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# Hydrogen Bond and Geometry Effects of Thioamide Backbone Modifications

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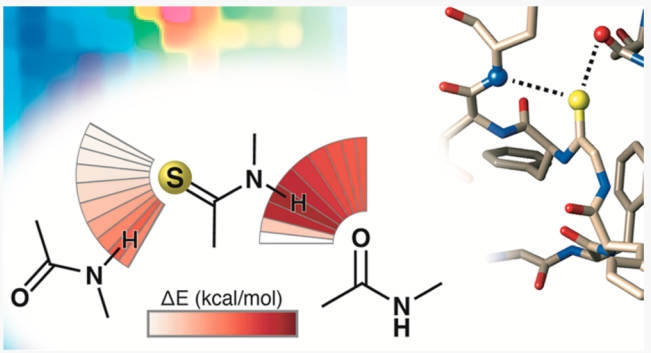
**ABSTRACT:** Thioamide substitution of backbone peptide bonds can probe interactions along the main chain of proteins. Despite theoretical predictions of the enhanced hydrogen bonding propensities of thioamides, previous studies often do not consider the geometric constraints imposed by folded peptide secondary structure. This work addresses drawbacks in previous studies that ignored the geometry dependence and local dielectric properties of thioamide hydrogen bonding and identifies cases where thioamides may be either stronger or weaker hydrogen-bonding partners than amides.






Mutational analysis of peptide residues can provide critical information about the role of side-chain functional groups in the structure and function of proteins. Such mutations can be readily achieved through solid-phase peptide synthesis (SPPS) or through recombinant protein expression, making the analysis of side chain identity an important and facile technique in biochemistry and chemical biology. Alternatively, evaluating the role of the peptide backbone in the structure and function of proteins requires alteration of the defining feature of the biomolecule—the peptide bond.[1] Motivated by this challenge, chemists have developed numerous isosteric surrogates of peptide bonds to interrogate effects along the polyamide backbone (Figure 1A).[2] The thioamide, however, is arguably the closest approximation to the canonical amide.[3]

The geometry and functional group pattern of amides and thioamides are nearly identical. In contrast to other amide isosteres presented in Figure 1A, thioamides retain the critical Brønsted−Lowry acidic and basic sites that are essential for hydrogen bonding and biomolecular recognition. However, several subtle differences between thioamides and amides do exist (Figure 1B). For instance, the larger van der Waals radii of sulfur results in a longer C═S bond (1.66 Å) than the C═O bond (1.22 Å) in amides. Further, because of the lower Lewis basicity of sulfur, thioamides are thought to be weaker hydrogen-bond acceptors than amides. The carbonyl bond of thioamides is also considered to be weaker than in amides. As a result, the C−N bond in thioamides are slightly shorter due to an increase in contribution of its resonance form **2b**. An increase in the zwitterionic resonance structure of thioamides thus lends credence to the notion that thioamides are stronger hydrogen-bond donors than amides. Additionally, a greater C═N double-bond character results in a larger rotational barrier, which ultimately limits the conformational entropy of thioamides.[4,5]

Collectively, the subtle differences that thioamides exhibit from amides has driven their use in a variety of settings to probe effects along the peptide backbone. Thioamides have been shown to be compatible in several protein secondary structure motifs, which allows for the exploration of hydrogen-bonding effects to and from the backbone.[6−10] Thioamides

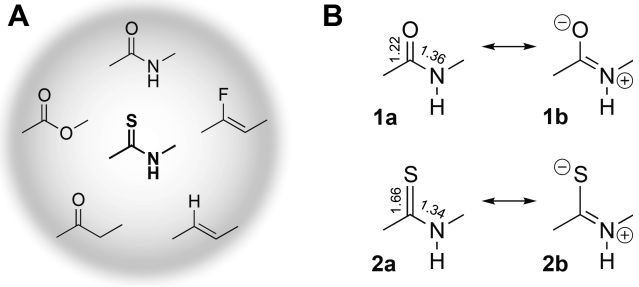



**Figure 1.** (A) Commonly used isosteres of the peptide bond.[2] (B) Comparison of amide (**1**) and thioamide (**2**) geometries (bond distances in Å).

