

Progress in understanding the stability of strong hydrogen-bonded systems

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Strong hydrogen-bonded systems, characterized by high interaction energies, short interaction distances, and pronounced directionality, play a central role in modulating molecular structures, tuning condensed-phase properties, and sustaining biological functions. The nature of strong hydrogen bonds (SHBs) encompasses not only classical noncovalent interactions dominated by electrostatics, but also non-negligible covalent contributions arising from orbital overlap and charge transfer; moreover, their stability is often coupled to variations in chemical composition, spatial structure, and external environments. Here, we systematically survey the fundamental theories, structural and energetic characteristics, governing factors, investigative approaches, and representative applications of strong hydrogen-bonded systems. Our goal is to summarize key advances and outstanding issues in the field, and to provide guidance for the rational design and performance tuning of strong hydrogen-bonded systems in materials science, energy science, and biomolecular engineering.

strong hydrogen bonds; low-barrier hydrogen bonds; stability; multiscale characterization and simulation

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1. Introduction

Hydrogen bonding, as one of the most important weak interactions in both intermolecular and intramolecular contexts, has attracted extensive attention since the twentieth century and has become a central topic in the fields of chemistry, materials science, and the life sciences^[1-4]. Among the diverse classes of hydrogen bonds, so-called strong hydrogen bonds (SHBs) are particularly noteworthy. They typically exhibit interaction energies substantially higher than those of conventional hydrogen bonds (often exceeding 20–30 kJ·mol⁻¹), markedly shorter donor-acceptor (D···A) separations within the donor–H···acceptor (D–H···A) motif than those in typical hydrogen bonds (frequently below 0.25 nm), and enhanced directionality together with a certain degree of saturation^[5-6]. Consequently, SHBs play indispensable roles in dictating the three-dimensional architectures of molecules and materials, optimizing the properties of solids and soft matter, and maintaining the conformational integrity and functional stability of biomacromolecules. For instance, in materials

science, SHBs enhance the stability of hydrogen-bond networks in proton exchange membrane materials, optimizing ion conductivity and thereby improving the ion conduction efficiency and overall performance of the membrane; in energy science, SHBs increase intermolecular interactions, enhancing the mechanical properties of polymers and thus improving the strength and durability of the materials; in biomolecular systems, SHBs stabilize the binding between substrates and enzymes, increasing the structural and functional stability of enzymes, thereby enhancing the efficiency of biological catalysis. These factors contribute to the development of more efficient energy storage systems, functional materials, and catalytic reactions^[3-6]. Therefore, the study of the stability mechanisms of SHBs has become an important frontier in advancing these fields.

From a fundamental perspective, investigating the stability of strong hydrogen-bonded systems offers a powerful window into the nature of intermolecular interactions^[7-9]. Traditionally, hydrogen bonds were largely regarded as noncovalent interactions dominated by electrostatics^[10-11]. However, with the advent of high-accuracy quantum-chemical methods and high-resolution experimental techniques, it has become increasingly clear that many SHBs involve substantial electron-density overlap and charge delocaliza-

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tion between donor and acceptor sites, rendering the covalent component non-negligible^[12-13]. Some short, strong hydrogen bonds even fall in the intermediate regime between hydrogen bonding and covalent bonding; their potential-energy surfaces (PES) may display a single-well profile or an approximately symmetric double-well character, accompanied by atypical proton behavior^[6,14].

Against this backdrop, SHB research has expanded to encompass a broad spectrum of organic, inorganic, and biological systems. Representative examples range from carboxylic-acid dimers, intramolecular hydrogen bonds, and supramolecular assemblies^[15-17], to liquid HF networks^[18] and proton transfer/ionic conduction associated with $[F\cdots H\cdots F]^-$ and short, strong $O-H\cdots O$ motifs^[19-22], and further to cooperative hydrogen-bond networks in base pairing and protein architectures^[23-25]. Although different communities emphasize different diagnostic criteria, a general consensus has emerged: when geometric compression, enhanced interaction energies, and corroborating spectroscopic/electronic-structure evidence converge, SHBs tend to impose stronger structural constraints and exhibit more distinctive proton dynamical behavior^[26-27]. At the same time, quantitatively disentangling, within a unified framework, the respective contributions of electrostatics, covalency, and nuclear quantum effects to stability, and developing transferable descriptive models, remain key open questions^[12-13,25].

