Review Article

Experimental and Theoretical Approaches for a characterizing Halogen Bonding



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<u>ABSTRACT</u>

The interaction between a halogen atom and an electron-rich species is known as halogen bonding. Due to its importance in numerous scientific domains, including materials science, drug design, and others, it has attracted considerable interest. Halogen bonding interactions are investigated using experimental characterization methods such X-ray crystallography, NMR spectroscopy, and vibrational spectroscopy. Halogen bonding interactions are also studied theoretically using techniques like quantum mechanical topology (QMT), molecular dynamics simulations, and density functional theory (DFT). Understanding the nature of halogen bonding and its applications in diverse sectors holds great potential for the combination of experimental and theoretical methodologies. This article provides a succinct assessment of different methods for characterizing halogen bonding, emphasizing their significance in deepening our understanding of halogen bonding and its uses in a variety of fields.

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1. Introduction

eak intermolecular forces, commonly referred to as noncovalent interactions, are important in a variety of biological, chemical. and physical processes. These bonds are often weaker than covalent ones and take place between molecules or different portions of the same molecule. [1-2]. Numerous scientific domains can benefit from understanding and using non-covalent interactions. Drug-target interactions depend greatly on non-covalent interactions. Understanding and improving non-covalent interactions between small molecules and target proteins is essential for rational drug design to obtain the appropriate binding affinities and selectivity. In addition, supramolecular chemistry, which focuses on the design and synthesis of complex molecular assemblies by non-covalent bonding, is fundamentally dependent on non-covalent interactions. Non-covalent interactions are also necessary for the engineering and design of materials with desired qualities. For instance, well-defined nanostructures and useful materials can be created when molecules selfassemble through non-covalent interactions. The characteristics of polymers, liquid crystals, molecular recognition, and catalysis, and crystal engineering are further influenced by non-covalent interactions [2-5].

Halogen atoms and electron-rich substances can interact noncovalently through halogen bonding. Due to its importance in numerous scientific domains, including materials science, drug design, and others, it has attracted considerable interest. Halogen bonds are a particular kind of intermolecular interaction that are crucial for the development of supramolecular structures [6]. The halogen atom serves as an electrophile and the electronrich species as a nucleophile in this interaction. of the The size halogen atom, its electronegativity, and the makeup of the electron-rich species are only a few of the variables that affect how strong the halogen bond is. To characterize halogen bonding interactions and comprehend their applications in many sectors, experimental and theoretical methods are used [7]. Furthermore, to characterize and comprehend the nature of halogen bonding interactions as shown in Figure 1, as well as to gain important insights into its behavior and applications, experimental and theoretical approaches play a significant role. The direct observation and measurement of halogen bonding are made possible by various techniques used in experimental procedures. One of these methods is X-ray crystallography, which offers highly detailed structural details



Figure 1. Schematic diagram of halogen bonding

and enables researchers to see the spatial arrangement and geometrical characteristics of halogen bonds in crystal structures. Strength, kinetics, and electronic characteristics of halogen bonding interactions are revealed by spectroscopic techniques such nuclear magnetic resonance (NMR), IR, and ultravioletvisible (UV-Vis) spectroscopy [7, 8]. These experimental methods help identify and characterize halogen bonding in various chemical systems when paired with computational tools. Halogen bonding at the molecular level can be studied and understood using theoretical methodologies, particularly computational chemistry techniques. Density functional theory (DFT) studies, molecular simulations. dynamics and quantum mechanical calculations all shed light on the electronic structure, energetics, and geometric characteristics of halogen bonds. The strength and selectivity of halogen bonding interactions can be predicted and explained using these theoretical techniques, which can also give us a better knowledge of the underlying causes influencing their behavior [9].

