and intermolecular distances in chalcogen-bonded complexes using the diffraction patterns because they reveal data about the arrangement of atoms within the crystal lattice. For example, the presence of chalcogen bonding between a selenium atom and a nitrogen atom in a molecule was discovered by an investigation of the crystal structure. It was found that the selenium atom's distance from the nitrogen atom was 2.8, pointing to a robust chalcogen connection. It was discovered that the angle created by the selenium-nitrogen interaction was around 160 degrees, illuminating the bent geometry present in chalcogen bonding, as illustrated in Figure 4 [24].
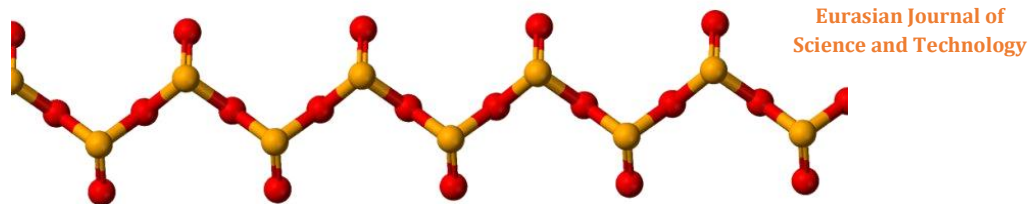
Figure 4 Chalcogen bonding in selenium [24]

Overview of Computational Approaches for Chalcogen Bond Analysis

The study of chalcogen bonding interactions has become impossible without the use of computational approaches. In addition to the experimental methods, these methods offer comprehensive insights into the electronic structure, energetics, and dynamics of chalcogen-bonded complexes [25]. The four main computational methods for chalcogen bond analysis are discussed in this section as follow:quantum mechanics (QM), molecular mechanics (MM), and molecular dynamics simulations (MD). An overview of the approaches was done based on quantum mechanics (QM), density functional theory

(DFT), molecular dynamics, and molecular mechanics (MM).

i. *Quantum mechanics (QM)*:At the quantum level, quantum mechanics is a fundamental theory that explains how atoms and molecules behave. In chalcogen bond analysis, the electronic structure and energetics of chalcogen-bonded complexes are ascertained by solving the Schrödinger equation using QM calculations. Although QM approaches produce reliable findings, because to their high computing cost, they can be computationally taxing for big systems [26].

ii. *Molecular mechanics (MM)*:Molecular mechanics is a condensed method for modelling the potential energy surface of

molecules and molecular compounds. Atoms are modelled as spheres with partial charges in MM computations, and force fields are used to characterize interatomic interactions [27]. Even while MM is computationally effective, it ignores electronic effects and quantum interactions, which makes it less effective for researching chalcogen bonding.

iii.   *Density Functional Theory (DFT)*:One of the most popular quantum mechanical techniques for examining chalcogen bonding interactions is density functional theory (DFT). DFT works effectively for big systems for chalcogen bond analysis because it strikes a fair balance between accuracy and computational expense. By resolving the Kohn-Sham equations in DFT, where the total energy is given as a function of the electron density, it is possible to ascertain the electronic structure of chalcogen-bonded complexes [28].

Characteristics of DFT in Chalcogen Bond Analysis

1. *Bond Lengths and Angles*:DFT simulations reliably predict bond lengths and angles in chalcogen-bonded complexes, offering important insights into the spatial organization of chalcogen bonding interactions. DFT enables energy decomposition analysis, which divides the interaction energy of chalcogen bonding into many contributions, including electrostatic, dispersion, and orbital interactions. Understanding the nature and power of chalcogen bonding is made easier by this analysis [29].

2. *NBO Analysis*:The characterization of chalcogen bond polarity is aided by Natural Bond Orbital (NBO) analysis in DFT, which offers insights into the charge transfer and electron density redistribution in chalcogen-bonded complexes. DFT calculations were utilized to ascertain the complex's electronic structure and energetics in a study of a chalcogen-bonded complex between a Lewis base and a ligand that contains a chalcogen [30]. By calculating the bond lengths, angles, and interaction energies, it was possible to both validate the existence of chalcogen bonding and learn more specifics about the type of interaction that was taking place [31].

iv.   *Molecular Dynamics (MD) Simulations*:Computing techniques called molecular dynamics (MD) simulations are used to track the dynamic behaviour of chalcogen-bonded complexes throughout time. Using force fields obtained from actual data or quantum mechanical computations, MD simulations simulate the motion of atoms based on classical mechanics [32]. The stability and adaptability of chalcogen-bonded complexes can be better understood by using MD simulations to gain knowledge about the lifetimes, fluctuations, and cooperativity of chalcogen bonds.

An example on tellurium and nitrogen chalcogen-bonded complexes, as illustrated in Figure 5, MD simulations revealed several conformations and the dynamics of the chalcogen bond, revealing information on the bond's preferred orientations and flexibility [33].
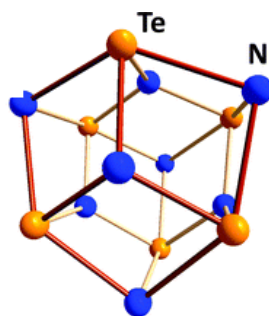
Figure 5 Tellurium and nitrogen complex [33]

Key Features of Chalcogen Bond Analysis MD Simulations'

i. *Lifetimes of Chalcogen Bonds*:By monitoring the formation and dissociation of these interactions over time, MD simulations can calculate the lifetimes of chalcogen bonds. Understanding the stability of chalcogen-bonded complexes requires this knowledge [34].

ii. *Fluctuations and Dynamics*:The dynamic behaviour of chalcogen bonds is revealed by MD simulations, demonstrating how they fluctuate and adjust to changes in the molecular environment. Understanding the adaptability and flexibility of chalcogen bonding interactions depends on this dynamic information [35].

iii. *Cooperativity and Solvent Effects*:In complex systems, MD simulations can be used to examine how solvent molecules affect chalcogen bonding and how cooperatively different chalcogen bonds interact. For example, MD simulations were used to examine the dynamics and variations of the chalcogen bond over a time scale of nanoseconds in a study of a chalcogen-bonded complex in a solvent environment [36]. The simulations demonstrated the collaborative impacts of numerous chalcogen bonds inside the complex and shed light on the stability of the chalcogen bond under various solvent conditions.

In the study of chalcogen bonding interactions, computational techniques like density functional theory (DFT) and molecular dynamics (MD) simulations have become essential tools. DFT provides accurate knowledge of the electronic structure and energy decomposition analyses, whereas MD simulations offer dynamic insights into the lifetimes and variations of chalcogen bonds. Our knowledge of chalcogen bonding and its significance in diverse chemical and biological systems is further improved by the combination of experimental data with computer models [37-39].

Machine Learning in Chalcogen Bonding Analysis algorithm

Artificial intelligence's specialty of machine learning, which can analyze complex data, find patterns, and anticipate outcomes without explicit programming, has become extremely popular in recent years [40]. Machine learning offers a potent and cutting-edge method for comprehending and forecasting the interactions between chalcogen atoms and Lewis base acceptors in the context of chalcogen bonding studies. Researchers can learn more about the nature and properties of chalcogen bonding by combining machine learning algorithms with experimental and computational data, advancing disciplines like chemistry, materials science, and drug discovery [41]. Algorithms for machine learning allow computers and other devices to learn from data and make predictions or judgments without the need for explicit programming. These algorithms, which are a core component of the broader subject of artificial intelligence (AI), are made to find patterns, connections, and trends in data so that systems can become more effective over time [42]. The three primary categories of machine learning algorithms are supervised learning, unsupervised learning, and semi-supervised learning. In chalcogen bonding analysis, each kind of algorithm has a particular function that is detailed as follow:

i. *Supervised Learning*:On labelled datasets, where the input data (features) and the associated output (labels) are known, supervised learning algorithms are trained. In order to generate predictions on fresh, unforeseen data, the algorithm learns to translate the input data to the appropriate output [43]. Using supervised learning, it is possible to categorize chalcogen-bonded compounds, forecast the strength of chalcogen bonding, or pinpoint

important characteristics that influence chalcogen bond formation in the context of chalcogen bonding studies. In a supervised learning technique, for instance, the algorithm is trained using a dataset of labelled chalcogen-bonded complexes and non-chalcogen-bonded complexes. The labels indicate if the complex displays chalcogen bonding, whereas the properties could include bond lengths, angles, and charge distributions. The algorithm can forecast complexes once it has been trained [44].

ii. *Unsupervised Learning*:When a dataset lacks labels and the output labels are unknown, unsupervised learning algorithms are utilized. Finding patterns and structure in the data without the use of predetermined categories is the aim of unsupervised learning. Unsupervised learning can be used in chalcogen bonding analysis to cluster related chalcogen-bonded compounds or find hidden trends in huge datasets [45]. A dataset of chalcogen-bonded complexes is employed in an unsupervised learning method without any labels. The program evaluates the complexes' characteristics and clusters them according to their similarity. This grouping of chalcogen-bonded compounds might show shared structural traits or patterns [46].

iii. *Semi-Supervised Learning*:Algorithms for semi-supervised learning combine aspects of supervised and unsupervised learning. To identify trends and generate predictions, they combine a smaller labelled dataset with a larger unlabelled dataset. When it is difficult or expensive to collect a fully labelled dataset, semi-supervised learning is helpful [47]. A limited fraction of chalcogen-bonded complexes are labelled in a semi-supervised learning strategy for chalcogen bonding analysis, whereas a much larger set of unlabelled complexes is utilised. The program first

learns to recognize patterns in the labelled complexes before generalizing its understanding to forecast chalcogen bonding in the unlabelled complexes [48].

Utilizing Machine Learning to Classify and Prediction of Chalcogen-Bonded Interactions

A potential strategy in chalcogen bonding research is the use of machine learning to categorize and forecast chalcogen-bonded interactions. Traditional computational methods have a difficult time analyzing complex datasets, extracting pertinent features, and identifying trends [49]. The following are some essential components of the application of machine learning to categorize and forecast chalcogen-bonded interactions:

1. *Data Preparation*:A dataset of chalcogen-bonded compounds with their accompanying attributes is necessary to train a machine learning model. Bond lengths, angles, charge distributions, and other pertinent structural descriptors are examples of these characteristics. The dataset may additionally include details about the nature or strength of the chalcogen bond, as determined by experimental analysis or computations based on quantum mechanics [50].