Meanwhile, the stability of strong hydrogen-bonded systems is not governed by any single factor, but instead arises from the coupled influences of chemical composition, spatial geometry, and external environments. From the standpoint of composition, the electronegativity and acid-base properties of donor/acceptor atoms, substituent inductive and resonance effects, and multicenter conjugation can markedly modulate D—H bond polarity and electron enrichment at the acceptor site, thereby influencing SHB strength, coordination patterns, and the topology of hydrogen-bond networks^[28-30]. Structurally, molecular conformation, ring strain, and steric effects jointly constrain the geometry (bond lengths and angles) and accessibility of the D—H $\cdots$ A motif, determining whether an SHB can approach a near-linear arrangement and how multiple hydrogen bonds cooperate or compete within a network^[31-32]. In addition, external variables such as temperature, pressure, and solvent polarity regulate SHB formation and rupture kinetics, as well as the statistical characteristics of hydrogen-bond networks, by altering thermal motions, dielectric screening, and the shape of the proton-transfer PES^[33-35]. This three-dimensional “composition-structure-environment” coupling provides an important conceptual framework for understanding and rationally tuning condensed-phase structures in molecules and materials, and it underpins subsequent applications in materials design, biomolecular engineering, and functional molecular design^[3,4,7,28-35]. Given the pronounced impact of SHB stability on the behavior of SHB-containing compounds in both liquid and solid environ-

ments, and the fact that SHB lifetimes are constrained by multiple factors, we summarize recent advances in the study of SHB stability.

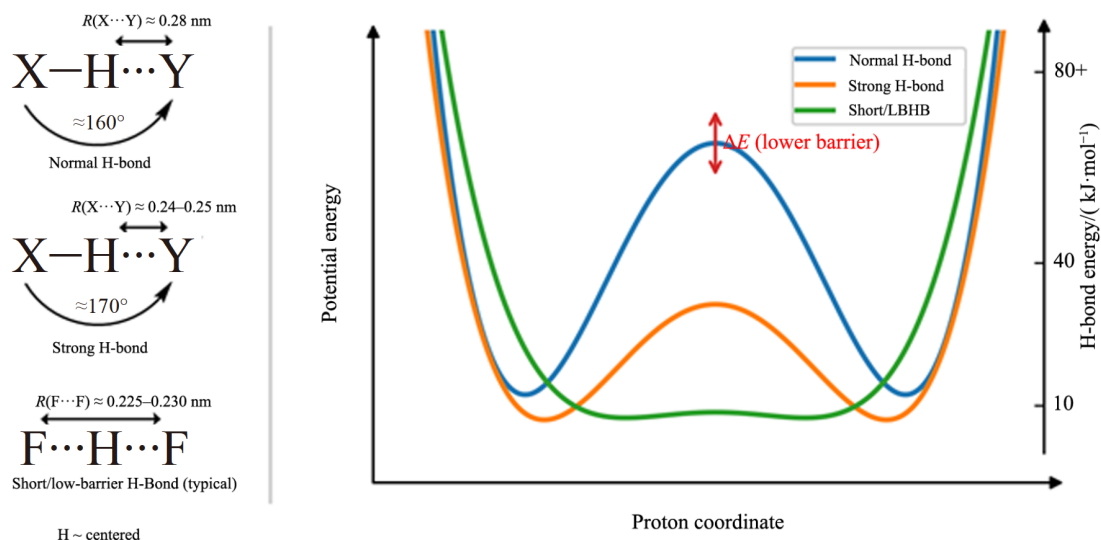
2. Definition and diagnostic criteria of SHBs

SHBs generally refer to a class of $X-H\cdots Y$ interactions in which the hydrogen-bond strength is substantially enhanced and the interaction exhibits more pronounced short-range and enhanced bonding character^[12,36-37]. Compared with conventional hydrogen bonds, SHBs are often accompanied by a marked contraction of the $X\cdots Y$ separation, a displacement of the proton toward the region between X and Y with an increased tendency for proton sharing/delocalization, as well as more prominent contributions from charge transfer and orbital overlap^[12,37-38]. In the limiting case, the structure can approach an approximately symmetric $X-H\cdots Y$ arrangement, and the PES along the proton-transfer coordinate may display a low-barrier, or even near single-well profile^[37-39]. The progressive geometric compression and the concomitant evolution of the PES from conventional hydrogen bonding to the strong/short-strong (low-barrier) limit are schematically summarized in Figure 1.

2.1 Geometric criteria

Geometrical metrics provide one of the most direct and widely used structural bases for identifying SHBs. For general $X-H\cdots Y$ interactions, the separation between the two heavy atoms is commonly denoted as $R(X\cdots Y)$. Together with $r(X-H)$, $r(H\cdots Y)$, and $\angle X-H\cdots Y$, it is used to describe the structural evolution of hydrogen bonds from conventional to strong and ultimately to the short-strong/low-barrier limit^[33,36-37]. Upon strengthening, $R(X\cdots Y)$ typically decreases markedly, the directionality of $X-H\cdots Y$ becomes more pronounced and approaches linearity, and the H atom migrates along the $X\cdots Y$ axis toward the midpoint, so that the geometry progressively approaches a more centered $X-H-Y$ motif. This concerted trend of “distance compression-proton centering-enhanced directionality” constitutes one of the defining geometric signatures that distinguish SHBs from ordinary hydrogen bonds^[33,37].