It is very beneficial to combine theoretical and experimental methods to characterize halogen bonding. Experimental data offer essential benchmarks and validation for theoretical calculations, allowing for the development of more accurate and efficient computer models [10]. On the other hand, theoretical calculations can help explain complex experimental data by providing insights into experimental observations. The interaction of these methods enables a thorough comprehension of halogen bonding interactions, bridging the discrepancy between experimental findings and theoretical forecasts [11]. The aim of this article is to examine experimental and theoretical methods for characterizing halogen bonding. The objectives include exploring the experimental techniques used for characterizing halogen bonding, such as X-ray crystallography, NMR spectroscopy, IR spectroscopy, and UV-Vis spectroscopy. Theoretical methods include density functional theory, molecular dynamics simulations. and quantum mechanical topology. Combinations of experimental and theoretical methods are also explored, along with their respective advancements [12].

1.1. Experimental approaches

Halogen bonding must be well characterized to get important understanding of its structural, energetic, and dynamic features. Various methods are used to investigate and assess halogen bonding interactions [13-15]. The following list of experimental techniques is detailed:

1.1.1. X-ray crystallography

One of the most often utilized methods for describing halogen bonding is X-ray crystallography. It enables scientists to pinpoint the specific atom arrangement in a crystal lattice. The locations of halogen atoms and their interactions with electron-rich species can be seen by obtaining highresolution X-ray diffraction data. This method offers important insights into the geometry and configuration of the interaction by providing information about the halogen bond lengths, angles, and other structural factors [16].

Getting a good single crystal of the target chemical that displays halogen bonding is the initial stage in X-ray crystallography. To ensure the creation of a crystal lattice with clear boundaries, the compound should crystallize under the proper circumstances. The crystal can be turned to different orientations because it is positioned atop a goniometer. The crystal is subsequently exposed to X-ray radiation, and the diffracted X-rays are gathered on a detector [17]. A complete dataset is generated by methodically rotating the crystal and gathering data from various angles. The interference patterns that are the consequence of X-rays interacting with the crystal lattice are described in the obtained diffraction data. An electron density map is produced after processing this data with mathematical techniques to extract the amplitudes and phases of the diffracted waves. The positions of individual atoms within the crystal can be seen and understood using the electron density map generated from the diffraction data. It makes it possible to identify and characterize the donoracceptor pairs involved in halogen bonding [18]. The particular distances and orientations between the halogen atom (donor) and the electron-rich site (acceptor) involved in the halogen bonding interaction can be seen in the electron density **Ouantitative** map. characteristics can be obtained if the halogen bonding interaction is identified in the crystal structure. These include additional geometric factors as well as the halogen bond length (the separation between the donor and acceptor) and halogen bond angle (the angle created by the donor, acceptor, and halogen atom). These findings provide insight into the structure and strength of the halogen bonding interaction. Finding similar patterns and qualities across many compounds that exhibit halogen bonding can be done by comparing and analyzing the crystallographic data. One can verify the observed halogen bonding by looking at the geometrical parameters and comparing them to recognized norms for halogen bonding interactions [19].

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1.1.2. Nuclear magnetic resonance (NMR) spectroscopy

The structure and power of the halogen bonding interaction are now better understood thanks to these discoveries. By comparing and evaluating the crystallographic data, similar patterns and traits can be found in different compounds that display halogen bonding. By examining the geometrical characteristics and contrasting them with accepted standards for halogen bonding interactions, one can confirm the presence of the observed halogen bonding [20].

(i) Chemical Shift Analysis: The resonance frequencies of atomic nuclei in a magnetic field are examined using NMR spectroscopy. The chemical shift, expressed in parts per million (ppm), provides information regarding the electrical configuration of the atom. In the case of halogen bonding, it is possible to detect whether an atom is a part of a halogen bond by looking at its chemical shift. If the chemical shift value differs from a reference compound, a halogen bond might be present [21].

(*ii*) Proton NMR (1H NMR) Spectroscopy: This technique determines the resonance frequencies of hydrogen atoms. When a halogen atom establishes a halogen bond, the electrical environment around the hydrogen atoms nearby may alter. As a result, the chemical shifts of these hydrogen nuclei may differ. By looking at the chemical alterations of the hydrogen atoms nearby the halogen, it is possible to show the presence and kind of the halogen bonding relationship [22-23].