2. *Engineering Relevant Features*:To improve the performance of the machine learning model, engineering relevant features entails choosing or modifying the characteristics. In order to decide which features are most relevant for the classification or prediction task, domain experience in chalcogen bonding is crucial [51].

3. *Supervised Learning for Chalcogen Bond Classification*:In this context, the dataset is labelled with data about whether each complex exhibits chalcogen bonding or not, and the algorithm learns to distinguish between chalcogen-bonded and non-chalcogen-

bonded complexes based on the input features. Examples of supervised learning algorithms for chalcogen bond classification include Support Vector Machines (SVM), Decision Trees, and Neural Networks [52].

4. *Semi-Supervised Learning for Better Predictions*:Obtaining a properly labelled dataset can frequently be difficult or expensive. Prediction accuracy can be increased by using a combination of labelled and unlabelled data using semi-supervised learning methods [53]. This method is especially helpful in chalcogen bonding studies, where there may not be enough experimental data for labelling.

5. *Chalcogen Bond Strength and Type Prediction*:Based on input features, machine learning models can also be trained to predict the strength or type of chalcogen bonds. Understanding the stability and specificity of chalcogen bonding interactions can be greatly aided by this information [53]. For example, in a regression task, the model is trained using a dataset of labelled chalcogen-bonded complexes with known bond strengths. By predicting the bond strength of chalcogen bonds in new complexes based on their characteristics, the model gains knowledge about the energetics of chalcogen bonding.

6. *Chalcogen-Bonded Complexes Can Be Clustered Using Unsupervised Learning*:Chalcogen-bonded complexes can be grouped together according to comparable properties using unsupervised learning methods. The identification of new chalcogen-bonded systems is aided by this technique, which can identify common structural motifs or features among chalcogen-bonded complexes. In addition to the experimental methods and quantum mechanical computations, machine learning in chalcogen bonding research

offers a quicker and more effective means to pore over a huge chemical space. For gaining fresh understanding of chalcogen bonding interactions and expediting the creation of novel materials, drugs, and molecular systems, the combination of machine learning with chalcogen bonding research has enormous promise [54-57].

Datasets and Features for Machine Learning in Chalcogen Bonding

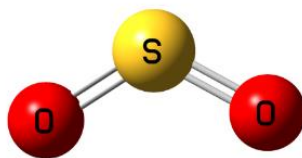### *Selection and Preparation of Datasets Containing Chalcogen-bonded Complexes*

When using machine learning for chalcogen bonding analysis, the selection and preparation of datasets are essential processes. To develop precise and trustworthy machine learning models, a well-curated and representative dataset is necessary [58]. The important factors to take into account while choosing and setting up datasets that contain chalcogen-bonded complexes:

i. *Data sources*:A number of sources, including experimental research, quantum mechanical simulations, and crystallographic databases, provide datasets with chalcogen-bonded complexes. Theoretical data can be produced from calculations using density functional theory (DFT) or other computational techniques, whereas experimental data may come from spectroscopic methods like infrared (IR) and nuclear magnetic resonance (NMR) spectroscopy [58].

ii. *Data Correctness and Consistency*:The data correctness and consistency acquired from various sources may vary. To prevent biases and artifacts in the dataset, it is essential to guarantee data quality and consistency [59]. Datasets need to be extensively vetted and cross-referenced against databases and existing literature.

iii. *Labelling*:To distinguish between chalcogen-bonded and non-chalcogen bonded complexes for supervised learning tasks, chalcogen-bonded complexes should be labelled. Depending on the specific study issue, labels may be categorical (e.g., mild, moderate, or strong chalcogen bonding) or binary (1 for chalcogen bonding, 0 for non-chalcogen bonding) [60].

iv. *Dataset Balancing*:Unbalanced datasets, when one class (for example, chalcogen-bonded) is significantly larger than the other (for example, non-chalcogen bonded), can result in inaccurate model predictions. To balance the dataset, strategies like over- or under-sampling the minority class or using artificial data generating techniques (like SMOTE, or Synthetic Minority Over-sampling Technique) might be used [61].

v. *Representative Sampling*:The dataset ought to reflect the variety of chalcogen-bonded complexes that are observed in real-world situations. To guarantee that the machine learning model generalizes well to fresh, unexplored data, it should cover a wide variety of chalcogen-bond strengths, geometries, and chemical conditions.

vi. *Data Pre-Processing*:A dataset may need to be pre-processed before being fed into a machine learning model. This involves dealing with missing data, eliminating duplicates, and formatting the data for analysis [62].

vii. *Data Privacy and Ethics*:Data privacy and intellectual property issues should be taken into account when employing experimental data collected from research subjects or exclusive databases. To use such data, the appropriate permits and agreements must be in place [63].

viii. *Open Access Databases*:Researchers can access databases that are freely accessible and that contain curated information on chalcogen-bonded complexes. Examples include the Protein Data Bank (PDB), the Cambridge Structural Database (CSD), and other repositories of crystallographic structures and computational results [64].

ix. *Data Size*:In machine learning, the dataset's size is significant. Larger datasets allow for improved generalization of the model while smaller datasets may lead to overfitting. However, in some circumstances, the availability of chalcogen-bonded compounds may restrict the dataset's size.

Fundamental steps in utilizing machine learning for chalcogen bonding studies include the selection and development of datasets containing chalcogen-bonded compounds. Researchers can create precise and dependable machine learning models that offer important insights into the nature and properties of chalcogen bonding interactions by selecting high-quality datasets that are diverse, balanced, and reflective of real-world situations [65-67].

Extraction of Relevant Molecular Features for Machine Learning Models

A critical step in utilizing machine learning models to examine chalcogen bonding interactions is the extraction of pertinent molecular characteristics. The crucial details regarding the chalcogen-bonded complexes are captured by these characteristics, which act as input variables for the model [68]. The model's effectiveness and its capacity to deduce meaningful patterns from the data depend greatly on the features' selection and representation. As examples of pertinent chemical features for machine learning in chalcogen bonding analysis, the following points should be kept in mind:

i. *Geometric Features*:In chalcogen-bonded complexes, the spatial arrangement of the atoms determines

the geometric features. Between chalcogen atoms and Lewis base acceptors, they reveal details regarding bond lengths, bond angles, and distances. These qualities are crucial for describing the structural traits of chalcogen bonding interactions. A typical geometric aspect in chalcogen bonding analysis is the length of the bond between the chalcogen atom (for instance, oxygen or sulfur) and the Lewis base acceptor (for instance, nitrogen or oxygen) [69].

ii. *Charge Distributions*:Chalcogen bonding is strongly influenced by electrostatic interactions. For capturing the electrical components of chalcogen bonding, characteristics relating to charge distributions surrounding chalcogen atoms and Lewis base acceptors are crucial. For instance, the partial charges on the chalcogen atom and the Lewis base acceptor that were discovered using charge distribution analysis or quantum mechanical calculations can be useful properties [70].

iii. *Orbital Features*:The electrical structure of chalcogen-bonded complexes is connected to orbital features. As they relate to the electron density and charge transfer in chalcogen bonding, they can shed light on the highest occupied molecular orbital (HOMO) and lowest unoccupied molecular orbital (LUMO) energies [71]. As an illustration, the energy levels of the chalcogen atom's HOMO and LUMO orbitals as well as the Lewis base acceptor can be employed as orbital characteristics.

iv. *Interaction Energies*:Chalcogen bonding analysis requires precise measurement of the interaction energies that characterize chalcogen bonding interactions. The stability and power of chalcogen bonds can therefore be represented by characteristics relating to interaction energies. The strength of the chalcogen bonding in the complexes can be measured using features derived from interaction energies computed using quantum mechanical techniques, such as density functional theory (DFT).

v. *Hybrid Features*:To capture thorough representations of chalcogen bonding interactions, hybrid features incorporate many forms of information, such as geometric and electrical features. An instance of a hybrid feature would be the sum of the absolute value of the partial charge on the chalcogen atom and the bond length between the chalcogen atom and the Lewis base acceptor. This characteristic captures the electrostatic and geometric properties of chalcogen bonding [72-73].

vi. *Physical Characteristics*:Physical Characteristics can also be important elements in chalcogen bonding analysis. Examples include molecular weight, Van der Waals volume, and polarizability. For instance, information on steric interactions in the chalcogen-bonded complex can be obtained from the Van der Waals volume of the chalcogen atom or the Lewis base acceptor [74].

vii. *Derived Characteristics from Machine Learning*:Using machine learning models, one can create fresh characteristics that are tailored for chalcogen bonding investigation. As an illustration, Principal Component Analysis (PCA) can be used to decrease the dimension of the feature space while keeping significant data fluctuations, resulting in more effective feature representation [75].

viii. *One-Hot Encoding*:One-hot encoding can be used to transform categorical characteristics into numerical representations appropriate for machine learning models, such as the type of chalcogen-bonded interactions (for example, hydrogen bonding, halogen bonding). Examples include

oxygen-hydrogen and sulfur-oxygen chalcogen bonds, as demonstrated in Figure 6. These features can be one-hot encoded into binary vectors [76].

Eurasian Journal of Science and Technology

Figure 6 Sulphur and oxygen chalcogen bond [76]

One of the most important steps in applying machine learning to chalcogen bonding studies is the extraction of pertinent chemical characteristics. Researchers can create robust and understandable machine learning models that offer useful insights into the nature and characteristics of chalcogen bonding interactions by carefully choosing and modelling these features. To ensure that the machine learning model captures the most crucial characteristics of chalcogen bonding in the dataset, the choice of features should be guided by domain expertise and the specific study objectives [76].

Machine Learning Models for Chalcogen Bond Characterization

Supervised Learning Models for Classification and Regression Tasks

For both classification and regression problems, supervised learning models are frequently employed in the characterisation of chalcogen bonds. These models are trained on labelled datasets, where the input features represent chalcogen-bonded complexes and the corresponding output labels or goal values denote the existence, strength, or kind of chalcogen bonding [77]. In this article, we go over a few popular supervised learning models for characterizing chalcogen bonds and provide pertinent examples.

i. *Support Vector Machines (SVM)*:SVM is a potent classifier that divides data into various groups based on hyperplanes.