For specific bond types, the empirical range of $R(X\cdots Y)$ is inherently system dependent. Taking $O-H\cdots O$ as a representative case, extensive crystallographic statistics and high-level calculations indicate that the $O\cdots O$ distances in conventional $O-H\cdots O$ hydrogen bonds typically fall in a relatively long-distance regime. By contrast, when the $O\cdots O$ separation enters a distinctly compressed short-range domain (often reported around 0.24 to 0.26 nm), the system frequently exhibits simultaneously stronger structural constraints and anomalous spectroscopic responses, and is therefore commonly classified as a strong hydrogen bond or a short-strong hydrogen bond. The threshold of $O\cdots O$ distance for strong $O-H\cdots O$ hydrogen bonds varies slightly



Left: Representative geometries across the strengthening sequence (normal $\rightarrow$ strong $\rightarrow$ short/low-barrier), highlighting $R(X\cdots Y)$ and $\angle X-H\cdots Y$; Right: One-dimensional potential-energy profiles along the proton-transfer coordinate, showing the transition from a double-well to a single-well (or nearly symmetric double-well) landscape; the reference hydrogen-bond strength range is about 10 to 80 $\text{kJ}\cdot\text{mol}^{-1}$

Figure 1 Comparison of geometric descriptors and proton-transfer potential-energy profiles for conventional, strong, and short-strong/low-barrier ($X-H-Y$) hydrogen bonds (LBHB)

among different studies (0.24 to 0.26 nm), and its core judgment should be combined with synergistic characteristics such as proton centering degree and directionality. With further shortening, a near-symmetric proton distribution and a flatter proton potential-energy profile become increasingly likely, approaching the short-strong/low-barrier limiting behavior^[33,40]. Accordingly, $R(X\cdots Y)$ can serve as a first-order structural yardstick for strength enhancement; however, the corresponding threshold is most meaningful when comparisons are made within the same hydrogen-bond type and under closely related chemical environments^[37-38,41]. In this sense, $R(X\cdots Y)$ is among the primary geometric descriptors for tracking the strengthening of a hydrogen bond from conventional to strong regimes.

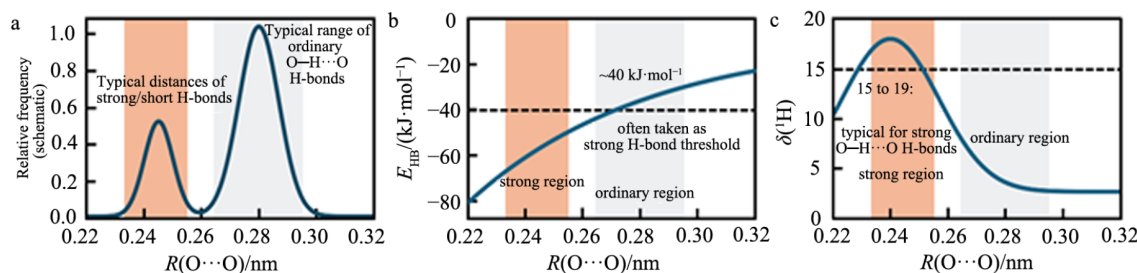
Beyond $R(X\cdots Y)$, SHBs can be further characterized by the degree of proton centering. A commonly used asymmetry parameter is $\delta = r(X-H) - r(H\cdots Y)$, which quantifies the bias of the proton position: large $|\delta|$ values indicate a proton localized toward one side, consistent with a typical $X-H\cdots Y$ configuration, whereas a substantially reduced $|\delta|$ approaching 0 signifies increasingly shared proton character and a geometry closer to the symmetric $X-H-Y$ limit^[37-38,41]. Overall, distance-based metrics constitute key structural evidence for identifying SHBs, but they are most robust when integrated with energetic and spectroscopic/electronic-structure signatures to reach reliable classification conclusions^[33,37,41-42].

2.2 Energetic criteria

The hydrogen-bond interaction energy is among the most frequently used quantitative metrics for defining SHBs and is also convenient for cross-system comparisons. Here, it is quantified as the hydrogen-bond stabilization energy E_{HB} ,

defined as the energy difference between the hydrogen-bonded complex and the separated fragments. Within an energy-based classification framework, Jeffrey roughly grouped hydrogen bonds into weak, moderate, and strong categories according to interaction energies, with SHBs typically falling in the range of 63 to 168 $\text{kJ}\cdot\text{mol}^{-1}$, thereby providing an operational strength scale and empirical boundary^[36]. From a physical standpoint, such energy enhancement is often accompanied by an evolution of the proton PES from a double-well to a low-barrier and even a near single-well profile, as schematically illustrated in Figure 1.

