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Critical Assessment of the Strength of Hydrogen Bonds between the Sulfur Atom of Methionine/Cysteine and Backbone Amides in Proteins

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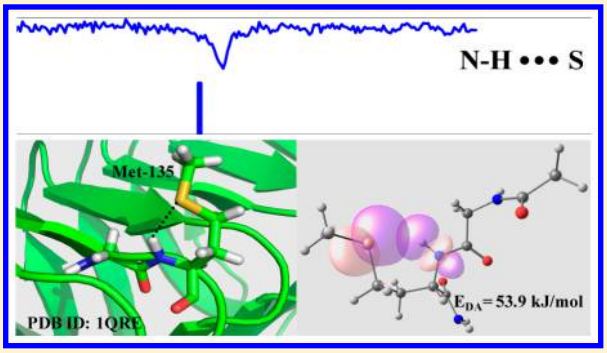
Supporting Information

ABSTRACT: Gas-phase vibrational spectroscopy, coupled cluster (CCSD(T)), and dispersion corrected density functional (B97-D3) methods are employed to characterize surprisingly strong sulfur center H-bonded (SCHB) complexes between cis and trans amide NH and S atom of methionine and cysteine side chain. The amide N—H···S H-bonds are compared with the representative classical σ- and π-type H-bonded complexes such as N—H···O, N—H···O═C and N—H···π H-bonds. With the spectroscopic, theoretical, and structural evidence, amide N—H···S H-bonds are found to be as strong as the classical σ-type H-bonds, despite the smaller electronegativity of sulfur in comparison to oxygen. The strength of backbone-amide N—H···S H-bonds in cysteine and methionine containing peptides and proteins are also investigated and found to be of similar magnitudes as those observed in the intermolecular model complexes studied in this work. All such SCHBs also confirm that the electronegativities of the acceptors are not the sole criteria to predict the H-bond strength.



The enormous importance and widespread occurrences of hydrogen bonds (H-bond) are well known as evidenced from the several volumes of books[1−7] published in this active area of research. The books and the references describe the strength, geometry, and nature of H-bonds observed in biomolecules, organic crystals, and simple molecular and ionic dimers. In spite of exhaustive research carried out on different types of H-bonds, IUPAC's report on the new definition[8] of H-bonds emphasizes the poor understanding of this century-old concept. New concepts have been conceived and new types of H-bonds are being brought to the forefront;[9] one such example is the recently proposed "anti-electrostatic H-bonds".[10−15] The iron-clad rule about the strength of H-bonds, represented by D—H···A, is that "more electronegative is D or A, more is the H-bond strength". Many exceptions to this rule have been seen.[16−18] For example, there are cases where "S" forms as strong H-bonds as "O", even though "S" is less electronegative than "O".[16−18]

In an effort to justify the claim, "S" can be a potential H-bond acceptor as "O" and "N", many systems forming inter- and intramolecular N—H···S and O—H···S H-bonds have been studied.[16−28] The systems consist of simple model compounds to methionine and cysteine containing tripeptides. On the basis of the inputs obtained from the model systems containing OH, SH, and NH donors as well as O and S acceptors, it was extended to sulfur containing peptides to explore the role of SCHBs on local structures of the main chain induced by a Met or Cys residue.[18,27] The atomic scale information was obtained by gas phase spectroscopy of isolated model peptide chains. The approach was based on IR/UV double resonance spectroscopy of mass-selected jet-cooled molecules and their clusters, a technique very elegantly deployed on various model biomolecular systems as well as peptide chains.[29−35] It was observed that sulfur atoms in the side chain of methionine and cysteine are capable of forming strong amide N—H···S H-bonds. In the methionine containing peptides (e.g., Ac—Phe—Met—NH_2; in short FM) N—H···S H-bonds were surprisingly found to be the strongest among other H-bonds (N—H···O═C and N—H···π H-bonds).[18] But in case of cysteine containing peptides (e.g., Ac—Phe—Cys—NH_2; in short FC) the strengths of N—H···S H-bonds were similar or even weaker than N—H···O═C H-bonds.[27] In fact, the C_5 intraresidue interaction of cysteine (Cys) has a similar bonding pattern as the methionine (Met) residue. However, the C_6 intraresidue H-bond of methionine linking NH_{Met} to the Met side chain S sulfur atom was found to be stronger than its cysteine