(iii) ¹³*C-NMR spectroscopy of carbon*: This method investigates the resonance frequencies of the carbon nuclei. In the context of halogen bonding, the halogen bond may affect the electrical characteristics of the carbon atoms close by. Chemical alterations in these carbon nuclei may undergo visible changes. By examining the ¹³C-NMR spectra, it is able to gain a better understanding of how the halogen bond impacts the electrical environment of surrounding carbon atoms.



Figure 2. Block diagram of IR and Raman spectrometer [28]

(*iv*) The Nuclear Overhauser Effect (NOE), which occurs when one nucleus' magnetization affects another nucleus' magnetization through dipolar coupling, is the fourth phenomenon. A halogen bond may cause the hydrogen atom that forms the bond to transfer its magnetization to nearby hydrogen atoms in the case of halogen bonding. As a result, the NMR signals of these hydrogen nuclei will be amplified, indicating that the halogen bond is close by and affects them.

(v) Nuclear Spin Relaxation Times: NMR spectroscopy also reveals nuclear spin relaxation times, such as the spin-lattice relaxation time (T1) and the spin-spin relaxation time (T2). The relaxation periods of the nuclei participating in the bonding interaction can be impacted by the existence of a halogen bond. Insights on the dynamics and mobility of molecules participating in halogen bonding can be gleaned by analyzing the relaxation times [24].

1.1.3. Vibrational spectroscopy

Halogen bonding interactions can be studied using vibrational spectroscopy techniques including IR and Raman spectroscopy as shown in **Figure 2**. Molecular absorption of infrared light, which corresponds to the excitation of molecular vibrations, is measured in IR spectroscopy. Frequency shifts, red-shifted halogen bond vibrations, intermolecular vs. intramolecular vibrations. and Raman spectroscopy measure the inelastic scattering of photons when incident light interacts with a molecule. These IR spectroscopy features are pertinent to characterizing halogen bonding. It offers details on the molecular structure and vibrational modes [25]. These spectroscopic techniques examine molecules' vibrational frequencies, which are responsive to the type and strength of the interaction. Specific halogen atom vibrational modes, such as stretching or bending frequencies, might change as a result of halogen bonding. Molecular adsorption of CO on metallic surfaces is one of the well-known instances of a field in which vibrational spectroscopy has made а substantial contribution to the comprehension of the surface chemistry of an adsorbate. Adsorbed carbon monoxide typically results in significant absorptions at the (C-O) stretching frequency in both the IR and EELS spectra. Typically, EELS has also access to the metal-carbon stretching mode (400 cm⁻¹). Since the structure of these complexes is often known from x-ray single crystal diffraction investigations, the interpretation of CO's spectra as an adsorbed surface species primarily relies on IR spectra from related inorganic cluster and coordination complexes. According to this comparison, the CO stretching frequency can give a reliable indication of the molecule's surface

coordination. As an illustration, CO chemisorbed on a spotless Pt surface [26-28].

1.2. Theoretical approaches

To fully understand the electronic structure, energetics, and other characteristics of halogen bonding, theoretical approaches are essential. They also offer in-depth insights into these interactions' other characteristics. Halogen bonding systems are studied using a variety of computational methods, which provide an additional viewpoint to experimental findings. Here are a few of the theoretical techniques that are frequently used to characterize halogen bonding:

1.2.1. Density functional theory (DFT)

The idea of non-covalent interactions is used by density functional theory (DFT), a quantum mechanical modeling technique, to forecast the electronic structure and characteristics of molecules solids Non-covalent and interactions, often known as weak interactions. occur between atoms or molecules as a result of various factors, including hydrogen bonds, electrostatic interactions, Van der Waals forces, and stacking of ions. Calculations are made easier in DFT because the electronic structure of a system is described by the electron density rather than the wavefunction [20, 21]. The fundamental idea behind DFT is shown by the mechanism in Figure 3 which is by minimizing the total electronic energy in relation to the electron density, one may ascertain a system's ground state attributes. The electron density in DFT is often found by solving the Kohn-Sham equations, which are derived from a set of selfconsistent equations. An effective potential is used in these equations to reflect the average interaction between the electrons and the external potential, including non-covalent interactions [29].