In many strong hydrogen-bonded systems, geometric compression, increasing E_{HB} , and spectroscopic/NMR responses tend to evolve cooperatively. Using the prototypical $O-H\cdots O$ hydrogen bond as an example, the correspondence among structure, energetics, and spectroscopic signatures is summarized in Figure 2. Furthermore, Gilli emphasized that “strength” is not solely reflected by an increased E_{HB} , but is closely linked to donor-acceptor acid-base matching (e.g., ΔpK_a), which promotes proton sharing/delocalization and barrier lowering; the pK_a equalization/slide-rule concept establishes a more mechanistically constrained mapping between energy scales, the degree of structural centering, and the shape of the proton PES^[37]. Overall, E_{HB} provides a direct quantitative yardstick for SHB strength and a practical basis for cross-system comparisons. However, its absolute value and threshold are sensitive to the computational level, zero-point/thermal corrections, BSSE treatment, and environmental conditions (gas phase, solution, or condensed phase). Accordingly, robust classification requires that E_{HB} -based grading be performed under a consistent energy definition and a uniform computational/correction protocol, and be interpreted in conjunction with geometric compres-



The orange and gray shaded intervals correspond to strong/short-strong and conventional O—H $\cdots$ O hydrogen bonds, respectively. a: distributions of $R(\text{O}\cdots\text{O})$ for conventional vs. strong/short-strong regimes; the left peak in the orange interval corresponds to strong/short-strong O—H $\cdots$ O hydrogen bonds, whereas the right peak in the gray interval corresponds to conventional O—H $\cdots$ O hydrogen bonds; b: dependence of the stabilization energy E_{HB} on $R(\text{O}\cdots\text{O})$; the horizontal reference at about $40 \text{ kJ}\cdot\text{mol}^{-1}$ marks an empirical boundary between conventional and strong H bonds; c: correlation between $\delta(\text{H})$ and $R(\text{O}\cdots\text{O})$, highlighting the typical 15 to 19 range for strong intramolecular O—H $\cdots$ O hydrogen bonds

Figure 2 Geometric-energetic-spectroscopic correlations for strong hydrogen bonds, illustrated with intramolecular O—H $\cdots$ O motifs using $R(\text{O}\cdots\text{O})$ as a common structural coordinate

sion features, acid-base matching, and proton PES characteristics, with additional validation from spectroscopic/NMR and electronic-structure evidence to yield conclusions that are more interpretable and broadly transferable^[36-37].

2.3 Complementary criteria

Beyond geometric and energetic descriptors, SHBs can be identified using spectroscopic, NMR, and electronic-structure signatures that provide more direct evidence for “bond formation”^[3-4,33,43]. In infrared (IR) and Raman spectroscopy, strengthening of an X—H $\cdots$ Y interaction is typically accompanied by a pronounced red shift of the X—H stretching vibration, band broadening, and concomitant intensity changes^[44-46]. For strong intramolecular O—H $\cdots$ Y hydrogen bonds, $\nu(\text{OH})$ is often observed in a substantially lower-frequency region and exhibits useful empirical correlations with $R(\text{O}\cdots\text{O})$ or, more generally, $R(\text{X}\cdots\text{Y})$ ^[40-41,47]. In ^1H NMR, the chemical shift of the hydrogen-bonded proton is highly sensitive to interaction strengthening and commonly displays a marked downfield displacement^[5,41,48]. For example, in strong intramolecular O—H $\cdots$ O systems, $\delta(^1\text{H})$ of the O—H proton can move far downfield and is frequently used as an empirical marker to differentiate conventional hydrogen bonds from strong/short-strong ones^[40-41,49-51].

From a theoretical perspective, the characteristic enhancement of covalent/delocalized contributions in SHBs can be quantified using approaches such as QTAIM and NBO analyses. Within QTAIM, the electron density (ρ_{BCP}) at the hydrogen-bond critical point (BCP), increases, while the sign of the total energy density (H_{BCP}) may change from positive to negative; within NBO analysis, the donor-acceptor interaction $n(\text{Y}) \rightarrow \sigma^*(\text{X}-\text{H})$ strengthens, accompanied by increases in stabilization energy and charge transfer^[12,43,52-55,56]. Collectively, these electronic-structure descriptors indicate that, upon entering the SHB regime, the interaction can no longer be viewed as a weakly coupled electrostatic attraction, but instead exhibits more pronounced multicenter bonding character and proton-sharing

behavior, consistent with geometric compression and enhanced stabilization energies.