When the data cannot be separated linearly, it effectively transforms the features into a higher-dimensional space. Based on their geometrical and electrical characteristics, SVM has been used to categorize complexes that are chalcogen-bonded and those that are not. For instance, SVM was trained on a dataset of labelled complexes with geometric (e.g., bond lengths and angles) and electronic (e.g., partial charges) properties in a study of chalcogen bonding interactions. Based on their characteristics, the SVM model correctly identified novel compounds as chalcogen-bonded or non-chalcogen-bonded [78].

ii. *Decision Trees*:Based on the values of the features, decision trees are straightforward but efficient classification models that build a tree-like structure. They can identify non-linear relationships in the data and are simple to comprehend. Chalcogen bonding interactions have been categorized using decision trees based on geometric and physicochemical parameters [79]. An example is a dataset containing chalcogen-bonded compounds and the accompanying physicochemical descriptors (such as Van der Waals volume and polarizability), were employed in a decision tree-based technique. The chalcogen bonding-indicating combinations of descriptors were found by the decision tree model [80].

iii. *Random Forests*:An ensemble learning technique known as Random Forests mixes several decision trees to increase predicted accuracy and decrease overfitting. They are frequently employed in chalcogen bond characterisation for classification jobs because of their dependability and capacity for handling large amounts of data. Using variables from molecular dynamics simulations, such as bond fluctuations and hydrogen bonding patterns, a random forest model was trained on a dataset of chalcogen-bonded complexes. Based on these dynamic properties, the random forest model successfully predicted the intensity of chalcogen bonding in novel complexes, as shown in Figure 7.
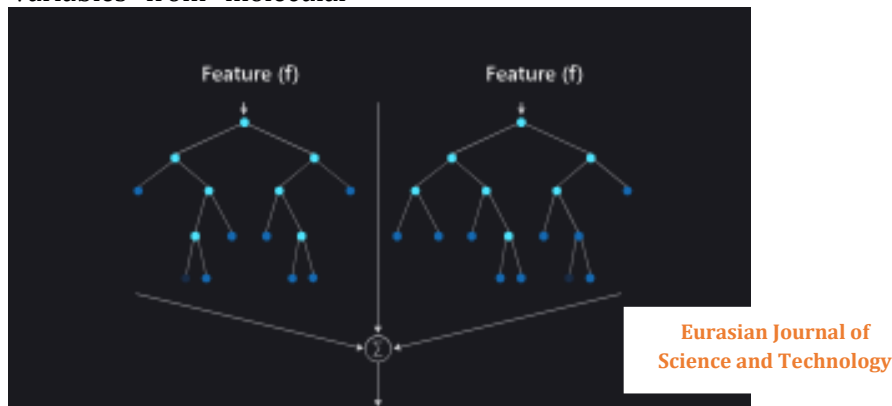

Figure 7 Diagram showing random forest [80]

iv. *Neural Networks*:Deep learning architectures such as Convolutional Neural Networks (CNNs) and Multi-Layer Perceptrons (MLPs) have demonstrated excellent performance in chalcogen bond characterisation tasks. They are appropriate for high-dimensional feature spaces because they automatically learn complicated representations from unstructured input. An example is using a deep learning approach; a CNN was trained on a collection of volumetric data representing the 3D molecular structures of chalcogen-bonded complexes [81]. Intricate patterns in the electron density distribution were recognized by the CNN, which also developed the ability to precisely foresee the existence and strength of chalcogen bonding.

v. *Regression Models*:Regression models are used to characterize chalcogen bonds when the target variable is a continuous variable, such as when estimating the interaction energy or bond strength of chalcogen-bonded complexes. Commonly used regression methods include linear regression, ridge regression, and support vector regression (SVR) [82]. An example is a dataset with labelled chalcogen-bonded complexes and the computed interaction energy of those complexes from quantum mechanical computations was used in a regression exercise. To forecast the interaction energies of fresh chalcogen-bonded complexes based on their characteristics, a Support Vector Regression model was trained [83-85].

vi. *Gradient Boosting Models*:Gradient Boosting models, including XGBoost and LightGBM, are well-liked ensemble techniques that pool the predictions of several weak learners to produce a potent model. They are strong and frequently perform better in challenging classification and regression tasks than other models. A Gradient Boosting

model was used, for instance, to categorize chalcogen-bonded complexes according to their geometrical and electrical characteristics. Chalcogen bond classification accuracy was enhanced by the model's capacity to handle non-linear correlations and interactions between features (Figure 8) [86].
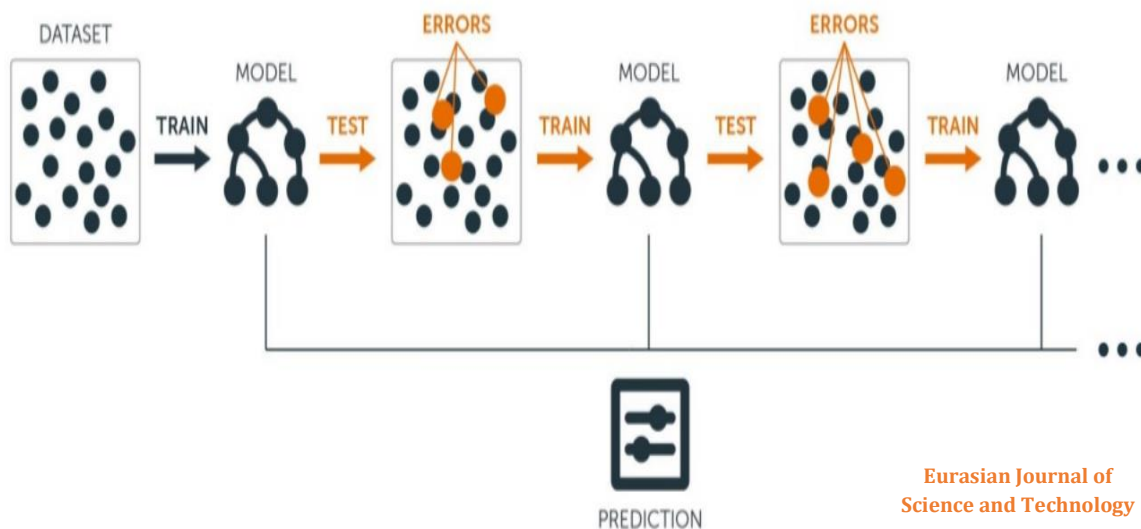
Figure 8 Graphical representation of GBM algorithm [86]

Chalcogen bond characterisation relies heavily on supervised learning models, including SVM, decision trees, random forests, neural networks, regression models, and gradient boosting models. These models use labelled datasets to categorize complexes, forecast the strength of chalcogen bonds, or pinpoint particular chalcogen bonding patterns. The precise research question and the type of data that are available will determine the best model to use in disciplines like materials science, drug design, and catalysis by applying supervised learning in chalcogen bond characterization to acquire important insights into the behaviour and properties of chalcogen-bonded complexes [87].

Unsupervised Learning Methods for Clustering and Pattern Recognition

Chalcogen bond characterization relies heavily on unsupervised learning techniques, particularly when grouping chalcogen-bonded compounds based on similarities and spotting patterns in the data. Unsupervised learning algorithms, in contrast to supervised learning, do not rely on labelled data or need explicit target labels. Instead, they seek to identify hidden patterns and connections in the data that will shed light on the variety and complexity of chalcogen bonding interactions [88]. The following list includes some popular unsupervised learning techniques for chalcogen bond characterization:

i. *K-Means Clustering*:One of the most widely used clustering methods in unsupervised learning is K-Means. The data will be divided into K clusters, and each data point will be assigned to the cluster with the closest mean. Chalcogen bonding has been classified into several classes or types using K-Means clustering to group complexes with comparable structural and electrical characteristics [89-90]. A dataset of chalcogen-bonded complexes is clustered using K-Means based on

their geometrical and electrostatic characteristics in a chalcogen bond study in Figure 9. The technique reveals various chalcogen bonding interactions by locating separate clusters corresponding to different chalcogen bond strengths or bond kinds.

Eurasian Journal of
Science and Technology
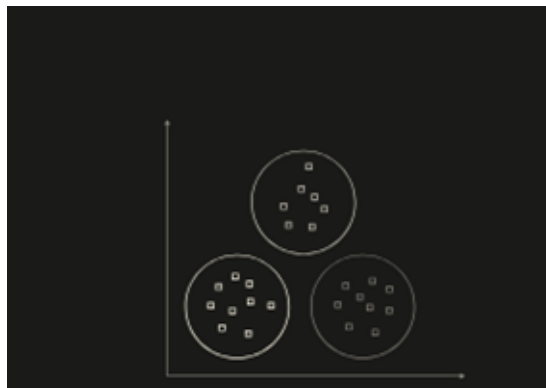
Figure 9 Graphical representation of K-mean clustering [90]

ii. *Hierarchical Clustering*:Another popular technique for unsupervised learning in chalcogen bond characterisation is hierarchical clustering. By repeatedly combining data points or clusters based on their similarity, it produces a structure resembling a tree (dendrogram) [91]. The hierarchical linkages and groupings of Chalcogen-bonded complexes have been investigated using hierarchical clustering. As an illustration, a dendrogram based on the pairwise distances of chalcogen-bonded complexes in terms of their structural and physicochemical characteristics is created using hierarchical clustering. The dendrogram provides a hierarchical picture of the chalcogen bonding patterns by exposing clusters at various levels of similarity [92].

iii. *Density-Based Spatial Clustering of Applications with Noise (DBSCAN)*:DBSCAN is a density-based clustering technique that arranges data points according to their density. It can successfully deal with noise and outliers and recognizes dense areas as clusters [93]. DBSCAN has been used in chalcogen bond analysis to locate tightly packed chalcogen-bonded complexes and find outliers or non-chalcogen-bonded complexes. An example is using DBSCAN on a dataset of chalcogen-bonded complexes; the algorithm recognizes densely packed areas that correspond to complexes with potent chalcogen bonds. Noise is defined as outliers or complexes with little to no chalcogen bonding interactions (Figure 10) [94].