Figure 3. Mechanism of Density Functional Theory [29]

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Halogen bonding research frequently uses the theoretical framework of DFT. The foundation of it is the solution of the quantum mechanical equations that describe the properties and electronic structure of molecules. DFT approximates exchange-correlation the functional to determine the electron density distribution, energy, and other variables. Using this strategy, researchers can examine the geometrical characteristics, energy profiles, and electron density redistribution connected to halogen bonding interactions. DFT can be used to determine the strength, directionality, and type of halogen bonds, according to [30].

1.2.2. Molecular dynamics (MD) simulations

Non-covalent interactions are used to simulate the motion and behavior of atoms and molecules over time using computational techniques referred to as molecular dynamics (MD) simulations. Non-covalent interactions are essential for accurate MD simulations because they play a crucial role in shaping the properties dynamics, and structure, of systems.MD simulations molecular are computational methods for simulating atom and molecule motion and interactions over time. Halogen bonding system dynamics and behavior can be studied using MD simulations [31-32].

By accounting for intermolecular forces, temperature variations, and solvent effects, MD simulations can shed light on the stability, conformational changes, and lifetimes of halogen bonding complexes. These simulations can be further used to study how variations in solvent, temperature, and pressure impact the interactions between halogen atoms [33-35].

1.2.3. Quantum Mechanical Topology (QMT)

Non-covalent interactions are used in a theoretical framework known as quantum mechanical topology (QMT) to study and comprehend the electronic structure of molecules and other materials. It concentrates on the topological properties of the electron density and the associated quantum mechanically produced fields [36]. Quantum mechanical theory (QMT) is based on the electron density function, which expresses the



Figure 4. Quantum mechanical model [38]

probability density of finding an electron at a specific location in space. The pattern and distribution of the electron density are significantly influenced by non-covalent interactions, such as Van dar Waals forces, hydrogen bonds, and stacking [37].

Through topological analysis, QMT offers a distinctive viewpoint for describing halogen bonding interactions. Halogen bonds can be quantitatively described and categorized using QMT by examining the electron density distribution as shown in Figure 4. In-depth research on halogen bonding interactions has been conducted using these theoretical techniques, which offer important insights into the electronic structure, energetics, and other characteristics of these interactions [39]. In QMT, the modification of the electron density resulting from the creation of the halogen bond is also examined. Bond pathways, which are trajectories linking the BCPs and revealing details about the redistribution of electron density during the halogen bonding interaction, are examined as part of this investigation density of electrons [40].

Applications of QMT in Characterizing Halogen Bonding

Halogen bonding interactions in various systems have been extensively studied and characterized using QMT techniques. A few noteworthy applications are:

a) Quantitative Analysis of Halogen Bond Strength: QMT enables the evaluation of characteristics such the electron density at the BCP (BCP) to quantitatively quantify the strength of halogen bonding interactions. This analysis makes it possible to compare several halogen bonding systems and pinpoint elements that affect the interaction's potency.

b) Determination of Halogen Bonding Geometry: Halogen bonding geometry can be determined via QMT, which also sheds light on the directionality and geometry of halogen bonds. QMT can determine the preferred orientation and arrangement of the halogen bond by examining the electron density topology and bond routes, which aids in understanding the variables influencing the geometric preferences of halogen bonding [41].

c) Halogen Bonding Analysis in Complex Systems: QMT has been utilized to examine halogen bonding in more complex environments, including supramolecular assemblies and protein-ligand complexes. The understanding of molecular recognition, selfassembly, and halogen bonding in biological systems is aided by this method [42-44].