Taken together, the criteria for identifying SHBs can be summarized as a convergence of three classes of evidence. Geometrically, SHBs feature a significantly shortened $R(\text{X}\cdots\text{Y})$, an X—H $\cdots$ Y arrangement approaching linearity, and an increasingly centered proton position; energetically, E_{HB} enters and often exceeds the characteristic SHB range; and spectroscopic, NMR, and electronic-structure analyses provide observable or computable signatures consistent with strong interactions and proton sharing^[37-38,40-41,49]. This unified framework also establishes a comparable basis for the subsequent discussion of stability across different strong hydrogen-bonded systems.

3 Factors governing the stability of strong hydrogen-bonded systems

3.1 Chemical composition

The chemical composition of a strong hydrogen-bonded system largely sets the attainable upper limit of interaction strength and the overall stability landscape. In general, highly electronegative donors X (e.g., F, O, and N) render the X—H bond more strongly polarized, thereby increasing the positive character of H, and strengthening both the electrostatic attraction and the donor-acceptor orbital interactions with an electron-rich acceptor Y. This combination typically results in a deeper potential well and enhanced thermodynamic stabilization of the complex^[49]. A representative example is provided by $(\text{HF})_n$ aggregates, in which F—H $\cdots$ F interactions can yield substantial stabilization energies, underscoring how a strongly polarized donor paired with a strong acceptor promotes SHB formation.

Beyond elemental identity, the electronic environment around donor/acceptor sites is equally critical. Substituent electron-withdrawing or electron-donating effects modulate donor acidity and acceptor basicity, thereby systematically tuning E_{HB} and the degree of geometric compression: elec-

tron-withdrawing groups generally increase X–H acidity and favor SHB formation, whereas electron-donating groups may weaken donor ability and reduce stability^[49]. Related DFT/QTAIM studies have shown that hydrogen-bond distances, bond energies, and electron density at the BCP can correlate well with Hammett constants, indicating that electronic effects provide an effective chemical handle for regulating SHB stability^[49]. In addition, competition between intramolecular and intermolecular hydrogen bonding can reshape the availability of donor/acceptor sites and the resulting network topology. For instance, when ortho substitution facilitates the formation of a stable intramolecular SHB, it often suppresses opportunities for constructing intermolecular SHBs, thereby altering the overall stability and structural organization in the condensed phase^[57–58]. Chemical composition determines the inherent potential of strong hydrogen-bond interactions, while spatial structure further regulates the effective release of this potential through geometric constraints, and the two together constitute the core internal regulatory factors of stability.

3.2 Spatial structure

Spatial arrangement and steric effects influence the propensity for formation and stability of SHBs by imposing direct geometric constraints. SHBs typically require a short X···Y separation and an X–H···Y orientation close to linearity in order to simultaneously maximize electrostatic attraction and orbital overlap. Accordingly, conformational constraint imposed by a rigid scaffold is often favorable for generating SHB motifs with shorter distances, stronger directionality, and larger stabilization energies^[57–58]. In biological and polymeric systems, such geometric constraints can be effectively “amplified”. For example, structural elements in DNA and proteins that rely on multipoint hydrogen bonding are highly sensitive to whether local hydrogen-bond geometries remain near optimal; deviations from near-ideal arrangements frequently weaken network cooperativity and thereby reduce overall structural stability^[59–61].

Conversely, steric hindrance and conformational flexibility can suppress SHB formation. Bulky substituents or unfavorable conformations may impede donor-acceptor approach and directional alignment, leading to elongated hydrogen-bond distances, increased angular deviations, or reduced numbers of hydrogen bonds, and ultimately lowering network connectivity and macroscopic stability. Studies on materials and supramolecular systems have broadly shown that tuning substituent size and placement can shift the balance between intramolecular and intermolecular hydrogen bonding, thereby modulating crosslink density, thermal-transition behavior, and mechanical properties^[62–64]. In natural polymers, sterically induced rearrangement of hydrogen-bond networks can likewise alter crystallinity and interchain packing modes, with consequent impacts on material stiffness and thermal stability^[59].

3.3 Environmental effects (temperature, pressure, and solvation)

External environments can markedly modulate SHB stability by altering molecular thermal motions, dielectric screening, and solvent competition for donor/acceptor sites. Increasing temperature typically enhances thermal fluctuations and shortens hydrogen-bond lifetimes, rendering hydrogen-bond networks more prone to rupture and rearrangement. Experimental and simulation studies on water and biomacromolecules widely show that heating is accompanied by a decrease in the average number of hydrogen bonds and a reduction in network order, and can further trigger relaxation of protein secondary/tertiary structures or even denaturation^[59,65–66]. Pressure effects are more intricate: moderate compression may favor short-range contacts from a geometric standpoint, whereas at higher pressures, particularly under elevated temperatures, network distortion, solvent displacement, or phase transitions/proton-transfer events may occur, thereby altering the conformational distribution and lifetimes of SHBs and ultimately impacting overall stability^[65–66].