Eurasian Journal of
Science and Technology
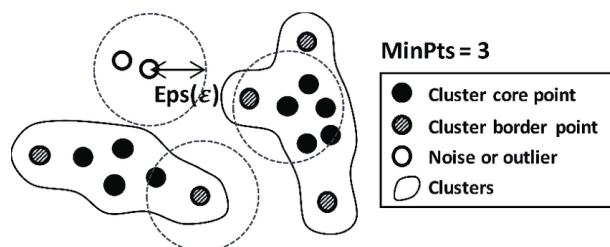
Figure 10 Graphical representation of DBSCAN [94]

iv. *Self-Organizing Maps (SOM)*:SOM is a kind of unsupervised learning technique based on neural networks that reduces the dimension of high-dimensional data to a low-dimensional representation, which is commonly represented as a grid. Chalcogen bond characterisation has used SOMs to map complex datasets and find groups of related chalcogen-bonded compounds. A two-dimensional grid with comparable complexes mapped to nearby places is produced by training a SOM on a dataset of chalcogen-bonded complexes utilizing their geometric and electrical properties is an example of SOM. Finding patterns and areas of interest in the data is made easier with the help of this display [95].

v. *T-Distributed Stochastic Neighbour Embedding (t-SNE)*:This dimensionality reduction approach is frequently used to visualize high-dimensional data in a lower-dimensional environment. It is very helpful for exploratory data analysis and pattern recognition in chalcogen bond characterisation. For example, in chalcogen bond analysis, t-SNE is used to minimize the dimensionality of the dataset while maintaining the local structures and connections between chalcogen-bonded complexes. The reduced data can then be displayed in a two-dimensional space, emphasizing clusters or groups of related complexes [96].

The underlying structures and patterns in chalcogen bond characterisation can be explored and understood using unsupervised learning techniques including K-Means, hierarchical clustering, DBSCAN, SOM, and t-SNE. Without the need for labelled data, these methods allow researchers to identify patterns and clusters among chalcogen-bonded complexes. To better comprehend this crucial non-covalent interaction and its applicability in numerous scientific domains, researchers can use unsupervised learning to gather insightful knowledge about the diversity and structure of chalcogen bonding interactions [97].

Interpretability and Visualization of Machine Learning Results

Characterizing chalcogen bonding interactions depends heavily on the interpretability and indicating machine learning outcomes. Understanding the rationale behind machine learning models' predictions becomes more crucial as they get more complicated and sophisticated. Researchers can learn more about the models' decision-making processes, which characteristics are most important for making predictions, and whether the model accurately depicts the underlying scientific ideas underpinning chalcogen bonding [97]. The use of visualization, on the other hand, offers a potent tool for representing highly dimensional data and modelling results in a manner that is more accessible and straightforward. Learning the underlying chemistry of chalcogen bonding interactions and comprehending the factors impacting model predictions require the interpretation of machine learning models in chalcogen bonding analyses. To analyze machine learning models used in chalcogen bonding studies, a variety of methodologies can be used:

1. *Feature Importance Analysis*:This technique identifies the most important attributes that have a big impact on the model's predictions. These methods offer a numerical assessment of each feature's impact on the model's output [98].

a. *Permutation Feature Importance*:This technique includes randomly rearranging the values of distinct features and gauging how much the performance of the model suffers as a result. The most crucial features are those whose performance suffers the greatest when they are shuffled. For instance, permutation feature importance demonstrates that the bond length between the chalcogen atom and the Lewis base acceptor is the feature that has the greatest impact on a random forest model that predicts the strength of chalcogen bonds [99].

b. *SHAP (SHapley Additive exPlanations)*:By taking into account all potential feature interactions, SHAP values offer a single measure of feature relevance. They quantify how much each attribute contributes to a particular prediction in relation to how much it contributes to other predictions. A certain geometric parameter in a chalcogen-bonded complex, for instance, has a greater positive SHAP value according to SHAP analysis, indicating that it has a considerable positive influence on the model's prediction of strong chalcogen bonding.

2. *Partial Dependence Plots (PDPs)*:PDPs illustrate how the expected result changes when a particular feature is varied while holding all other features constant. PDPs aid in comprehending the connection between particular features and the model's forecasts. For example, a partial dependence plot for the bond angle between the Lewis base acceptor and the chalcogen atom reveals that as the bond angle increases, the projected strength of the chalcogen bonding gradually decreases [100].

3. *SHAP Summary Plots*:SHAP summary plots show the average influence of each feature across all predictions in the dataset, giving a broad perspective of feature relevance. They aid in determining which characteristics influence the model's predictions most consistently. An illustration of a SHAP summary plot shows how the partial charge on the chalcogen atom consistently influences the model's predictions of the strength of the chalcogen bond.

4. *Rule-Based Methods*:Rule-based models, such decision trees and rule-based classifiers, offer understandable, interpreted models. On the basis of the input features, they produce transparent decision rules. When the length of the chalcogen-acceptor bond is below a particular threshold and the partial charge on the chalcogen atom is negative, a decision tree model predicts that a chalcogen bond is likely to form [101].

Visualization tools for chalcogen bonding characterization

a. *3D Complex Visualization*:Researchers can better comprehend the spatial properties and structural arrangements of chalcogen bonding interactions by visualizing chalcogen-bonded complexes in three dimensions. The spatial orientation of the chalcogen and Lewis base atoms, the bond angles, and the presence of hydrogen bonds or other secondary interactions in the chalcogen-bonded complex can all be seen by researchers using 3D visualization tools [102].

b. *t-SNE and UMAP*:Dimensionality reduction methods such as t-SNE (t-distributed Stochastic Neighbor Embedding) and UMAP (Uniform Manifold Approximation and Projection) are used to visualize high-dimensional data in a lower-dimensional space and reveal clusters or groupings of related chalcogen-bonded complexes. Examples include the identification of discrete clusters of chalcogen-bonded complexes with related characteristics using t-SNE or UMAP, which can shed light on the various forms or intensities of chalcogen bonding interactions.

c. *Interactive Visualizations*:With the aid of interactive visualization tools, researchers can examine the data, adjust model parameters, and see in real time how features affect model predictions. To better understand the energetics of chalcogen bonding, researchers can alter geometric factors of a complex that is chalcogen-bonded and see how the interaction energy changes as a result [103].

d. *Heatmaps and Plots*:By providing a visual depiction of feature interactions and correlations, heatmaps and plots allow researchers to pinpoint connections between certain features and the results of chalcogen bonding. A heatmap illustration showing the link between bond lengths and partial charges in a dataset of chalcogen-bonded complexes

shows which properties are more common in interactions that are either strong or weak [104].

Characterizing chalcogen bonding interactions requires machine learning findings to be interpretable and visually appealing. These features help to deepen our understanding of chalcogen bonding patterns and advance the development of novel materials and pharmaceuticals based on this significant non-covalent interaction. They also offer transparency and insights into the decision-making process of machine learning models [105].

Applications of Machine Learning in Chalcogen Bonding Studies

Chalcogen bonding studies have made extensive use of machine learning techniques, which has helped scientists learn more about the nature, characteristics, and practical uses of chalcogen bonding interactions [106]. In chalcogen bonding investigations, machine learning has found major uses in:

1. *Chalcogen Bonding Interaction Prediction*:To predict the presence, strength, or type of chalcogen bonding in new molecular structures, machine learning models can be trained on datasets containing chalcogen-bonded complexes with labelled interactions. This prediction ability is especially beneficial for screening and spotting potential chalcogen bonding interactions in novel materials, drug candidates, and catalysts.

2. *Characterization of Chalcogen Bond Strength*:Understanding the influence of chalcogen bonds on molecular characteristics and reactivity depends on being able to quantify the strength of chalcogen bonds. Based on geometric, electrical, and energetic properties, chalcogen bond strengths can be predicted using machine learning algorithms, such as regression models or neural networks [107].

3. *Structure-Property Relationship*:Chalcogen-bonded complexes and particular physical, chemical, or biological features can be related in terms of their structure through the use of machine learning. Machine learning models are able to pinpoint crucial characteristics that affect how properties vary and can help with property optimization by learning from big datasets [108].

4. *Chalcogen Bonding Motif Identification*:Recurring patterns and motifs in chalcogen bonding interactions can be found using machine learning algorithms. The preferred geometry and electrical characteristics of chalcogen bonds in particular chemical conditions may be learned from these motifs [109].

5. *Analysis of Chalcogen-Bonded Supramolecular Assemblies*:The production of supramolecular assemblies and materials frequently depends on chalcogen bonding. In order to create new materials with the appropriate features, machine learning can help analyze the stability and characteristics of these assemblies.

6. *Chalcogen-Bonding Catalyst Rational Design*:Chalcogen bonding has been investigated as a potent method for designing catalysts. By predicting the catalytic performance of chalcogen-bonding catalysts based on structural and electrical characteristics, machine learning can help with the rational design of these materials.

7. *Exploration of Chalcogen Bonding in Crystal Engineering*:Chalcogen bonding can affect the packing and characteristics of crystals in crystal engineering. Understanding the effects of chalcogen bonding on crystal structures and characteristics might aid in the optimization of materials for particular applications [110].

Overall, machine learning has emerged as a crucial tool in chalcogen bonding research, allowing scientists to quickly analyze sizable datasets, forecast chalcogen bonding interactions, gain understanding of the structure-property relationships, and develop novel materials and pharmaceuticals with improved properties. Machine learning methods are projected to advance in chalcogen bonding research as they develop, helping to advance a variety of scientific disciplines [111].

Advantages of Machine Learning over Experimental and Computational Methods

In many scientific fields, machine learning has a number of advantages over conventional experimental and computational techniques. These benefits result from its capacity to recognize patterns, extrapolate generalizations from data, and forecast events without explicit programming [112]. The following are some significant benefits of machine learning over conventional methods:Compared to conventional experimental or computational approaches, machine learning can process enormous amounts of data rapidly and efficiently, allowing researchers to examine complicated issues at a considerably faster rate [113]. When working with huge datasets or high-dimensional data, where conventional methods may be computationally expensive and time-consuming, this efficiency is very important. Machine learning automates feature extraction, model training, and prediction, requiring less manual intervention and conserving resources. Because of the time and resource savings from this automation, researchers can concentrate on more complex activities and problem-solving instead of tedious, time-consuming jobs [114-115].

Machine learning algorithms have the ability to recognize complicated and nonlinear correlations in data, which may be difficult for conventional approaches to do. Because of its adaptability, machine learning can tackle more challenging scientific issues involving nonlinear relationships between variables [116]. Machine learning discovers patterns from data instead of relying on explicit models or assumptions like

traditional methods do. This data-driven methodology enables the identification of hidden patterns and insights that might not be visible in theory-driven models [117]. Machine learning algorithms are robust in situations where traditional approaches may find it difficult to produce correct findings owing to data constraints. Machine learning techniques are suited for big data applications across a range of scientific disciplines because they are easily scaled to accommodate vast and complicated datasets. As new data becomes available, machine learning models can be updated and improved, enabling continual improvement and adaption to altering settings or knowledge [118-120].