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counterpart as supported by larger red shift of N—H streching (-124 cm^{-1} shift vs -46 cm^{-1}), shorter calculated NH···S distances (~245 pm vs 277 pm) and more linear H-bond geometries (N—H—S angle in the 130–140° range vs 100–110°). The stronger C_6 intraresidue H-bond of methionine compared to cysteine can be ascribed to the additional methylene group in the Met side chain, which provides an extra degree of freedom, facilitating the formation of a stronger and shorter H-bond. Hence, it is the intrinsic structural constraints of the peptides that decide strength of the SCHBs. At this point, it is noteworthy to mention that irrespective of their strengths, the N—H···S H-bonds are very important in controlling the conformational landscape of methionine and cysteine containing peptides.[18,27] The same structural pattern has also been observed in proteins; however, the importance and the strength of N—H···S H-bonds are belittled in the literature, and in some cases, it is even regarded as weak H-bond as N—H···π H-bond.[36,37] The discrepancies between the IR measurements on methionine and cysteine containing peptides and statistics on PDB structures put a challenge to the spectroscopists to gauge the absolute strength of amide N—H···S H-bond in peptides and proteins. The simplest way to answer this question is to study 1:1 intermolecular complexes of amide and S/O containing small molecules in gas phase isolated conditions, eliminating environmental and conformational effects. Moreover, bench mark computation on such noncovalent interactions in proteins is an insurmountable task, whereas choosing appropriate model systems provides the means to carry out the computation at high levels of theory such as CCSD(T).

The model compounds for H-bond acceptors and donors studied in the present work are shown in Figure 1. The H-bond donors consist of both cis and trans amides, representing the amides in peptides and nucleobases, respectively. The H-bond acceptors are chosen so as to form four different types of H-bonds, namely, N—H···S, N—H···O=C, N—H···O, and N—H···π H-bonds. These H-bonds are depicted in the rightmost panel of Figure 1.

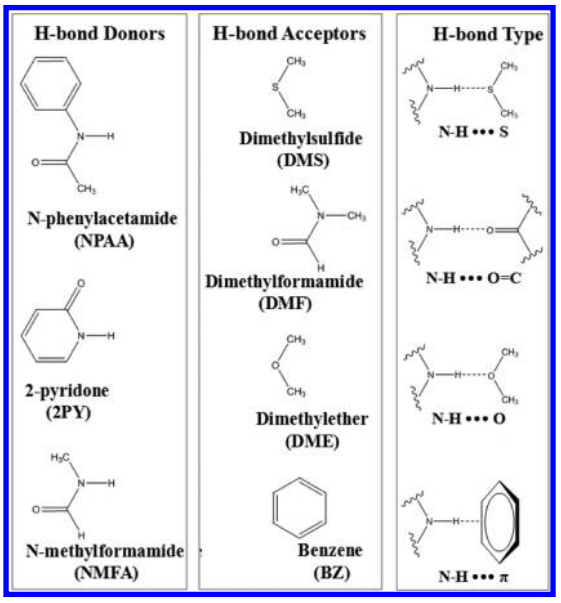

Figure 1. Left: Representative cis and trans amides as H-bond donors investigated herein. Middle: the four different H-bond acceptors. Right: four different types of H-bonds formed between the donors and acceptors.

Results and Discussion. Mass resolved and conformer selective IR/UV double resonance spectroscopy and quantum chemical calculations were employed to obtain gas-phase IR spectrum and structural information on isolated jet-cooled monomers and their 1:1 H-bonded complexes. The amide N—H stretching frequency can be used as the spectroscopic ruler to measure the H-bond strengths. Figure 2 presents the gas phase IR spectra of trans amide monomer (*N*-phenylacetamide, NPAA) and its 1:1 H-bond complexes with different H-bond acceptors. In all the complexes the amide N—H frequencies were red-shifted with respect to the monomer frequency.