Solvent effects are particularly critical for SHBs. Solvents with high dielectric constants and strong hydrogen-bonding/accepting abilities can screen electrostatic interactions and competitively engage donor/acceptor sites, thereby weakening solute-solute SHBs; conversely, in nonpolar or weakly competitive solvents, SHBs are often more stable and exhibit larger effective binding energies^[67–69]. For charged strong hydrogen-bonded systems, the local solvation shell can further influence ion coordination motifs and dissociation equilibria. Reviews on anion recognition have emphasized that high binding stability in strongly polar media can be maintained by strategies such as constructing multipoint coordination pockets and excluding solvent ingress into the binding site^[69]. In contrast, dimethyl sulfoxide (DMSO), owing to its strong acceptor character and high dielectric constant, can substantially reconfigure hydrogen-bond networks in mixed solvents: with increasing DMSO content, water-water hydrogen bonds decrease while water-DMSO and/or solute-DMSO interactions strengthen, which can weaken or even disrupt specific SHBs^[70–73]. As a representative example, in the nonpolar solvent benzene, owing to its low dielectric constant and weakly competitive hydrogen-bonding/accepting character, O–H···N hydrogen-bonded complexes can remain highly stable; for instance, the benzoic acid···triethylamine (O–H···N) complex exhibits an association constant of $K_a = 3.76 \times 10^3 \text{ L} \cdot \text{mol}^{-1}$ in benzene (298 K)^[74].

Furthermore, Van der Waals interactions, particularly dispersion forces, also play a significant role in the stability of SHBs. In condensed phases and supramolecular assemblies, dispersion forces are crucial for stabilizing these systems. Dispersion forces, especially many-body dispersion (MBD) effects, can provide additional stability in long-range molecular interactions, particularly in nonpolar sol-

vents, where solvent competition for hydrogen bond donor/acceptor sites is weak. In such environments, dispersion forces can effectively enhance the stability of SHBs. These interactions complement the hydrogen bonding, further stabilizing supramolecular complexes. Studies have shown that dispersion forces are particularly significant in supramolecular hydrogen-bonded systems, where they help reduce solvent interference with hydrogen bonding and strengthen the interactions between hydrogen bonds^[75-76].

4 Methodologies for probing SHB stability

4.1 Experimental approaches

On the experimental side, studies of SHB stability have evolved from early qualitative assignments based on single spectroscopic “fingerprints” toward an integrated paradigm that enables multidimensional characterization of structural constraints, energetic scales, and proton behavior across diverse chemical environments (gas vs. condensed phase; crystals vs. solutions; biomacromolecular systems)^[72-82].

Vibrational spectroscopy (IR and Raman) is often employed as a primary probe, where red shifts of the X–H stretching mode, together with changes in bandwidth and intensity, provide rapid signatures of hydrogen-bond strengthening. When combined with temperature-dependent measurements, time-resolved techniques, or two-dimensional spectroscopies, these methods can further track network reorganization and proton localization processes in strong hydrogen-bonded systems^[72-73]. Nuclear magnetic resonance (especially ¹H NMR, together with multinuclear and isotopic experiments) provides complementary constraints on proton position, symmetry, and dynamic exchange through chemical shifts and their environmental dependence^[41,83].