To produce thorough analyses and predictions, machine learning can efficiently integrate data from multiple sources, including experimental data, computer simulations, and external databases. Exploratory data analysis is made possible by machine learning, which helps researchers to spot patterns, trends, and connections in data that might not have been apparent using more conventional approaches [121]. Optimization and hyperparameter tuning are two machine learning strategies that are frequently used to fine-tune model performance and help researchers get the best outcomes for particular tasks [122-126].

Machine learning is an effective tool for tackling challenging scientific problems, processing big datasets quickly, and drawing insightful conclusions from data due to its many benefits over conventional experimental and computational approaches. Machine learning is an essential tool in many scientific fields, from chemistry and materials science to biology, medicine, and beyond, due to its capacity to automate operations, manage nonlinearities, and continuously improve models [127].

Conclusion

Machine learning has been a revolutionary and potent method for characterizing chalcogen bonding interactions. In numerous chemical and biological processes, chalcogen bonding-a crucial non-covalent interaction involving

elements like oxygen, sulfur, selenium, and tellurium-plays a critical role. Chalcogen bonding is a crucial non-covalent interaction that plays a significant role in various chemical and biological processes. Experimental techniques, such as infrared (IR), nuclear magnetic resonance (NMR) spectroscopy, and X-ray crystallography, have been used to study chalcogen bonding, but they often suffer from inherent experimental challenges. Computational approaches, including quantum mechanics (QM) and molecular dynamics (MD) simulations, offer valuable insights into the electronic structure and energetics of chalcogen bonding, but they can be computationally demanding and may not fully encompass the diversity of chalcogen bonding interactions. Machine learning has emerged as a powerful tool for studying molecular interactions, including chalcogen bonding. By integrating experimental data and computational results, machine learning models offer a holistic approach to understanding chalcogen bonding in various molecular systems. Machine learning algorithms, such as supervised and unsupervised learning, can be employed to classify and predict chalcogen-bonded complexes using neural network potentials to assess the persistence of chalcogen bonds in solution and ML models to predict two key solid-state synthesis conditions that must be specified for chalcogenide glasses. The integration of experimental and computational data maximizes the accuracy and applicability of machine learning models and envisions a promising future for machine learning in characterizing chalcogen bonding interactions. Chalcogen bonding research has been transformed by the use of machine learning to experimental and computational techniques, yielding fresh perspectives and quickening scientific advancement in this area. The ability of machine learning to process huge and complicated datasets quickly is one of its main advantages. Machine learning models have the ability to examine enormous volumes of data from computational simulations and experimental measurements, revealing subtle patterns and correlations that might not be seen using conventional methods. It is possible to anticipate and characterize chalcogen bonds

in novel chemical systems using machine learning models that can recognize significant geometric, electrical, and energetic properties that control chalcogen bonding interactions. Another important factor that improves our comprehension of chalcogen bonding is the interpretability of machine learning outcomes. Understanding the variables affecting the nature and strength of chalcogen bonds is possible with the use of methods like feature importance analysis and partial dependence plots. The discovery of important molecular descriptors that control chalcogen bonding interactions is made easier by this interpretability, which helps in the rational design and optimization of molecular systems with particular chalcogen bonding properties.

Machine learning has evolved into a crucial technique for characterizing chalcogen bonding. Our understanding of chalcogen bonding interactions has been completely transformed by its capacity to handle and learn from data, give interpretability, and combine different information sources. It is anticipated that the uses of machine learning in chalcogen bonding investigations will expand as machine learning techniques develop and more data becomes accessible, leading to new discoveries and improvements across a range of scientific fields. In the end, the use of machine learning in chalcogen bonding characterisation opens the door to the design and optimization of molecular systems with specialized functionalities and characteristics for a variety of real-world uses. The use of machine learning in chalcogen bonding has completely changed how scientists see, describe, and foresee chalcogen bonding interactions. In order to better understand the nature and features of chalcogen bonding, which is essential to many chemical and biological processes, scientists have combined experimental and computational methodologies. In comparison to conventional experimental and computational approaches, machine learning has shown to be an effective technique for chalcogen bond characterisation. With its help, enormous datasets can be analysed effectively, chalcogen bonding interactions can be predicted quickly, and important factors affecting the strength and

characteristics of chalcogen bonds may be found. Researchers have been able to investigate complex molecular systems and detect tiny chalcogen bonding patterns that were previously difficult to identify thanks to machine learning models' capacity to learn patterns, generalize from data, and handle nonlinear interactions. Through the provision of a thorough and all-encompassing method to investigate these interactions, the integration of experimental data with computational models has significantly improved our understanding of chalcogen bonding.

Overall, the combination of machine learning with research on chalcogen bonds has sped up scientific advancement and opened up new possibilities for the construction and improvement of molecular systems with particular properties and capabilities. There is a progress in comprehending chalcogen bonding by utilizing the benefits of machine learning, leading to advancements in areas including drug design, crystal engineering, catalysis, and materials sciences. The scope and effect of machine learning in chalcogen bonding investigations are anticipated to grow as these techniques continue to advance and more data becomes accessible. The full potential of chalcogen bonding interactions and its applications across several scientific fields can be revealed by the seamless integration of experimental data, computational simulations, and machine learning models. In the end, the combination of human expertise and machine learning capabilities promises a deeper comprehension of chalcogen bonding and the capacity to harness its strength in the design and development of novel molecular systems for various applications.

Conflict of Interest

The authors declare that there is no conflict of interest in this study.

Funding

Informed Consent Statement

Not applicable.

Ethical approval statement

Not applicable.

ORCID

Humphrey Sam Samuel
https://www.orcid.org/0009-0001-7480-4234
Emmanuel Edet Etim
https://www.orcid.org/0000-0001-8304-9771

References

[1] Alikhani E., Fuster F., Madebene B., Grabowski S.J., Topological reaction sites–very strong chalcogen bonds. *Physical Chemistry Chemical Physics*, 2014, **16**:2430 [Crossref], [Google Scholar], [Publisher]

[2] Andrews S.S., Tretton J., Physical principles of circular dichroism. *Journal of Chemical Education*, 2020, **97**:4370 [Crossref], [Google Scholar], [Publisher]

[3] Alkorta I., Elguero J., Frontera A., Not only hydrogen bonds:Other noncovalent interactions. *Crystals*, 2020, **10**:180 [Crossref], [Google Scholar], [Publisher]

[4] Alfuth J., Zadykowicz B., Wicher B., Kazimierczuk K., Połoński T., Olszewska T., Cooperativity of Halogen-and Chalcogen-Bonding Interactions in the Self-Assembly of 4-Iodoethynyl-and 4, 7-Bis (iodoethynyl) benzo-2, 1, 3-chalcogenadiazoles:Crystal Structures, Hirshfeld Surface Analyses, and Crystal Lattice Energy Calculations. *Crystal Growth & Design*, 2022, **22**:1299 [Crossref], [Google Scholar], [Publisher]

[5] Bleiholder C., Werz D.B., Köppel H., Gleiter R., Theoretical investigations on chalcogen–chalcogen interactions:what makes these nonbonded interactions bonding?. *Journal of the American Chemical Society*, 2006, **128**:2666 [Crossref], [Google Scholar], [Publisher]

[6] Eikås K.D.R., Beerepoot M.T., Ruud K., A computational protocol for vibrational circular dichroism spectra of cyclic oligopeptides. *The*

Journal of Physical Chemistry A, 2022, **126**:5458 [Crossref], [Google Scholar], [Publisher]

[7] Fellowes T., White J.M., Simulating chalcogen bonding using molecular mechanics:a pseudoatom approach to model ebselen. *Journal of Molecular Modeling*, 2022, **28**:66 [Crossref], [Google Scholar], [Publisher]

[8] Galmés B., Juan-Bals A., Frontera A., Resnati G., Charge-assisted chalcogen bonds:csd and dft analyses and biological implication in glucosidase inhibitors. *Chemistry–A European Journal*, 2020, **26**:4599 [Crossref], [Google Scholar], [Publisher]

[9] Garrett G.E., Gibson G.L., Straus R.N., Seferos D.S., Taylor M.S., Chalcogen bonding in solution:interactions of benzotelluradiazoles with anionic and uncharged Lewis bases. *Journal of the American Chemical Society*, 2015, **137**:4126 [Crossref], [Google Scholar], [Publisher]

[10] Ito A., Asato M., Asami Y., Fukuda K., Yamasaki R., Okamoto I., Synthesis and Conformational Analysis of *N*-Aromatic Acetamides Bearing Thiophene:Effect of Intramolecular Chalcogen–Chalcogen Interaction on Amide Conformational Stability. *The Journal of Organic Chemistry*. 2023, **88**:7075 [Crossref], [Google Scholar], [Publisher]

[11] Artemjev A.A., Kubasov A.S., Zaytsev V.P., Borisov A.V., Kritchenkov A.S., Nenajdenko V.G., Gomila R.M., Frontera A, Tskhovrebov A.G., Novel Chalcogen Bond Donors Derived from [3+2] Cycloaddition Reaction between 2-Pyridylselenyl Reagents and Isocyanates:Synthesis, Structures and Theoretical Studies. *Crystal Growth & Design*, 2023, **23**:2018 [Crossref], [Google Scholar], [Publisher]

[12] Samuel H.S., Etim E.E., Nweke-Maraizu U., Approaches for Special Characteristics of Chalcogen Bonding:A mini ReviewApplied Organometallic Chemistry, 2023, 3:199 [Crossref], [Google Scholar], [Publisher]

[13] Scheiner S., Various sorts of chalcogen bonds formed by an aromatic system. *The Journal of Physical Chemistry A*, 2022, **126**:4025 [Crossref], [Google Scholar], [Publisher]

[14] Scheiner S., Principles guiding the square bonding motif containing a pair of chalcogen bonds between chalcogenadiazoles. *The Journal of Physical Chemistry A*, 2022, **126**:1194 [Crossref], [Google Scholar], [Publisher]

[15] Osigbemhe I.G., Louis H., Khan E.M., Etim E.E., Odey D.O., Oviawe A.P., Edet H.O., Obuye, F., Synthesis, characterization, DFT studies, and molecular modeling of 2-(-(2-hydroxy-5-methoxyphenyl)-methylidene)-amino) nicotinic acid against some selected bacterial receptors. *Journal of the Iranian Chemical Society*, 2022, **19**:3561 [Crossref], [Google Scholar], [Publisher]