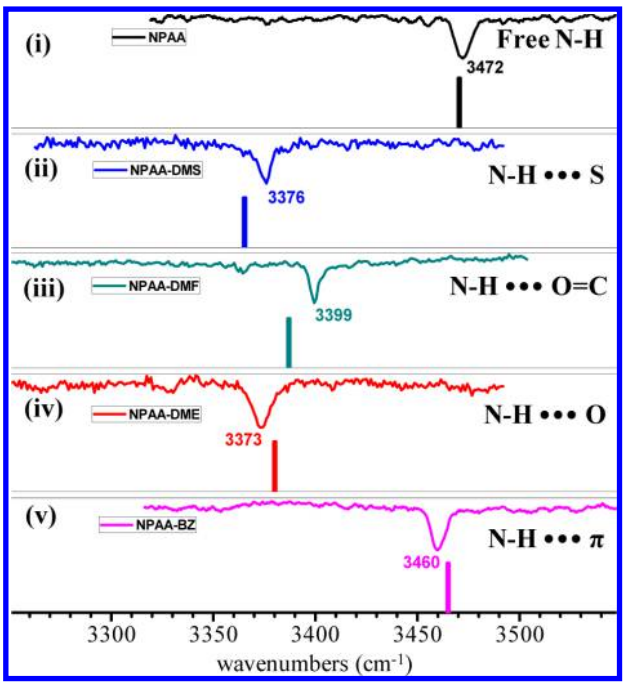

Figure 2. Gas phase vibrational spectra of monomer (NPAA) and its H-bond complexes with S, O, and π acceptors in the N—H stretch region, obtained by IR/UV double resonance spectroscopy. Underneath the experimental spectra, DFT-D (B97-D3/def2-TZVPP) calculated stick spectra are presented for the sake of comparison and assignment. The computed vibrational frequencies of the complexes are scaled by 0.9869.

In order to assign these IR signatures, dispersion corrected DFT functional (RI-B97-D3/def2-TZVPP) was chosen. Its ability in reproducing the structures, energetics, and vibrational frequencies of H-bonded complexes and peptides has been tested and reported to compare well with gas phase experiments.[18,27,38] Among the several complexes optimized, only the global minimum structures were found to be consistent with the experimental results based on both their energetics and their predicted spectra. The stick diagrams underneath the experimental IR spectra represent the computed N—H stretching frequencies of the global minimum structures.

The resulting assignment of the complexes reveals that the amide N—H is involved in H-bonding with different acceptors forming N—H···S, N—H···O=C, N—H···O, and N—H···π H-bonds. The redshift of the amide N—H stretch for NPAA—DME and NPAA—DMS complexes are similar ($\Delta\nu$ ~100 cm^{-1}) followed by NPAA—DMF ($\Delta\nu$ ~75 cm^{-1}) and

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Table 1. Computed Binding Energy[a] at CCSD(T)/aug-cc-pVDZ and in Parentheses Red Shift of N—H Stretching Frequency[b] for N—H···S, N—H···O=C, N—H···O, and N—H···π H-Bond Complexes

	acceptors			
donors	DMS	DMF	DME	BZ
NPAA	40.6 (−96.0)	55.1 (−73.0)	39.2 (−99.0)	40.3 (−12.0)
2-PY	49.0 (−291.0)	57.8 (−311.0)	44.9 (−250.0)[c]	38.1 (−56.0)[d]
NMFA	28.0 (−182.5)[e]	32.1 (−173.7)[e]	27.2 (−147.3)[e]	30.2 (−11.6)[e]

[a]D_0 in kJ/mol. [b]$\Delta\nu$ in cm^{-1}. [c]Experimental $\Delta\nu$ value was taken from ref 39. [d]Experimental $\Delta\nu$ value was taken from ref 40. [e]RI-B97-D3/def2-TZVPP computed $\Delta\nu$ values. Scaling factor: 0.9869.

NPAA—BZ ($\Delta\nu$ ~15 cm^{-1}) complexes. If one considers the N—H red shift as a ruler for the H-bond strength, it can be inferred that N—H···O or N—H···S H-bonds are stronger in comparison to N—H···O=C and N—H···π H-bonds in case of the H-bonded complexes of trans amide N—H.