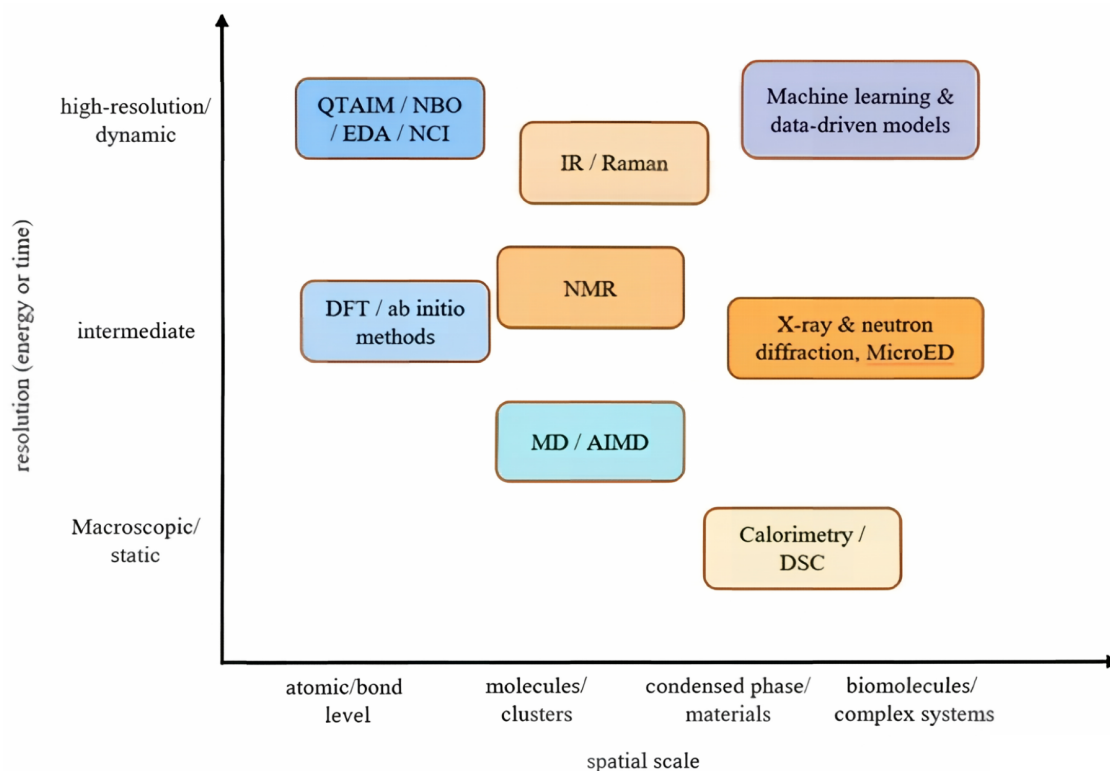
For structural determination, single-crystal X-ray diffraction offers high-precision geometries for the heavy-atom framework and X···Y separations. By contrast, neutron diffraction, owing to its sensitivity to H/D, provides unmatched capabilities for the precise determination of proton positions, enabling discrimination between symmetric and asymmetric short-strong hydrogen bonds and tracking proton symmetrization processes^[79-81]. Emerging electron-diffraction techniques such as MicroED further extend the feasibility of resolving SHB networks in microcrystalline samples, especially in cases where large-sized single crystals are difficult to obtain, providing a new path for the analysis of strong hydrogen-bond structures in biomacromolecules or new functional material systems^[82]. In addition, calorimetry and thermal-analysis methods (e.g., DSC and related calorimetric techniques) link enthalpic changes, transition temperatures, and thermal signatures of phase or conformational transitions to hydrogen-bond-network rearrangements and overall thermal stability, and are particularly useful for stability assessments in materials and biological systems^[77-78,84]. Overall, experimental studies of

SHB stability are moving from single-metric diagnoses toward coordinated validation that integrates structure, spectroscopy, and thermodynamics, thereby yielding conclusions that are more robust, comparable, and mechanistically interpretable.

4.2 Theoretical and computational approaches

Relative to experimental characterization, theoretical calculations offer the advantage of providing structural, energetic, and electronic-structure information on a unified energy scale, establishing a foundation for consistent cross-system comparisons of SHB stability^[85-87]. In practice, investigations typically begin with static quantum-chemical calculations: density functional theory (DFT), commonly supplemented with dispersion corrections and appropriate basis sets, is used to optimize candidate geometries and perform vibrational analyses, yielding equilibrium structures, hydrogen-bond stabilization energies, E_{HB} , vibrational signatures, and barriers associated with proton transfer and related motions^[85-87]. Systematic comparisons among symmetric versus asymmetric motifs, intra- vs. inter-molecular arrangements, and multicenter hydrogen-bonding motifs enable identification of the most stable structures and their PES characteristics, while also providing quantitative calibration for IR/Raman-based diagnostics^[85-87].

However, geometries and energies alone are often insufficient to rationalize the physical origin of “strength”. Consequently, electronic-structure decomposition and diagnostic analyses have become essential complements in SHB research. Tools such as QTAIM, NBO, NCI, and energy-decomposition frameworks (e.g., EDA/ETS-NOCV) characterize electrostatic, orbital (covalent), and dispersion contributions from the perspectives of electron-density topology, orbital interactions, and energy partitioning, thereby integrating geometric compression, proton sharing/delocalization, and enhanced E_{HB} into a coherent physical picture^[86,88-92]. When SHBs occur in condensed phases or under substantial environmental perturbations (temperature, pressure, solvation), static results often require dynamical refinement. Classical molecular dynamics (MD) and *ab initio* molecular dynamics (AIMD) enable statistical characterization of hydrogen-bond lifetimes, geometric distributions, and network topologies at finite temperature and in explicit solvent environments, thereby revealing the dynamic stability of SHBs under realistic conditions and their responses to changes in temperature, pressure, and composition^[89-97]. Building on such multiscale information, recent efforts increasingly couple theoretical descriptors with experimentally observable quantities and employ regression or machine-learning models for rapid prediction, improving the practicality of SHB stability assessments for large systems and high-throughput screening^[86-87,98-101]. Overall, DFT provides an operational “structure-energy” baseline, electronic-structure analyses deliver mechanistically interpretable decomposition of underlying interac-



The horizontal axis represents spatial scale, and the vertical axis indicates the characteristic resolution in energy and/or time. Colored boxes denote representative methodological modules and their complementarity. The map is schematic and not intended to represent strict quantitative boundaries

Figure 3 Multiscale map of experimental and computational methods used to probe the stability of strong hydrogen-bonded systems

tions, and MD/AIMD capture realistic environment- and dynamics-driven effects; together with experiments, these approaches constitute the mainstream methodological framework for contemporary studies of SHB stability, as summarized in Figure 3.