[16] Osigbemhe I.G., Louis H., Khan E.M., Etim E.E., Oyo-Ita E.E., Oviawe A.P., Edet H.O., Obuye F., Antibacterial potential of 2-(-(2-Hydroxyphenyl)-methylidene)-amino) nicotinic Acid:Experimental, DFT Studies, and molecular docking approach. *Applied Biochemistry and Biotechnology*, 2022, **194**:5680 [Crossref], [Google Scholar], [Publisher]

[17] Osigbemhe I.G., Oyoita E.E., Louis H., Khan E.M., Etim E.E., Edet H.O., Ikenyirimba O.J., Oviawe A.P., Obuye F., Antibacterial potential of N-(2-furylmethylidene)-1, 3, 4-thiadiazole-2-amine:Experimental and theoretical investigations. *Journal of the Indian Chemical Society*, 2022, **99**:100597 [Crossref], [Google Scholar], [Publisher]

[18] Samuel H., Nweke-Maraizu U., Etim E., Experimental and Theoretical Approaches for Characterizing Halogen Bonding, *Journal of Applied Organometallic Chemistry*, 2023, **3**:169 [Crossref], [Publisher]

[19] Geboes Y., De Vleeschouwer F., De Proft F., Herrebout W.A., Exploiting the σ-Hole Concept:An Infrared and Raman-Based Characterization of the S⋯ O Chalcogen Bond between 2, 2, 4, 4-Tetrafluoro-1, 3-dithiethane

and Dimethyl Ether. *Chemistry–A European Journal*, 2017, **23**:17384 [Crossref], [Google Scholar], [Publisher]

[20] Gougoula E., Moxon J.A., Walker N.R., Legon A.C., A chalcogen-bonded complex (CH₃) 3N··· SCO characterised by rotational spectroscopy. *Chemical Physics Letters*, 2020, **743**:137177 [Crossref], [Google Scholar], [Publisher]

[21] Hu Q., Zhao H., Ouyang S., Understanding water structure from Raman spectra of isotopic substitution H_2O/D_2O up to 573 K. *Physical Chemistry Chemical Physics*, 2017, **19**:21540 [Crossref], [Google Scholar], [Publisher]

[22] Ito H., Hasegawa T., Tanimura Y., Effects of intermolecular charge transfer in liquid water on Raman spectra. *The Journal of Physical Chemistry Letters*, 2016, **7**:4147 [Crossref], [Google Scholar], [Publisher]

[23] Begušić T., Blake G.A., Two-dimensional infrared-Raman spectroscopy as a probe of water's tetrahedrality. *Nature Communications*, 2023, **14**:1950 [Crossref], [Google Scholar], [Publisher]

[24] Aitipamula S., Vangala V.R., X-ray crystallography and its role in understanding the physicochemical properties of pharmaceutical cocrystals. *Journal of the Indian Institute of Science*, 2017, **97**:227 [Crossref], [Google Scholar], [Publisher]

[25] Woińska M., Grabowsky S., Dominiak P.M., Woźniak K., Jayatilaka D., Hydrogen atoms can be located accurately and precisely by x-ray crystallography. *Science advances*, 2016, **2**:e1600192 [Crossref], [Google Scholar], [Publisher]

[26] Adhav V.A., Pananghat B., Saikrishnan K., Probing the Directionality of S··· O/N Chalcogen Bond and Its Interplay with Weak C–H··· O/N/S Hydrogen Bond Using Molecular Electrostatic Potential. *The Journal of Physical Chemistry B*, 2022, **126**:7818 [Crossref], [Google Scholar], [Publisher]

[27] Zhang J., Wang N., Liu W., Zhao X., Lu W., Intermolecular hydrogen bonding strategy to fabricate mechanically strong hydrogels with high elasticity and fatigue resistance. *Soft Matter*, 2013, **9**:6331 [Crossref], [Google Scholar], [Publisher]

[28] Zhao Z., Wang Y., Chalcogen Bonding Catalysis with Phosphonium Chalcogenide (PCH). *Accounts of Chemical Research*, 2023, **56**:608 [Crossref], [Google Scholar], [Publisher]

[29] Scheiner S., Various sorts of chalcogen bonds formed by an aromatic system. *The Journal of Physical Chemistry A*, 2022, **126**:4025 [Crossref], [Google Scholar], [Publisher]

[30] Breugst M., von der Heiden D., Schmauck J., Novel noncovalent interactions in catalysis:a focus on halogen, chalcogen, and anion-π bonding. *Synthesis*, 2017, **49**:3224 [Crossref], [Google Scholar], [Publisher]

[31] Kumar V., Triglav M., Morin V.M., Bryce, D.L., Predictability of Chalcogen-Bond-Driven Crystal Engineering:An X-ray Diffraction and Selenium-77 Solid-State NMR Investigation of Benzylic Selenocyanate Cocrystals. *ACS Organic & Inorganic Au*, 2022, **2**:252 [Crossref], [Google Scholar], [Publisher]

[32] Mohammadi M.D., Abdullah H.Y., Louis H., Etim E.E., Edet H.O., Godfrey O.C., Hexachlorobenzene (HCB) adsorption onto the surfaces of C60, C59Si, and C59Ge:Insight from DFT, QTAIM, and NCI. *Chemical Physics Impact*, 2023, **6**:100234 [Crossref], [Google Scholar], [Publisher]

[33] Erdelyi M., Halogen bonding in solution. *Chemical Society Reviews*, 2012, **41**:3547 [Crossref], [Google Scholar], [Publisher]

[34] Lim J.Y., Marques I., Félix V., Beer P.D., Chiral halogen and chalcogen bonding receptors for discrimination of stereo-and geometric dicarboxylate isomers in aqueous media. *Chemical Communications*, 2018, **54**:10851 [Crossref], [Google Scholar], [Publisher]

[35] Robinson S.W., Mustoe C.L., White N.G., Brown A., Thompson A.L., Kennepohl P., Beer P.D., Evidence for halogen bond covalency in acyclic and interlocked halogen-bonding receptor anion recognition. *Journal of the American Chemical Society*, 2015, **137**:499 [Crossref], [Google Scholar], [Publisher]

[36] Garrett G.E., Carrera E.I., Seferos D.S., Taylor M.S., Anion recognition by a bidentate chalcogen bond donor. *Chemical Communications*, 2016, **52**:9881 [Crossref], [Google Scholar], [Publisher]

[37] Docker A., Guthrie C.H., Kuhn H., Beer P.D., Modulating Chalcogen Bonding and Halogen Bonding Sigma-Hole Donor Atom Potency and Selectivity for Halide Anion Recognition. *Angewandte Chemie International Edition*, 2021, **60**:21973 [Crossref], [Google Scholar], [Publisher]

[38] Bunchuay T., Docker A., Eiamprasert U., Surawatanawong P., Brown A., Beer P.D., Chalcogen Bond Mediated Enhancement of Cooperative Ion-Pair Recognition. *Angewandte Chemie International Edition*, 2020, **59**:12007

[39] Etim E.E., Gorai P., Ghosh R., Das A., Detectable interstellar anions:Examining the key factors. *Spectrochimica Acta Part A:Molecular and Biomolecular Spectroscopy*, 2020, **230**:118011 [Crossref], [Google Scholar], [Publisher]

[40] Li G., Xu L., Zhang W., Zhou K., Ding Y., Liu F., He X., He G., Narrow-Bandgap Chalcogenoviologens for Electrochromism and Visible-Light-Driven Hydrogen Evolution. *Angewandte Chemie International Edition*, 2018, **57**:4897 [Crossref], [Google Scholar], [Publisher]

[41] Park G., Gabbaï F.P., Redox-controlled chalcogen and pnictogen bonding:The case of a sulfonium/stibonium dication as a preanionophore for chloride anion transport. *Chemical Science*, 2020, **11**:10107 [Crossref], [Google Scholar], [Publisher]

[42] Freire E., Schön A., Velazquez-Campoy, A., Isothermal titration calorimetry: general formalism using binding polynomials. *Methods in enzymology*, 2009, **455**:127 [Crossref], [Google Scholar], [Publisher]

[43] Franz D., Inoue S., Advances in the development of complexes that contain a group 13 element chalcogen multiple bond. *Dalton Transactions*, 2016, **45**:9385 [Crossref], [Google Scholar], [Publisher]

[44] Ho P.C., Wang J.Z., Meloni F., Vargas-Baca I., Chalcogen bonding in materials chemistry. *Coordination Chemistry Reviews*, 2020, **422**:213464 [Crossref], [Google Scholar], [Publisher]

[45] Huynh H.T., Jeannin O., Aubert E., Espinosa E, Fourmigué M., Chalcogen bonding interactions in chelating, chiral bis (selenocyanates). *New Journal of Chemistry*, 2021, **45**:76 [Crossref], [Google Scholar], [Publisher]

[46] Ikemoto H., Miyanaga T., Structure study of the chalcogens and chalcogenides by X-ray absorption fine structure. *Zeitschrift für Physikalische Chemie*, 2021, **235**:117 [Crossref], [Google Scholar], [Publisher]

[47] Setorg S., Investigating the Purposefulness of Relational Marketing on Customer Management in Companies, *International Journal of Advanced Studies in Humanities and Social Science*, 2023, **12**:222 [Crossref], [Publisher]

[48] Liu M., Han X., Chen H., Peng Q., Huang H., A molecular descriptor of intramolecular noncovalent interaction for regulating optoelectronic properties of organic semiconductors. *Nature Communications*, 2023, **14**:2500 [Crossref], [Google Scholar], [Publisher]

[49] Aragoni M.C., Arca M., Lippolis V., Pintus A., Torubaev Y., Podda E., A Structural Approach to the Strength Evaluation of Linear Chalcogen Bonds. *Molecules*, 2023, **28**:3133 [Crossref], [Google Scholar], [Publisher]

[50] Samuel H.S., Etim E.E., Shinggu J.P., Bako B., Machine learning of Rotational spectra analysis in interstellar medium, *Communication in Physical Sciences*, 2023, **10** [Google Scholar], [Publisher]

[51] Mahmudov K.T., Kopylovich M.N., da Silva M.F.C.G., Pombeiro A.J., Chalcogen bonding in synthesis, catalysis and design of materials. *Dalton Transactions*, 2017, **46**:10121 [Crossref], [Google Scholar], [Publisher]

[52] Merten C., Recent advances in the application of vibrational circular dichroism spectroscopy for the characterization of asymmetric catalysts. *European Journal of Organic Chemistry*, 2020, **2020**:5892 [Crossref], [Google Scholar], [Publisher]