Iodine, bromine, and chlorine bonds are only a few examples of the several halogen bonding interactions that can be compared using QMT. By quantitatively analyzing the topological properties of different halogen bonds, QMT can shed insight on the similarities and differences between various halogen bonding interactions. QMT also examines how the development of the halogen bond impacts the deformation of the electron density. Bond pathways, which are trajectories linking the BCPs and revealing details about the redistribution of electron density during the halogen bonding interaction, are examined as part of the investigation [45].

1.3. Combined experimental and theoretical approaches

1.3.1. X-ray crystallography and DFT

Although they do so in distinct ways, X-ray crystallography and density functional theory (DFT) are two complimentary approaches that make use of non-covalent interactions to investigate the structure and characteristics of molecules and materials. Density Functional Theory (DFT) computations in conjunction with X-ray crystallography provide a potent method for the thorough analysis of halogen bonding interactions. This integrative approach advances our understanding of halogen bonding phenomena by confirming, interpreting, and refining experimental results [46].

a) X-ray crystallography: X-ray crystallography is initially a very popular experimental technique for acquiring high-resolution structural data on molecules and their interactions. X-ray crystallography, which determines the positions of atoms inside a crystal lattice, allows for the direct observation of halogen bonding interactions. It provides crucial data on bond lengths, angles, and intermolecular distances that are necessary to characterize and understand the geometry and arrangement of halogen bonds in crystal structures.

Density Functional Theory b) (DFT) calculations: DFT is a widely used theoretical method that makes it possible to calculate the electronic structure, energy, and properties of molecules. The nature. energetics, and electrical properties of halogen bonding interactions can be furthered understood via DFT calculations. DFT calculations can be used to examine the redistribution of electron density, elucidate the orbital interactions involved in bonding, and determine the strength of halogen bonds [47].

Validation and Complementarily of c) Experimental Data: The combination of DFT calculations with X-ray crystallography enables the validation and adequacy of experimental data. DFT simulations can validate the results of the investigations by reproducing the structural features and attributes identified by X-ray crystallography. By guaranteeing the dependability and accuracy of the experimental results, this validation raises our level of confidence in the existence and characterization of halogen bonding interactions.

d) Interpretation and understanding of halogen bonding phenomena: The integration of X-ray crystallography and DFT calculations facilitates the interpretation and understanding of halogen bonding phenomena. DFT calculations,

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which can provide exact insights into the electronic structure and properties of halogen bonding systems, enable a clearer understanding of the parameters determining the strength, directionality, and type of these interactions. The mechanisms driving the formation and stability of halogen bonding complexes can be better understood by theoretical investigations, which can be further utilized to identify significant interactions and explain experimental results.

e) Prediction and Design of Halogen Bonding Systems: The prediction and design of halogen bonding systems are also made possible by the merging of experimental and theoretical methodologies. In systems with sparse experimental data, DFT computations can be used to investigate and forecast halogen bonding interactions. The properties and uses of molecules with certain halogen bonding motifs can be optimized in various domains, including materials science, drug design, and catalysis, by combining theoretical calculations with experimental validation [48].

1.3.2. NMR Spectroscopy and Molecular Dynamics Simulations

Both NMR spectroscopy and molecular dynamics (MD) simulations depend on noncovalent interactions, and these methods use non-covalent interactions to reveal important details about the structure, behavior, and characteristics of molecules. A potent method for understanding the dynamic behavior of halogen bonding interactions in solution is the integration of NMR spectroscopy and molecular dynamics (MD) simulations. A more thorough comprehension of the thermodynamics and kinetics of halogen bonding is possible thanks to this integrated approach, which enables the connection of experimental NMR data with hypothetical trajectory calculations [49].