To substantiate the spectroscopic outcome and to estimate the interaction energies, CCSD(T)/aug-cc-pVDZ energetics were carried out on isolated monomers and their complexes. The binding energy (D_0) and red shift of N—H stretches ($\Delta\nu$) are presented in Table 1. Figure 3 shows the correlation plot

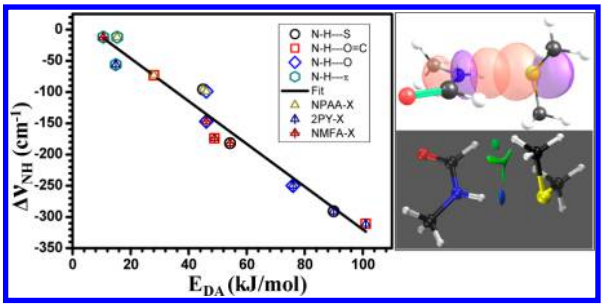

Figure 3. Left: Linear correlation plot between donor−acceptor interaction energies (E_{DA}) and red shift of N—H stretching frequencies. Right: The NBOs of interacting donor−acceptor (top) and 3D-NCI plot (bottom) representing primary and strong N—H···S H-bond (blue isosurface of reduced electron density gradient) and secondary and weak C−H···S H-bonds (green isosurface). The NBO calculation and NCI-plot topological analysis of the electron density were performed at the MP2/aug-cc-pVDZ level of theory.

between $\Delta\nu$ and donor−acceptor interaction energy (E_{DA}) obtained from natural bond orbital (NBO) analysis.[41,42] E_{DA} represents the interaction energy between the lone pair (lp) electrons/ π electrons of H-bond acceptors and the antibonding σ N—H orbital (σ^*_{N-H}) of H-bond donors. A linear correlation between the redshift of amide N—H frequency and donor−acceptor interaction energies is observed, which corroborate our experimental finding of very strong amide N—H···S H-bonds. However, there is no correlation observed between the binding energies and $\Delta\nu$(NH). This is mainly because the assigned conformers of NPAA-X display substantial secondary C−H···S/O/π interactions in addition to the primary N—H···S/O/π H-bonds (see the NCI plot, Supporting Information Figure S1).

We further extended our study to the cis amide, taking 2-PY as the H-bond donor. In this case, the red shift of the N—H stretch was found to follow the order N—H···O=C > N—H···S > N—H···O > N—H···π (see Table 1 and Supporting Information Figure S2), which is a slight deviation from the trans amide case. However, the computed binding energies do not follow the same trend as the red shift. We carried out computations on the complexes of simple amide (*N*-methylformamide) void of the aromatic ring and extended methyl groups. Figure 3 shows a linear correlation between the red shift of N—H stretch and donor−acceptor interaction energy for all the nine complexes. The right panel of Figure 3 represents the donor−acceptor NBO orbitals and NCI (noncovalent interaction) plot[43] for NMFA-DMS. In this case also, in addition to the N—H···S H-bond there is small contribution of C−H···S interaction to the total binding energy. For the NMFA-Bz complex, it seems that the N—H···π and C−H···π have almost the same contribution to the total binding energy (Supporting Information Figure S3). Nevertheless, an important result emerged from this study; the amide N—H···S H-bond is as strong as classical N—H···O and N—H···O=C H-bonds. The amide N—H···S H-bond energy at the CCSD(T) level is found to be ~30 kJ/mol.

Comparison with Backbone-Amide N—H···S H-Bonds in Peptides and Proteins. As shown in Figure 4, in methionine and cysteine containing peptides (FM and FC), there is substantial overlap