[53] Oliveira V., Cremer D., Kraka E., The many facets of chalcogen bonding:Described by vibrational spectroscopy. *The Journal of Physical Chemistry A*, 2017, **121**:6845 [Crossref], [Google Scholar], [Publisher]

[54] Ma W., Kirchhoff J.L., Strohmann C., Grabe B., Loh C.C., Cooperative Bifurcated Chalcogen Bonding and Hydrogen Bonding as Stereocontrolling Elements for Selective Strain-Release Septanosylation. *Journal of the American Chemical Society*. 2023, [Crossref], [Google Scholar], [Publisher]

[55] de Azevedo Santos L., Ramalho T.C., Hamlin T.A., Bickelhaupt F.M., Chalcogen bonds:Hierarchical ab initio benchmark and density functional theory performance study. *Journal of Computational Chemistry*, 2021, **42**:688 [Crossref], [Google Scholar], [Publisher]

[56] Sauder R., Seelig J., Ziegler A., Thermodynamics of lipid interactions with cell-penetrating peptides. *Cell-Penetrating Peptides:Methods and Protocols*, 2011, 129 [Crossref], [Google Scholar], [Publisher]

[57] Burgess M.R., Morley C.P., Electrochemical and NMR spectroscopic studies of selenium-and tellurium-substituted ferrocenes I:ferrocenyl alkyl chalcogenides [Fe(η-C_5H_5)(η-C_5H_4ER)]. *Journal of Organometallic Chemistry*, 2001, **623**:101 [Crossref], [Google Scholar], [Publisher]

[58] Etim E.E., Mbakara I.E., Khanal G.P., Inyang E.J., Ukafia O.P., Sambo I.F., Coupled Cluster Predictions of Spectroscopic Parameters for (Potential) Interstellar Protonated Species *Elixir Computational Chemistry*, 2017, **111**, 48818 [Crossref], [Google Scholar], [Publisher]

[59] Creste G., Groni S., Fave C., Branca M., Schöllhorn B., Comparative study of non-covalent interactions between cationic N-phenylviologens and halides by electrochemistry and NMR:the halogen bonding effect. *Faraday Discussions*, 2017, **203**:301 [Crossref], [Google Scholar], [Publisher]

[60] Docker A., Johnson T.G., Kuhn H., Zhang Z., Langton M.J., Multistate Redox-Switchable Ion Transport Using Chalcogen-Bonding Anionophores. *Journal of the American Chemical Society,* 2023, **145**:2661 [Crossref], [Google Scholar], [Publisher]

[61] Socha O., Osifová Z., Dračínský M., NMR-Challenge.com:An Interactive Website with Exercises in Solving Structures from NMR Spectra, *Journal of Chemical Education,* 2023**, 100**:962 [Crossref], [Google Scholar], [Publisher]

[62] Kumar V., Xu Y., Bryce D.L., Double Chalcogen Bonds:Crystal Engineering Stratagems via Diffraction and Multinuclear Solid-State Magnetic Resonance Spectroscopy. *Chemistry–A European Journal*, 2020, **26**:3275 [Crossref], [Google Scholar], [Publisher]

[63] Vogel L., Wonner P., Huber S.M., Chalcogen bonding:An overview, *Angewandte Chemie International Edition*, 2019, **58**:1880 [Crossref], [Google Scholar], [Publisher]

[64] Nakajima M., Nemoto T., Machine learning enabling prediction of the bond dissociation enthalpy of hypervalent iodine from

SMILES, *Scientific Reports*, 2021, **11**:20207 [Crossref], [Google Scholar], [Publisher]

[65] Takamura A., Tsukamoto K., Sakata K., Integrative measurement analysis via machine learning descriptor selection for investigating physical properties of biopolymers in hairs. *Sci Rep* 2021**, 11:**24359 [Crossref], [Google Scholar], [Publisher]

[66] Bayon A., de la Calle A., Ghose K.K., Page A., McNaughton R., Experimental, computational and thermodynamic studies in perovskites metal oxides for thermochemical fuel production:A review, *International Journal of Hydrogen Energy*, 2020, **45**:12653 [Crossref], [Google Scholar], [Publisher]

[67] Klarić M., Kuzle I., Holjevac N., Wind power monitoring and control based on synchrophasor measurement data mining, *Energies*, 2018, **11**:3525 [Crossref], [Google Scholar], [Publisher]

[68] Esparza A., Segundo J., Nuñez C., Visairo N., Barocio E., García H., Transient stability enhancement using a wide-area controlled SVC:An HIL validation approach, *Energies*, 2018, **11**:1639 [Crossref], [Google Scholar], [Publisher]

[69] Ivanković I., Kuzle I., Holjevac N., Algorithm for fast and efficient detection and reaction to angle instability conditions using phasor measurement unit data, *Energies*, 2018, **11**:681 [Crossref], [Google Scholar], [Publisher]

[70] Wang X., Shi D., Wang Z., Xu C., Zhang Q., Zhang, X., Yu Z., Online calibration of phasor measurement unit using density-based spatial clustering, *IEEE Transactions on Power Delivery*, 2017, **33**:1081 [Crossref], [Google Scholar], [Publisher]

[71] Ester M., Kriegel H.P., Sander J., Xu X., August. A density-based algorithm for discovering clusters in large spatial databases with noise. In *kdd* , 1996, **96**:226 [Google Scholar], [Publisher]

[72] Bakshi B.R., Multiscale PCA with application to multivariate statistical process monitoring, *AIChE journal*, 1998, **44**:1596[Crossref], [Google Scholar], [Publisher]

[73] Carugo O., Resnati G., Metrangolo P., Chalcogen bonds involving selenium in protein structures, *ACS chemical biology*, 2021, **16**:1622 [Crossref], [Google Scholar], [Publisher]

[74] Pina M.D.L.N., Frontera A., Bauza A., Charge Assisted S/Se Chalcogen Bonds in SAM Riboswitches:A Combined PDB and ab Initio Study, *ACS chemical biology*, 2021, **16**:1701[Crossref], [Google Scholar], [Publisher]

[75] Zeng R., Gong Z., Chen L., Yan Q., Solution self-assembly of chalcogen-bonding polymer partners, *ACS Macro Letters*, 2020, **9**:1102 [Crossref], [Google Scholar], [Publisher]

[76] Zeng R., Gong Z., Yan Q., Chalcogen-Bonding Supramolecular Polymers. *The Journal of Organic Chemistry*, 2020, **85**:8397 [Crossref], [Google Scholar], [Publisher]

[77] Skiba M.A., Sikkema A.P., Moss N.A., Lowell A.N., Su M., Sturgis R.M., Gerwick L., Gerwick W.H., Sherman D.H., Smith J.L., Biosynthesis of t-butyl in apratoxin A:Functional analysis and architecture of a PKS loading module, *ACS chemical biology*, 2018, **13**:1640 [Crossref], [Google Scholar], [Publisher]

[78] Chen L., Xiang J., Zhao Y., Yan Q., Reversible self-assembly of supramolecular vesicles and nanofibers driven by chalcogen-bonding interactions, *Journal of the American Chemical Society*, 2018, **140**:7079 [Crossref], [Google Scholar], [Publisher]

[79] Ghasemi S.S., A Mini Review of Social Semiotic and Critical Visual Studies in Language-Related Fields of Study', *International Journal of Advanced Studies in Humanities and Social Science*, 2023, **12**:268 [Crossref], [Publisher]

[80] Rahimipour S., Poetry and Drama: A Survey of Their Applicability to Language Teaching/Learning', *International Journal of*

Advanced Studies in Humanities and Social Science, 2020, **9**:59 [Crossref], [Publisher]

[81] Scheiner S., Assembly of effective halide receptors from components. Comparing hydrogen, halogen, and tetrel bonds, *The Journal of Physical Chemistry A*, 2017, **121**:3606 [Crossref], [Google Scholar], [Publisher]

[82] Joy J., Jemmis E.D., Contrasting behavior of the Z bonds in X–Z··· Y weak interactions:Z= main group elements versus the transition metals, *Inorganic Chemistry*, 2017, **56**:1132 [Crossref], [Google Scholar], [Publisher]

[83] Stefano M., Riccardo A., Valentina M., Lorenzo T., Gabriella C., Caterina V., Role of Noncovalent Sulfur··· Oxygen Interactions in Phenoxyl Radical Stabilization:Synthesis of Super Tocopherol-like Antioxidants, 2016 [Crossref], [Google Scholar], [Publisher]

[84] Dar'in Dmitry V., Yu K.V., Difference in Energy between Two Distinct Types of Chalcogen Bonds Drives Regioisomerization of Binuclear (Diaminocarbene) PdII Complexes, 2016 [Crossref], [Google Scholar], [Publisher]

[85] Artemjev A.A., Kubasov A.S., Kuznetsov M.L., Grudova M.V., Khrustalev V.N., Kritchenkov A.S., Tskhovrebov A.G., Mechanistic investigation of 1, 3-dipolar cycloaddition between bifunctional 2-pyridylselenyl reagents and nitriles including reactions with cyanamides, *CrystEngComm*, 2023, **25**:3691[Crossref], [Google Scholar], [Publisher]

[86] Amonov A., Scheiner S., Comparison of the Ability of N-Bases to Engage in Noncovalent Bonds, *ChemPhysChem*, 2023, 202300326. [Crossref], [Google Scholar], [Publisher]

[87] Pizzi A., Daolio A., Beccaria R., Demitri N., Viani F., Resnati G., Chalcogen Bonding (ChB) as a Robust Supramolecular Recognition Motif of Benzisothiazolinone Antibacterials, *Chemistry–A European Journal*, 2023, **29** :202300571 [Crossref], [Google Scholar], [Publisher]

[88] Popov R.A., Novikov A.S., Suslonov V.V., Boyarskiy V.P., Molecular Switching through Chalcogen-Bond-Induced Isomerization of Binuclear (Diaminocarbene) PdII Complexes, *Inorganics*, 2023, **11**:255 [Crossref], [Google Scholar], [Publisher]

[89] Scheiner S., Competition Between the Two σ-Holes in the Formation of a Chalcogen Bond, *ChemPhysChem*, 2023, **24:**202200936 [Crossref], [Google Scholar], [Publisher]

[90] Scheiner S., Assessing the Possibility and Properties of Types I and II Chalcogen Bonds, *Crystals*, 2023, **13**:766 [Crossref], [Google Scholar], [Publisher]