NMR Spectroscopy: NMR spectroscopy is a flexible experimental method that sheds light on the dynamics, interactions, and structural characteristics of molecules in solution. NMR spectroscopy can shed light on how halogen bonding complexes behave in solutions when it comes to halogen bonding. NMR spectroscopy

can reveal details regarding the geometry, stability, and dynamic characteristics of halogen bonding interactions by keeping an eye on chemical shifts, coupling constants, and relaxation parameters.

Simulations based on molecular dynamics (MD) are computer methods for simulating the interactions and behavior of molecules over time. MD simulations can offer atomistic-level insights into the dynamics and behavior of halogen bonding complexes in solution in the setting of halogen bonding. The dynamic behavior of halogen bonding systems can be captured by MD simulations by taking into account intermolecular interactions, solvent effects, and thermal fluctuations.

a) Correlation of Experimental NMR Data with Simulated Trajectories: NMR spectroscopy and MD simulations work together to make it possible to correlate experimental NMR data with simulated trajectories. The corresponding values produced from MD simulations can be compared with experimental NMR parameters, such as chemical shifts and relaxation rates. The thermodynamics and kinetics of halogen bonding interactions in solution are better understood because to this correlation.

b) Halogen Bonding Thermodynamics: NMR spectroscopy and MD simulations can shed light on the thermodynamics of halogen bonding interactions. By examining binding temperature constants, dependence of chemical shifts, and thermodynamic variables (such as enthalpy and entropy changes), one can compute the energetics of halogen bonding. Experimental NMR data and MD simulations are compared to validate and enhance theoretical models and provide a more precise understanding of the thermodynamics of halogen bonding [49].

c) Halogen Bonding Kinetics: To understand the kinetics of halogen bonding interactions, both NMR spectroscopy and MD simulations can be used. Relaxation measurements and exchange spectroscopy research can be used to ascertain the rates of halogen bonding complex generation and dissociation. MD simulations can provide insights into the dynamics and kinetics of halogen bonding at the molecular level and enable the interpretation of experimental NMR data and the generation of kinetic parameters.

d) Solvent Effects and Dynamics: By combining NMR spectroscopy and MD simulations, it is feasible to investigate the effects and dynamics of solvents on halogen bonding interactions. MD simulations must account for solvent molecules and their interactions with the halogen bonding complex to comprehend how solvents affect the stability, shape, and dynamics of halogen bonds. To comprehend how solvation affects halogen bonding, experimental NMR characteristics like solvent shifts and relaxation rates can be compared to MD models [49].

2. Advancements in Experimental Approaches

The characterization and comprehension of halogen bonding, a particular type of noncovalent contact involving the interaction between a halogen atom (such as chlorine, bromine, or iodine) and an electron donor atom or group, have significantly benefited from advances in experimental methods. Halogen bonding has been studied using various experimental techniques, and recent improvements in these methods have improved our understanding of its characteristics and practical uses [50]. The following significant developments:

i. *High-Resolution X-ray Crystallography*: The development of advanced X-ray diffraction techniques and equipment has made it possible to determine high-resolution crystal structures, providing specific details about the geometry, arrangement, and intermolecular interactions of halogen bonding complexes. By enhancing the accuracy and precision of structural characteristics through improved data gathering techniques and refinement algorithms, halogen bonding can now be more precisely characterized.

ii. *Solid-State NMR Spectroscopy*: This powerful method has become increasingly popular for examining halogen bonding in solid-state materials. This approach can shed light on the immediate surroundings and dynamics of halogen bonding complexes even in the absence of crystals with a clear structure. The application and sensitivity of solid-state NMR have improved as a result of advancements in hardware, pulse sequences, and data analysis methodologies. Because of this, halogen bonding in a larger range of materials may now be studied [51].

iii. *Solution-State NMR Spectroscopy*: The dynamics, kinetics, and thermodynamics of halogen bonding complexes in solution have all been clarified through diffusion NMR, relaxation investigations, and the invention of particular labeling techniques. These advancements have given us a better understanding of how halogen bonding functions in practical situations [52].

