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Evaluation of Hydrogen Bonding Complementarity between a Secondary Sulfonamide and an α-Amino Acid Residue

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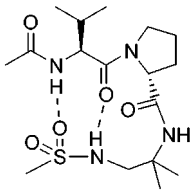
ABSTRACT



We report an initial step toward the development of sulfonamide-based complements for extended peptide strands. A molecule containing one secondary sulfonamide unit and one valine residue linked by a turn-forming segment was found by IR and NMR to exhibit a doubly hydrogen-bonded folding pattern in chloroform.

Non-peptidic molecules that display hydrogen bonding complementarity to peptides in the extended ("β-strand") conformation[1] are of interest for biomedical applications. Such molecules might disrupt the formation of amyloid fibrils,[2] β-sheet type aggregates that are associated with a variety of diseases.[3] Non-peptidic β-strand complements could also provide a basis for disrupting protein−protein interactions that depend on the recognition of peptide segments in an extended conformation.[4] Here we explore the prospect that secondary sulfonamide groups might be employed to generate hydrogen bonding complements to peptide β-strands.

Secondary sulfonamides differ conformationally from secondary carboxamides in two important ways: (i) the barrier to rotation about the S−N bond is much smaller than the barrier to rotation about the C−N bond,[5] and (ii) one of the H−N−S═O torsion angles is often near 0°,[5] while the H−N−C═O torsion angle is usually around 180°. These

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conformational disparities lead to a difference in hydrogen bonding behavior. The N−H and C═O of a secondary carboxamide cannot interact simultaneously with a closely spaced acceptor/donor pair. In contrast, the N−H and S═O of a secondary sulfonamide can achieve this type of two-point interaction. These structural considerations led us to contemplate the hydrogen bonding motif shown in Figure 1, in which a secondary sulfonamide interacts with both the

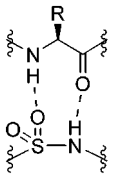


Figure 1. The two-point hydrogen-bonded interaction between a secondary sulfonamide group and the C═O and N−H of a single peptide residue.

C═O and N−H of a single α-amino acid residue. A general strategy for designing sulfonamide-based β-strand mimics could be achieved if this two-point interaction were favorable, and if we could identify amino sulfonic acid residues that allow complementary hydrogen bonding between an oligosulfonamide[6,7] and an extended peptide strand.

Here we report our initial step toward the development of sulfonamide strand mimics, using a hairpin folding motif to evaluate hydrogen bonding complementarity between a single secondary sulfonamide group and an α-amino acid residue in an organic solvent. Molecular hairpins have been previously employed to evaluate hydrogen bonding complementarity in the context of amide, vinylogous amide, urea, and hydrazine functionalities.[1,8] To achieve the desired two-point hydrogen bond between the peptide and sulfonamide groups (Figure 1), we required a turn unit containing two amino termini. The prolyl-(1,1-dimethyl)-1,2-diaminoethyl turn previously described for linking two peptide strands via their C-termini[9] appeared suitable. Thus, molecule **1**, containing one secondary sulfonamide unit and one valine residue to which the sulfonamide can form hydrogen bonds, was synthesized and examined for intramolecular hydrogen bonding using IR and NMR methods.[10]

We compared the N−H stretch region IR spectrum of **1** to the IR spectrum of non hydrogen bonded reference compounds **2** and **3** (Figure 2). The spectra were recorded

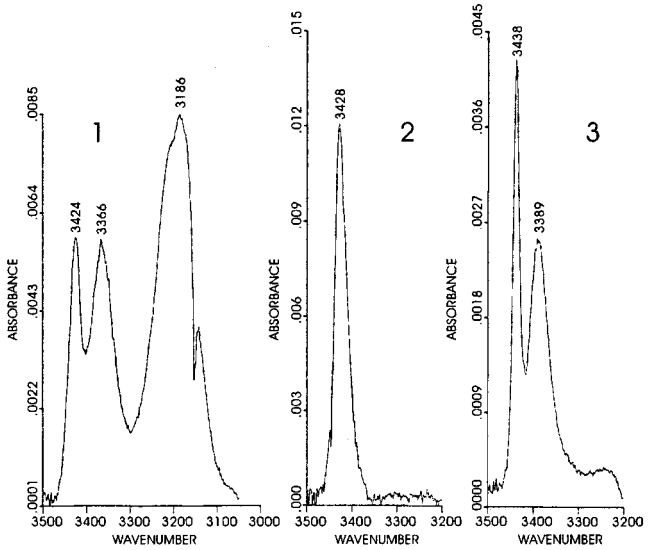
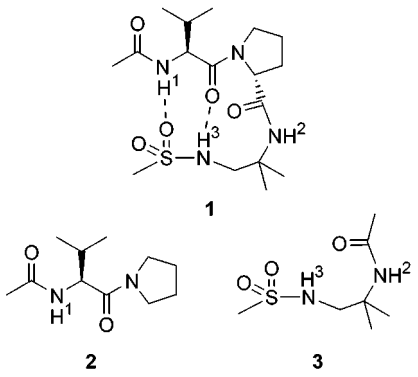


Figure 2. IR spectra of **1**−**3** at 1 mM in $CDCl_3$.