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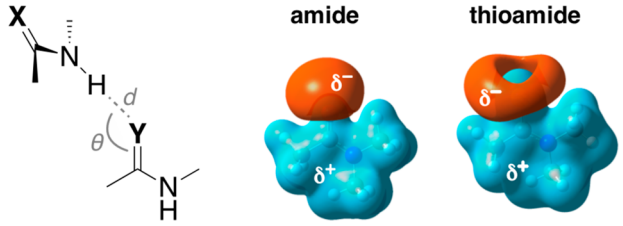
Table 1. Geometry Preferences and Interaction Energies in Both the Gas Phase and Implicit Water Solvent Model (SMD)




| | | | geometry | | interaction energy ($\Delta H$, kcal/mol) | |
|---|---|---|---|---|---|---|
| entry | X | Y | $d$ (Å) | $\theta$ (deg) | gas phase | water (SMD) |
| 1 | O | O | 1.92 | 116 | −7.27 | −3.06 |
| 2 | S | O | 1.89 | 116 | −8.86 (−1.58)[a] | −4.00 (−0.93)[a] |
| 3 | O | S | 2.45 | 97 | −6.89 (+0.38)[a] | −3.30 (−0.23)[a] |

[a]Numbers in parentheses are the difference in energy relative to the N-acetamide dimer in entry 1. Energies calculated at CCSD(T)-SMD/aug-cc-pVDZ//$\omega$B97XD-SMD/aug-cc-pVDZ. Electrostatic potential maps (from total SCF electron density) computed using B3LYP/6-311+g(d,p) with an isovalue of 0.04. Please see SI for full computational details.

have also been useful in the study of other noncovalent interactions such as the n → $\pi^*$ interaction between neighboring peptide C═O groups.[11−16] The different properties of thioamides and amides have also allowed thioamides to serve as minimal probes for the study of larger peptides and proteins. For instance, thioamides have been implemented as photoswitchable units to effect *cis*/*trans* isomerization of the thioamide unit.[17,18] Likewise, the thioamide can act as a quencher of fluorescent dyes to study peptide conformation and proteolysis.[19−27] In general, thioamides are viewed as subtle single-atom substitutions that provide an analytical handle for a variety of biochemical and biophysical techniques and therefore suggests their indispensable role in peptide sciences.

The hydrogen bonding properties of thioamides have been explored computationally. An early computational study employing formamide and thioformamide dimers suggested that thioamides can be up to 2 kcal/mol stronger hydrogen bond donors than amides and up to 1 kcal/mol weaker hydrogen bond acceptors.[28] More recently, however, it has been argued that thioamides accept hydrogen bonds at the same magnitude as amides.[29] Despite these computational predictions, however, experimental manifestations are slow to emerge. Many studies that have sought to explore the hydrogen-bonding properties of thioamides in the context of proteins have shown that they are only merely tolerated and show net destabilization.[6,7,10] In fact, one of the most thorough studies of thioamides in proteins examined 14 thioamide mutations in three different proteins and found only thionation of the internal (4-hydroxy)proline/glycine dipeptide in the repeating (Pro-Pro/Hyp-Gly)$_n$ motif in collagen to be stabilizing.[9] Moreover, attempts to computationally assess the hydrogen bonding potential of thioamide isosteres often do not consider hydrogen-bond geometries that are typically associated with folded peptide structure, whereas the hydrogen-bonding behavior of thioamides in proteins are obviously constrained by the folded secondary structure.

This study seeks to resolve the contrast between computational and experimental approaches to studying thioamide isosteres by examining how hydrogen-bonding strength varies with geometry. Moreover, thioamides are being increasingly discovered in natural products,[3] suggesting that there are specific advantages to these isosteres that drove Nature to developed the biochemical machinery for their installation. Unravelling the context-specific nature of the hydrogen-bonding strength of thioamide isosteres will therefore inform strategies intent on employing them to study protein structure.

There are several limitations of previous computational studies with respect to thioamides, including the use of nonbiologically relevant motifs, nonbiologically relevant hydrogen bonding geometries, and an overestimation of the hydrogen-bond interaction energies from gas-phase treatment of such interactions.[28] To this end, we provide a more comprehensive view of thioamide hydrogen bonding propensities in the context of folded peptide structure.

The secondary amide, *N*-methylacetamide, was used in this study as a minimal model of polypeptide backbone amides that participate in inter-residue hydrogen bonding (entry 1, Table 1). When the thioamide operates as the hydrogen-bond donor (entry 2), the dimer optimized to the same hydrogen-bonding contact angle of 116°. This contact angle matches well with the canonical hybridized $sp^2$ model of oxygen lone pairs. In contrast, when the thioamide operates as a hydrogen-bond acceptor (entry 3), the model dimer optimized to a contact angle closer to 100°. While unconventional, this result is not unprecedented or unexpected because concepts of hybridization cannot be generalized to main-group elements lower than the first row, where higher row elements in the main group do not hybridize their atomic orbitals.[30] This effect is further exemplified by the electrostatic potential maps of amides versus thioamides (Table 1), which reveal a distinct "bald spot" of electron density along the C═S bond.[31] Additionally, such acute contact angles have been observed in computational studies of thioamide hydrogen bonding in nucleic acid models as well as other sulfur acceptors such as thioethers and thiocarbonyls.[29,32−34]