[91] Walker M.G., Mendez C.G., Ho P.S., Non-classical Non-covalent σ-Hole Interactions in Protein Structure and Function:Concepts for Potential Protein Engineering Applications, *Chemistry–An Asian Journal*, 2023, **18**:202300026 [Crossref], [Google Scholar], [Publisher]

[92] Carugo O., Interplay between hydrogen and chalcogen bonds in cysteine. *Proteins:Structure, Function, and Bioinformatics*, 2023, **91**:395-399 [Crossref], [Google Scholar], [Publisher]

[93] Kolb S., Oliver G.A., Werz D.B., Chalcogen bonding in supramolecular structures, anion recognition, and catalysis, 2023 [Crossref], [Google Scholar], [Publisher]

[94] Lee L.M., Tsemperouli M., Poblador-Bahamonde A.I., Benz S., Sakai N., Sugihara K., Matile S., Anion transport with pnictogen bonds in direct comparison with chalcogen and halogen bonds, *Journal of the American Chemical Society*, 2019, **141**:810 [Crossref], [Google Scholar], [Publisher]

[95] Benz S., Macchione M., Verolet Q., Mareda J., Sakai N., Matile S., Anion transport with chalcogen bonds, *Journal of the American Chemical Society*, 2016, **138**:9093 [Crossref], [Google Scholar], [Publisher]

[96] Geng H., Chen F., Ye J., Jiang F., Applications of molecular dynamics simulation in structure

prediction of peptides and proteins, *Computational and structural biotechnology journal*, 2019, **17**:1162 [Crossref], [Google Scholar], [Publisher]

[97] Mihalovits L.M., Ferenczy G.G., Keserű G.M., Mechanistic and thermodynamic characterization of oxathiazolones as potent and selective covalent immunoproteasome inhibitors, *Computational and Structural Biotechnology Journal*, 2021, **19**:4486 [Crossref], [Google Scholar], [Publisher]

[98] Mihalovits L.M., Ferenczy G.G., Keserű G.M., Affinity and selectivity assessment of covalent inhibitors by free energy calculations, *Journal of Chemical Information and Modeling*, 2020, **60**:6579 [Crossref], [Google Scholar], [Publisher]

[99] Pyziak M., Pyziak J., Hoffmann M., Kubicki M., Experimental and Theoretical Charge Density Studies of Chalcogen Bonding and Other Intermolecular Contacts in 4-[[4-(Methoxy)-3-quinolinyl] thio]-3-thiomethylquinoline, *Crystal Growth & Design*, 2015, **15**:5223 [Crossref], [Google Scholar], [Publisher]

[100] Steve S., Interactions between Thiourea and Imines. Prelude to Catalysis, 2015 [Crossref], [Google Scholar], [Publisher]

[101] Uhl W., Wegener P., Layh M., Hepp A., Würthwein E.U., Chalcogen capture by an Al/P-based frustrated lewis pair:Formation of Al-EP bridges and intermolecular tellurium–tellurium interactions, *Organometallics*, 2015, **34**:2455 Crossref, [Google Scholar], [Publisher]

[102] Nziko V.D.P.N., Scheiner S., S··· π Chalcogen bonds between SF2 or SF4 and C–C multiple bonds, *The Journal of Physical Chemistry A*, 2015, **119**:5889 [Crossref], [Google Scholar], [Publisher]

[103] Guo X., An X., Li Q., Se··· N Chalcogen Bond and Se··· X Halogen Bond Involving F2C Se:Influence of Hybridization, Substitution, and Cooperativity, *The Journal of Physical Chemistry A*, 2015, **119**:3518 [Crossref], [Google Scholar], [Publisher]

[104] Garrett G.E., Gibson G.L., Straus R.N., Seferos D.S., Taylor M.S., Chalcogen bonding in solution:interactions of benzotelluradiazoles with anionic and uncharged Lewis bases, *Journal of the American Chemical Society*, 2015, **137**:4126 [Crossref], [Google Scholar], [Publisher]

[105] Setiawan D., Kraka E., Cremer D., Strength of the pnicogen bond in complexes involving group Va elements N, P, and As, *The Journal of Physical Chemistry A*, 2015, **119**:1642 [Crossref], [Google Scholar], [Publisher]

[106] Steve S., Intramolecular S··· O Chalcogen Bond as Stabilizing Factor in Geometry of Substituted Phenyl-SF3 Molecules, 2015 [Crossref], [Google Scholar], [Publisher]

[107] Azofra L.M., Alkorta I., Scheiner S., Chalcogen bonds in complexes of SOXY (X, Y= F, Cl) with nitrogen bases, *The Journal of Physical Chemistry A*, 2015, **119**:535 [Crossref], [Google Scholar], [Publisher]

[108] Nziko V.D.P.N., Scheiner S., Chalcogen bonding between tetravalent SF4 and amines, *The Journal of Physical Chemistry A*, 2014, **118**:10849 [Crossref], [Google Scholar], [Publisher]

[109] Guan L., Mo Y., Electron transfer in pnicogen bonds, *The Journal of Physical Chemistry A*, 2014, **118**:8911 [Crossref], [Google Scholar], [Publisher]

[110] Rolf G., Gebhard H., Long Chalcogen–Chalcogen Bonds in Electron-Rich Two and Four Center Bonds:Combination of π-and σ-Aromaticity to a Three-Dimensional σ/π-Aromaticity, 2014 [Crossref], [Google Scholar], [Publisher]

[111] Azofra L.M., Scheiner S.,. Substituent effects in the noncovalent bonding of SO2 to molecules containing a carbonyl group. The dominating role of the chalcogen bond, *The Journal of Physical Chemistry A*, 2014, **118**:3835 [Crossref], [Google Scholar], [Publisher]

[112] Adhikari U., Scheiner S., Effects of charge and substituent on the S··· N chalcogen bond, *The Journal of Physical Chemistry A*, 2014, **118**:3183 [Crossref], [Google Scholar], [Publisher]

[113] Felix-Sonda B.C., Rivera-Islas J., Herrera-Ruiz D., Morales-Rojas H., Höpfl H., Nitazoxanide cocrystals in combination with succinic, glutaric, and 2, 5-dihydroxybenzoic acid, *Crystal growth & design*, 2014, **14**:1086 [Crossref], [Google Scholar], [Publisher]

[114] Putta A., Mottishaw J.D., Wang Z., Sun H., Rational design of lamellar π–π stacked organic crystalline materials with short interplanar distance, *Crystal growth & design*, 2014, **14**:350 [Crossref], [Google Scholar], [Publisher]

[115] Xiao Q., Sakurai T., Fukino T., Akaike K., Honsho Y., Saeki A., Seki S., Kato K., Takata M., Aida T., Propeller-shaped fused oligothiophenes:a remarkable effect of the topology of sulfur atoms on columnar stacking, *Journal of the American Chemical Society*, 2013, **135**:18268 [Crossref], [Google Scholar], [Publisher]

[116] Bauza A., Alkorta I., Frontera A., Elguero J., On the reliability of pure and hybrid DFT methods for the evaluation of halogen, chalcogen, and pnicogen bonds involving anionic and neutral electron donors, *Journal of chemical theory and computation*, 2013, **9**:5201 [Crossref], [Google Scholar], [Publisher]

[117] Fick R.J., Kroner G.M., Nepal B., Magnani R., Horowitz S., Houtz R.L., Scheiner S., Trievel R.C., Sulfur–oxygen chalcogen bonding mediates adomet recognition in the lysine methyltransferase SET7/9, *ACS chemical biology*, 2016, **11**:748 [Crossref], [Google Scholar], [Publisher]

[118] Wang W., Ji B., Zhang Y., Chalcogen bond:a sister noncovalent bond to halogen bond, *The Journal of Physical Chemistry A*, 2009, **113**:8132 [Crossref], [Google Scholar], [Publisher]

[119] Seiji T., Naoki S., Origin of Attraction in Chalgogen–Nitrogen Interaction of 1, 2, 5-Chalcogenadiazole Dimers, 2013 [Crossref], [Google Scholar], [Publisher]

[120] Kozuch S., Martin J.M., Halogen bonds:Benchmarks and theoretical analysis, *Journal of Chemical Theory and Computation*, 2013, **9**:1918 [Crossref], [Google Scholar], [Publisher]

[121] Knight F.R., Randall R.A., Athukorala Arachchige K.S., Wakefield L., Griffin J.M., Ashbrook S.E., Bühl M., Slawin A.M., Woollins J.D., Noncovalent interactions in peri-substituted chalconium acenaphthene and naphthalene salts:a combined experimental, crystallographic, computational, and solid-state NMR study, *Inorganic Chemistry*, 2012, **51**:11087 [Crossref], [Google Scholar], [Publisher]

[122] Mukherjee G., Singh P., Ganguri C., Sharma S., Singh H.B., Goel N., Singh U.P., Butcher R.J., Selenadiazolopyridine:A synthon for supramolecular assembly and complexes with metallophilic interactions, *Inorganic Chemistry*, 2012, **51**:8128 [Crossref], [Google Scholar], [Publisher]

[123] Lechner M.L., Athukorala Arachchige K.S., Randall R.A., Knight F.R., Bühl M., Slawin A.M., Woollins J.D., Sterically crowded tin acenaphthenes, *Organometallics*, 2012, **31**:2922 [Crossref], [Google Scholar], [Publisher]

[124] Zhu L., Yang W., Meng Y.Y., Xiao X., Guo Y., Pu X., Li M., Effects of organic solvent and crystal water on γ-chymotrypsin in acetonitrile media:observations from molecular dynamics simulation and DFT calculation, *The Journal of Physical Chemistry B*, 2012, **116**:3292[Crossref], [Google Scholar], [Publisher]

[125] Scheiner S., Adhikari U., Abilities of different electron donors (D) to engage in a P··· D noncovalent interaction. *The Journal of Physical Chemistry A*, 2011, **115**:11101 [Crossref], [Google Scholar], [Publisher]

[126] Biot N., Bonifazi D., Chalcogen-bond driven molecular recognition at work, *Coordination Chemistry Reviews*, 2020,

413:213243 [Crossref], [Google Scholar], [Publisher]

[127] Bleiholder C., Gleiter R., Werz D.B., Köppel H., Theoretical investigations on heteronuclear chalcogen– chalcogen interactions:on the nature of weak bonds between chalcogen centers, *Inorganic Chemistry*, 2007, **46**:2249 [Crossref], [Google Scholar], [Publisher]