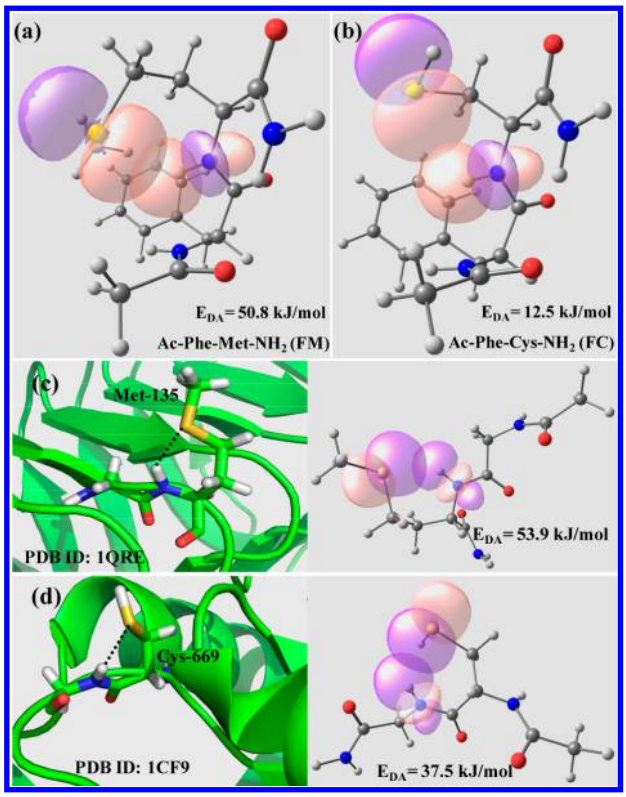

Figure 4. NBO 3D overlap diagrams for $n_S \rightarrow \sigma^*_{NH}$ donor−acceptor interaction in methionine and cysteine containing peptides. The structures presented in (a) and (b) are taken from the gas-phase data[18,27] and those presented in (c) and (d) are from RCSB protein data bank.[44,45]

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between the lp of S of methionine side chain with the σ^*_{N-H} orbital of backbone amide group, forming a strong N—H···S H-bonds. The E_{DA} and $\Delta\nu$ for FM are found to be 50.8 kJ/mol and −124 cm^{-1}, respectively, which are comparable with those of NPAA-DMS and NMFA-DMS complexes. The amide N—H···S H-bond energies of these complexes computed at the CCSD(T)/aug-cc-pVDZ are in the range of 30−40 kJ/mol. This in turn suggests that if one relaxes the structural constraints it is expected that amide N—H···S H-bonds of similar magnitudes should be present in methionine/cysteine containing peptides and proteins linking the backbone amide N—H and sulfur atom of methionine/cysteine side chains. For instance, Figure 4c and d display the intramolecular backbone amide N—H···S involving methionine and cysteine as they exist in the two proteins. We took the Cartesian coordinates of those amino acid sequences from their PDB structure[44] and added H atoms. They were subsequently subjected to partial geometry optimization at RI-B97-D3/def2-TZVPP by freezing all the nuclei except the added H atoms. The partially optimized structures were used to compute the donor−acceptor interaction energy. The E_{DA} were found to be 53.9 and 37.5 kJ/mol for amide N—H···S-methionine and amide N—H···S-cysteine H-bonds, respectively; very similar to those observed for simple model peptides. This justifies our claim that "amide N—H···S H-bonds in proteins and bio-molecules are equally strong H-bonds as their oxygen counterpart". Hence, their significance cannot be neglected or overlooked in comparison to amide N—H···O and amide−N—H···O═C H-bonds in biomolecules.

The long failure to recognize SCHB as strong as classical H-bonds invoke critical re-examination of many of its aspects at the molecular level using highly selective gas-phase spectroscopic methods combined with quantum chemical calculations. The spectroscopic data and the CCSD(T) energetics of the H-bonded complexes studied here certainly deserve the special attention of the structural biology and chemical science community toward the belittled SCHB. The SCHB needs to be considered seriously as an essential inter/intramolecular force while designing new force fields for the protein structure simulation. The results obtained in this work can be used for the benchmark purpose by experimentalists and theoreticians.

Method Section. The solid samples (H-bond donors: NPAA and 2-PY) were heated to 80−100 °C to get sufficient amount of these molecules in the vapor phase. About a 0.2−0.5% premixture of H-bond acceptors (DMS, DME, DMF, and BZ) in helium were used for the complex formation. The H-bonded complexes formed were then cooled down by supersonic expansion and skimmed prior to entering the ionization chamber of the linear time-of-flight spectrometer.[25,46] Mass-selective resonant two-photon ionization (R2PI) spectroscopy was used to record the ultraviolet (UV) spectra and IR/UV double resonance spectroscopy was used to obtain the IR spectra. The supersonic-jet cooling (∼10−20 K) reduces spectral congestion, allowing us to assign conformation-specific infrared spectra, in the form of well-separated narrow vibronic bands. The computed IR spectra of the H-bonded complexes were obtained using DFT-D (RI-B97-D3/def2-TZVPP)[47] calculations and compared with experimental ones. The binding energies of the complexes were estimated at the CCSD(T)/aug-cc-pVDZ level of theory. The natural bond orbital (NBO) and noncovalent interaction (NCI) analyses were carried out to determine the donor−acceptor pairwise interaction energy. The computations were carried out with Gaussian09[48] and Turbomole 6.5[49] software.

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

The FDIR spectrum of 2-PY and its H-bonded complexes as well as 3D-NCI-plot displaying Primary N—H···S/O/O═C/π H-bonds and secondary C—H···S/O/π H-bonds. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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