iv. *Cryo-Electron Microscopy (Cryo-EM)*: By making it possible to determine the highresolution structures of macromolecular complexes, cryo-EM has transformed the science of structural biology. This method has been used to investigate the interactions between halogen atoms and massive biomolecular systems, like protein-ligand complexes [52].

v. Over time, there have been substantial improvements in the experimental techniques used to examine halogen bonding. Detailed information regarding the geometry and intermolecular interactions of halogen bonding complexes can be found through highresolution X-ray crystallography. Insights into the local environment and dynamics of halogen bonding complexes in solid-state materials are provided by solid-state NMR spectroscopy. The investigation of halogen bonding interactions in solutions is made possible by solution-state NMR spectroscopy. By permitting the determination of the high-resolution structures of macromolecular complexes, cryo-electron microscopy has completely changed structural biology. These developments have helped us gain a deeper knowledge of how halogen bonding behaves in real-world settings [53].

2.1. Advancements in theoretical methods

Halogen bonding is a particular kind of noncovalent interaction in which an electron-donor

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atom or group interacts with a halogen atom (such as chlorine, bromine, or iodine). In addition to the experimental methods, theoretical techniques have greatly aided in characterizing and comprehending halogen bonding [54]. The nature, power, and attributes of halogen bonding are better understood by theoretical methods. Investigations into the nature of halogen bonding in recent years and the development of quantum mechanical, molecular mechanical, and empirical scoring function methods for accurately describing halogen-bonding interactions are recent developments in theoretical methods for characterizing halogen bonding [55]. Here are some significant developments in theoretical approaches to halogen bonding characterization:

(i) *Quantum Mechanical Calculations*: The accuracy of theoretical calculations for quantifying halogen bonding has substantially increased with the advent of more precise and effective quantum mechanical methods, such as high-level ab initio methods and hybrid density functionals. These methods provide insights into the electronic structure, energetics, and nature of halogen bonding interactions, enabling a quantitative description and prediction of halogen bonding properties [56].

(*ii*) *Quantum Mechanical Topology (QMT*): Quantum mechanical topology (QMT), which is based on the quantum theory of atoms in molecules (QTAIM), provides a precise framework for the topological exploration of halogen bonding. Halogen bonding can be quantitatively evaluated using QMT by examining electron density properties such as BCPs, Laplacian, and energy density [57]. This approach enables understanding of the intensity, directionality, and structure of halogen bonding interactions.

(iii) Molecular Dynamics Simulations: Advances in computer power and simulation methods have made it possible to explore halogen bonding interactions using molecular dynamics (MD) simulations. MD simulations can be used to investigate the dynamics, thermodynamics, and solvent effects of halogen bonding complexes. New force fields and sampling techniques have increased the precision of MD simulations in simulating the behavior of halogen bonding in real situations [58].

(iv) Machine Learning and Data Mining: These techniques are now frequently employed to analyze large datasets of halogen bonding interactions. These methods can identify trends. correlations, and patterns in experimental and theoretical data, enabling the investigation of structure-property connections, the discovery of fresh halogen bonding motifs, and the development of predictive models [60].

3. Limitations of the Study

Experimental techniques may be influenced by external factors such as solvent effects. temperature, and pressure, which can affect the strength and behavior of halogen bonding interactions. It can be challenging to accurately quantify and control these factors in experimental setups [61]. Some experimental techniques, such as NMR spectroscopy or X-ray crystallography, may have limitations in terms of sensitivity or resolution, which can affect the detection and precise characterization of halogen bonding interactions, especially in systems with weak or transient interactions. The available experimental data on halogen bonding interactions are still limited compared to other types of non-covalent interactions. This can constrain the understanding and characterization of halogen bonding, especially in complex biological or supramolecular systems [62-63].