To achieve the most accurate results for the energetic contribution of the different hydrogen bond cases in Table 1, we utilized post-Hartree-fock methods based on literature precedent.[29] Further, as hydrogen bond strength is inversely proportional to the dielectric of its environment, we calculated the hydrogen-bonding interaction energies in solvated environments using an implicit solvent model. In the gas phase, our calculations estimate thioamides to be ∼1.5 kcal/mol stronger donors (entry 2) and ∼0.4 kcal/mol weaker acceptors (entry 3) than amides, which matches well with previous reports.[28] As expected, when placed in an implicit water model, the overall calculated hydrogen bond strengths weaken. We predict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thioamide hydrogen-bond donors to still be stronger than amides, but only by ∼1.0 kcal/mol (entry 2). Intriguingly, the calculated hydrogen-bond strengths show that thioamides can be up to ∼0.3 kcal/mol *stronger* acceptors than amides in more polar environments. This result is surprising and contrary to the generally held view that thioamides are weaker hydrogen bond acceptors relative to their oxoamide counterparts. We attribute this result to a stabilization of the zwitterionic resonance contributor **2b** in more polar environments. This effect is further supported by a shortening of the C−N bond distance and a corresponding lengthening of the C═X bond as the solvent dielectric increases (see SI for details).

To further explore the hydrogen-bond contact angle, $\theta$, we calculated the interaction energies as a function of $\theta$ while maintaining the equilibrium NH−Y distance (Figure 2A). The

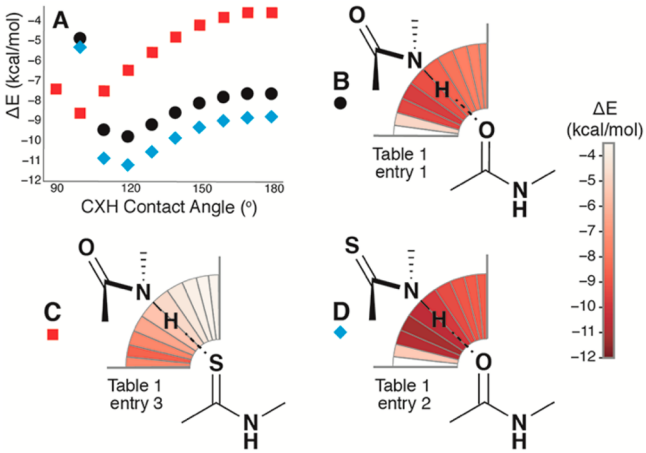


**Figure 2.** (A) Hydrogen bond interaction electronic energy as a function of the CO−H contact angle, $\theta$. (B−D) Dimer hydrogen bond interaction heatmaps. All values were calculated at rωB97X-D/aug-cc-pVDZ.

expected minima for $\theta$ were observed for each of the three *N*-methylacetamide dimer combinations (Figure 2B−D). In alignment with the above ESP maps, the amide H-bond acceptors (Figure 2B and 2D) show a greater tolerance for hydrogen bonding angles whereas the thioamide acceptor (Figure 2C) displays a more dramatic decrease in hydrogen-bonding potential as $\theta$ approaches 180°. Both amide H-bond acceptors (Figure 2B and 2D) exhibit identical $\theta$-dependent hydrogen bonding potentials that vary only in the magnitude of the interaction energy. This mirroring behavior suggests that thioamides, as hydrogen bond donors, can be well tolerated as point mutations in peptides and proteins.

Limitations arise, however, when thioamides are in positions as hydrogen bond acceptors. Thioamide hydrogen-bond accepting ability is strongest between 90° and 100° and becomes weaker as the contact angle approaches 180°. This effect, combined with the possibility for adverse steric effects due to the longer C═S bond, indicates that thioamide hydrogen-bond acceptors will be less tolerated as point mutations. Further, we show that the residue after a thioamide is critical toward thioamide stability due to steric interactions between the longer CS bond and the amino acid side chain and thus limiting available Φ and Ψ space (Figure S2).[35] Another implication of these results is that to capitalize on the stronger hydrogen-bond donating effects of thioamides (Figure 2D), the thioamide must be oriented such that the C═S bond is either solvent exposed or not involved in a stabilizing contact. Two experimental examples support these claims. (*i*) The first involves thioamide substitution within the proline-(4-hydroxy)proline-glycine repeat of collagen discussed above. The amide linkage between (4-hydroxy)proline-glycine within collagen only donates a hydrogen bond to maintain the secondary structure but does not accept a hydrogen bond. Other examples of a protein secondary structure that might suit these requirements include the outer edge of a $\beta$-sheet or the last three residues at the *C*-terminus of an $\alpha$-helix in which the C═S is oriented toward solution and the thioamide residue can operate only as a hydrogen-bond donor. Successful demonstration of thioamides in this manner, to our knowledge, has yet to be realized. (*ii*) The second is the poor solvation of the thioamide by water creates an area of increased lipophilicity,[5] which was recently shown to enhance the folded stability of Pin1 WW domains.[36]

Collectively, these results lead us to predict that, given the variously solvated protein environments and context dependent nature of backbone hydrogen bonds[37,38] in which to insert a peptide isostere, thioamides may contribute 1.0−1.5 kcal/mol as hydrogen bond donors. This effect can alter a binding event by up to an order of magnitude! Alternatively, these data suggest that thioamides are neither weaker nor stronger, as hydrogen-bond acceptors than amides. Instead, the thioamide hydrogen-bond accepting ability is more heavily determined by the geometry ($\theta$) of the accepting interaction. Indeed, this effect has gone unappreciated, as demonstrated in the following case study from Nature.