5. Outstanding issues and challenges

In recent years, substantial progress has been made in elucidating the stability of strong hydrogen-bonded systems. Experimental characterization and theoretical calculations have increasingly converged into mutually reinforcing frameworks, enabling more systematic comparisons and generalizations of structural features and stability variations across diverse strong hydrogen-bonded systems^[72-73,85-86]. Nevertheless, when the focus shifts to realistic complex environments, such as solutions, condensed-phase materials, and biomacromolecules, SHBs are often embedded within ensembles with multiple coexisting configurations and multiscale fluctuations. Their measured observables are jointly shaped by solvation, polarization, and other non-covalent interactions. Consequently, experimental readouts more frequently reflect integrated responses of local hydrogen-bond environments and networks, rather than an isolated thermodynamic quantity of a single or a direct “single-parameter” structural measure for one specific SHB^[56,67-69,93-94].

Accordingly, a central challenge is not merely to pursue “stronger criteria”, but to establish comparison and calibration pathways that remain valid in complex systems. Under consistent definitions, orthogonal experimental observables should be cross-constrained with benchmark computations to form reproducible analytical protocols and standardized workflows, thereby enabling reliable mapping from microscopic interaction changes to stability trends and functional responses^[56,85-86,93-94]. Only with such a framework can discussions of SHB stability advance from phenomenological correlations toward testable causal interpretations, providing a more solid basis for rational tuning and application-oriented design^[69,99-101].

6. Conclusions

Strong hydrogen-bonded systems are of substantial scientific significance in both fundamental studies and application-oriented research. In recent years, our understanding of SHB definitions, structural signatures, and energetic origins has continued to deepen. Increasingly, a more unified view has emerged in which SHBs are interpreted within an electrostatic-covalent continuum framework, and the synergistic roles of chemical composition, spatial structure, and external environments in regulating SHB stability have been increasingly recognized. Methodologically, the integration of experimental techniques, such as spectroscopy,

diffraction and calorimetry, together with theoretical approaches including quantum chemistry and molecular dynamics has enabled cross-scale interrogation of energetics, geometric constraints, and dynamical behaviors. These advances have facilitated more systematic generalizations of SHB phenomena across organic, inorganic, and biological systems, and have provided a firmer mechanistic basis for functional applications in materials science, energy conversion, and biomedicine.

Nevertheless, several critical bottlenecks remain. Quantitative separation and reliable calibration of SHB contributions in complex environments are still insufficient; high-accuracy theoretical models that simultaneously account for nuclear quantum effects, many-body polarization, and long-range environmental interactions remain computationally challenging for large systems; the causal pathways linking SHB networks to structure and under the interplay of multiple, coupled noncovalent interactions require clearer mechanistic resolution; and more broadly, systematic strategies are still needed to translate molecular-level hydrogen-bond modulation into designable and experimentally verifiable macroscopic performance metrics. Looking forward, continued advances in multidimensional spectroscopy and *in situ* structural characterization, together with deeper integration of quantum chemistry, molecular dynamics, and data-driven models, are expected to enable progress in unified criteria, comparable benchmarking, and cross-scale prediction. Such developments should further provide theoretical support for interdisciplinary applications, including the design of new hydrogen-bonded energy storage materials, the construction of energy devices, and the regulation of enzyme catalytic efficiency, thereby unlocking the potential of SHB research in practical applications across materials science, energy systems, and biomolecular engineering.

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强氢键体系稳定性的研究进展

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摘要 强氢键体系以其高键能、短键距和显著方向性为特征, 在分子结构调控、凝聚态性质调制及生物功能维持中扮演关键角色。该类相互作用的本质兼具双重属性: 既有静电主导的经典非共价特征, 亦包含源于轨道重叠与电荷转移的共价成分, 其稳定性与化学组成、空间架构及环境条件紧密耦合。本文系统综述强氢键体系的基础理论、结构能量特征、调控因素、研究范式及典型应用, 旨在梳理领域进展、凝练核心挑战, 并为材料科学、能源转换与生物分子工程中强氢键体系的理性设计与性能优化提供参考。

关键词 强氢键; 低势垒氢键; 稳定性; 多尺度表征与模拟