at 1 mM in $CDCl_3$, a concentration at which no aggregation of **1** occurs (vide infra). On the IR time scale hydrogen bonding equilibria are slow, and discrete bands representing hydrogen bonded and non hydrogen bonded states can be observed for a given NH group. The spectrum of reference **2** contains one NH absorbance, at 3428 cm^{-1}. This signal has been attributed to an NH involved in a "C_5 interaction," a weak intraresidue five-membered ring N−H···O═C interaction.[11] Two bands are observed in the spectrum of reference **3**, a non hydrogen bonded carboxamide NH



absorbance (3438 cm^{-1}) and an absorbance at 3389 cm^{-1}, which corresponds to the reported range for non hydrogen bonded sulfonamide NH stretch.[6a,12] These reference compound data allowed us to interpret the more complex

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spectrum of **1**. We assign the absorbance at 3424 cm^{-1} to a non hydrogen bonded carboxamide NH stretch. The broader band with a maximum at 3366 cm^{-1} can be attributed to a hydrogen bonded carboxamide NH stretch.[13] A discrete absorbance corresponding to a non hydrogen bonded sulfonamide NH (3389 cm^{-1} in reference **3**) is not observed in the IR spectrum of **1**; however, a small absorbance at this position could be obscured by the two carboxamide NH signals. The broad band at 3186 cm^{-1} is assigned to a hydrogen bonded sulfonamide NH[6a,12] (a hydrogen bonded secondary carboxamide NH is never observed below 3250 cm^{-1}).[13] These results are consistent with the desired doubly hydrogen bonded conformation of **1**.

Amide chemical shift (δNH) values in a nonpolar solvent such as $CDCl_3$ are sensitive to the amide group's involvement in hydrogen bonds.[13] A hydrogen bonded NH group exhibits a downfield chemical shift relative to a non hydrogen bonded amide. Equilibration between hydrogen bonded and non hydrogen bonded states is usually fast on the NMR time scale; thus, each δNH represents a population-weighted average. Because of the sensitivity of δNH to hydrogen bonding, δNH values can provide insight on intramolecular hydrogen bonding patterns. For this type of analysis, it is important that hydrogen bond-mediated intermolecular associations not contribute to δNH. A study of δNH versus concentration revealed that no aggregation of **1** occurs at $\leq$10 mM (Figure 3). Thus all further experiments were performed at $\leq$10 mM.

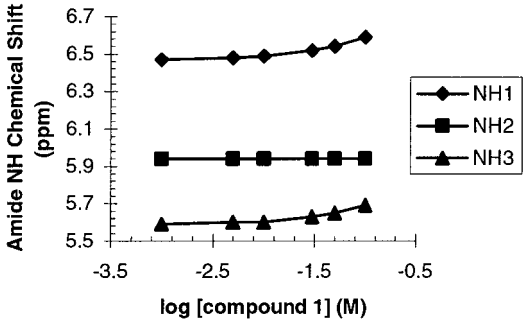

Figure 3. Amide proton NMR chemical shift of **1** at room temperature, as a function of the logarithm of concentration, in $CDCl_3$.

Table 1 contains δNH values measured at 24 °C for **1**−**3** in $CDCl_3$ (1 mM). Only one set of ^1H resonances was observed for **1**, suggesting the presence of only one amide rotamer about the proline/valine bond. Values of δNH for **2** and **3** are references for the non hydrogen bonded states of NH-1, NH-2, and NH-3. These data provide further evidence that the desired doubly hydrogen bonded conformation of **1** is populated in $CDCl_3$. The sulfonamide δNH of **1** (δNH-3) is 0.70 ppm downfield of the sulfonamide δNH in reference **3**, indicating significant involvement in hydrogen bonding. The valine δNH of **1** (δNH-1) is shifted downfield relative to the δNH of reference **2**, albeit to a lesser extent (0.30 ppm). Because the sulfonamide group is a weak hydrogen bond acceptor,[6a,12] only a small shift in δNH is expected for a carboxamide proton hydrogen bonded to a sulfonamide oxygen. The amide contained within the turn segment (δNH-2) exhibits only a modest downfield shift relative to the analogous amide in reference **3**, suggesting that there is little or no intramolecular hydrogen bonding to NH-2 in **1**. These observations indicate that the doubly hydrogen bonded conformation of **1** is populated to a significant extent in $CDCl_3$.

Table 1. Amide Chemical Shift Data (ppm) for **1** and Reference Molecules **2** and **3** at 1 mM in $CDCl_3$

molecule	δNH-1	δNH-2	δNH-3
1	6.47	5.59	5.94
2	6.17		
3		5.42	5.24

NOESY[14] data obtained for **1** in $CDCl_3$ (10 mM) provide further support for these conclusions. First, strong NOEs between a proline δ proton and both the valine α proton and the valine γ protons were observed (Figure 4). These

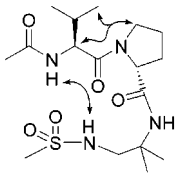

Figure 4. Selected NOEs for **1** in $CDCl_3$ (10 mM).

NOEs define the proline/valine rotamer as *Z* (as shown in Figure 4). In addition to the expected sequential NOEs (not shown), **1** displayed an interstrand NOE between the sulfonamide NH and the valine NH. The presence of this NOE provides strong evidence that a hairpin-like conformation is significantly populated in $CDCl_3$.

To the best of our knowledge, **1** is the first molecule for which a double hydrogen bonding pattern of the type shown in Figure 1 has been characterized. Preliminary results suggest that the prolyl-(1,1-dimethyl)-1,2-diaminoethyl turn unit is too short to allow formation of hairpins containing extended strands. Currents efforts involve the identification

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of new linkers. The data reported here are important because they demonstrate that the secondary sulfonamide unit represents a one-sided hydrogen bond complement to an α-amino acid residue in the β-strand conformation.

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