**Case Study: Structural Evidence in Nature of the Hydrogen Bonding and Geometric Preferences of Thioamides.** Only two examples of thioamides exist in naturally occurring proteins.[39,40] One of which appears in the Methyl-Coenzyme M Reductase (MCR) enzyme.[40] Although the role of the thioamide is debated,[3,41] examination of its crystal structure provides insight into the properties of thioamides in macromolecular environments (Figure 3).[42]

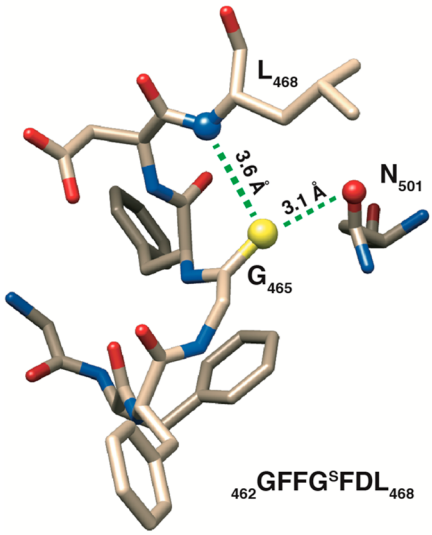


**Figure 3.** A naturally occurring thioamide in the active site of MCR (PDB: 1E6Y).[42] The thioglycine (G465) appears to make several noncanonical noncovalent interactions that are consistent with the electronic structure and geometric preferences of the thioamide sulfur.


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The glycine in position 465 (G465) is thionated and appears to make several noncovalent interactions with neighboring residues. First, the thioamide potentially forms a hydrogen bond with the NH of L468 with a S−N distance of 3.6 Å (approximately a 2.6 Å S−H(N) distance) and CS−(H)N contact angle of 108°. Both the distance and contact angle can now be rationalized in terms of the hydrogen-bonding properties of the thioamide discussed above (Table 1, Figure 2) and may indicate the potential of thioamides to stabilize kinked peptide folds. These hydrogen bond parameters appear to be consistent with other hydrogen bonding interactions with thioamide-containing small molecules found in the PDB (Figure S3, Table S2). Additionally, another noncovalent interaction is between the side-chain carbonyl of N501 and the G465, where the contact distance (3.1 Å) is shorter than the sum of VdW radii of each atom. This contact is evocative of a chalcogen-type bonding interaction[43−45] between the spherically symmetric electron density of the oxygen donor into the $\sigma$-hole of the thioamide (see electrostatic maps in Table 1).

Thioamides have earned a privileged space in peptide science.[3] In addition to demonstrated uses as probes to study protein structure and dynamics, exploitation of their unique properties in therapeutics is also emerging.[5,20,46,47] However, despite theoretical predictions of enhanced hydrogen bonding propensities of thioamides,[28,29] we demonstrate that special attention must be focused toward their geometric and conformational preferences in order to understand how thioamides can be most effectively utilized.

We have systematically investigated the hydrogen-bonding properties and geometric preferences of thioamides in the context of solvent effects and biologically relevant secondary structure. We predict the hydrogen bond donor strength enhancement to be between 1.0 and 1.5 kcal/mol (as opposed to the previously reported 2.0 kcal/mol). Intriguingly, experimental data from nearly four decades ago seem to validate this prediction.[46] We have also shown that thioamides *can be* as strong, if not stronger, hydrogen-bond acceptors than their amide counterparts depending on the local dielectric properties. The caveat here is that the charge distribution of the sulfur in thioamides dictates an accepting hydrogen-bond angle of between 90° and 100°. Further, the electronic structure of the sulfur atom displays a $\sigma$-hole that could be exploited in protein design. It is our hope that this study prompts interest in developing force-field parameters for thioamides, where tools for screening possible thioamide mutation sites *in silico* would expedite their development in a variety of biomolecular and therapeutic applications.

## ■ ASSOCIATED CONTENT

### Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acs.joc.1c02373.

Computational details, coordinates, Ramachandran analysis and discussion of thioamide peptides (PDF)

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### Notes

The authors declare no competing financial interest.

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