4. Conclusion

In a nutshell it has been critical to characterize theoretical and experimentally-based halogen bonding interactions. A few of the experimental methods that have provided insight into the geometry, organization, dynamics. and thermodynamics of halogen bonding complexes in various systems and contexts include cryo-EM, solid-state and solution-state NMR spectroscopy, and high-resolution X-ray crystallography. By permitting the direct visualization and validation of such

interactions, these techniques have increased our understanding of the fundamental properties of halogen bonding interactions.

However, theoretical methods have made it possible to better understand the electronic structure, energetic, dynamics, and properties of halogen bonding. Quantum mechanical computations, quantum mechanical topology (QMT), and molecular dynamics (MD) simulations are a few of these methods. Theoretical techniques have quantified and categorized halogen bonding interactions, enabling the improvement of halogen bonding systems as well as forecasting and logical design. They have also made it simpler to study kinetics, solvent effects, and halogen bonding behavior in real-world situations. Our understanding of halogen bonding has greatly benefited from improvements in theoretical and experimental techniques. Halogen bonding parameters can now be determined and validated with greater precision thanks to highresolution techniques. enhanced data processing, and the integration of numerous experimental approaches. The nature, strength, and behavior of halogen bonding interactions have been thoroughly analyzed thanks to theoretical developments such as more precise quantum mechanical calculations, the creation of QMT, and the use of cutting-edge simulation tools.

Because enables the validation. it interpretation, and improvement of experimental results using theoretical calculations, the combination of theoretical and experimental approaches has shown to be extremely potent. A thorough characterization of halogen bonding interactions, including their thermodynamics, kinetics, solvent effects, and dynamic behavior in solution, has been made possible bv the integration of X-ray crystallography and density functional theory (DFT), as well as the combination of NMR spectroscopy and molecular dynamics simulations.

In addition to increase our understanding of the fundamental characteristics and behaviors of halogen bonding, these developments in

experimental and theoretical methodologies have also created new opportunities for the design and use of halogen bonding interactions in a variety of scientific domains. The comprehension and control of halogen bonding have the potential to spur breakthroughs and progress significant applications in fields ranging from materials research to drug discovery and catalysis. Our understanding of halogen bonding interactions has substantially increased thanks to ongoing improvements in theoretical and experimental methods. This has opened the door to the investigation and application of these fascinating non-covalent interactions in various scientific fields. It is interesting to note that defining halogen bonding interactions has benefited greatly by the combination of theoretical calculations and experimental evidence. Density functional theory (DFT) simulations and X-rav crystallography have been used to provide a more thorough knowledge of the geometry, energetic, and dynamics of halogen bonding complexes. In the same vein, understanding the behavior of halogen bonding in solution has been aided by the combination of NMR spectroscopy and molecular dvnamics simulations.

The experimental and theoretical approaches for characterizing halogen bonding have several applications in different areas of bonding has chemistry. Halogen been acknowledged as a significant interaction in medication development. Understanding the nature of halogen bonding interactions between pharmacological compounds and target receptors is made easier by theoretical and experimental approaches. This information can be used to create more powerful and targeted medications. Halogen bonding is essential for the assembly and stabilization of materials including supramolecular structures. liquid crystals, and coordination polymers. The relationship between structure and property can be better understood through theoretical and experimental research, which can further help to design more sophisticated functional Halogen bonding in models. catalytic applications has demonstrated remarkable Experimental theoretical potential. and

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methods can help in the design of more effective and selective catalysts for diverse chemical transformations by analyzing the halogen bonding interactions in catalystsubstrate complexes. Crystal engineering, which is the creation of solid-state materials with certain properties, relies heavily on an understanding of halogen bonding interactions. Halogen bonding networks in crystal structures can be precisely characterized by combining theoretical predictions with experimental methods like X-ray crystallography. In the field of supramolecular chemistry, theoretical and experimental methods are used to clarify the mechanisms and driving forces underlying halogen-based supramolecular assemblages. This information aids in the creation and synthesis of useful supramolecular structures such molecular sensors, switches, and hostguest systems.

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