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Carboxamide versus Sulfonamide in Peptide Backbone Folding: A Case Study with a Hetero Foldamer

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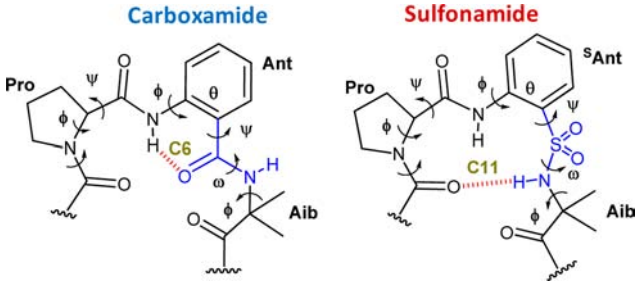
ABSTRACT



Strikingly dissimilar hydrogen-bonding patterns have been observed for two sets of closely similar hetero foldamers containing carboxamide and sulfonamides at regular intervals. Although both foldamers maintain conformational ordering, the hydrogen-bonding pattern and backbone helical handedness differ diametrically.

Sulfonamides are an important class of compounds which are widely used in the design of diverse classes of drug candidates.[1] In view of their biomedical importance, sulfonamide building blocks have been incorporated into many peptides.[2] Although both come under the class of amides, carboxamide and sulfonamide have strikingly different hydrogen-bonding and geometrical preferences: (i) as compared to carboxamide NH, the sulfonamide NH is more acidic, resulting in its better participation in H-bonding events; (ii) sulfonamide has two H-bonding acceptor oxygens; (iii) the sulfonamides have a favored dihedral angle, $\omega \leq 90°$, as opposed to carboxamides which usually favor a planar conformation with $\omega \leq 180°$; and (iv) the bond length S−N in sulfonamide is greater than C−N in carboxamide, thus sulfonamide has low S−N rotation barrier as compared to carboxamide.[3]

Intrigued by their distinctly different conformational propensities, we were interested in investigating the effect on swapping carboxamide with sulfonamide in foldamers. In order to realize this goal, we designed two sets of hetero foldamers[4] featuring regularly repeating α,*β*,α-tripeptide building blocks of the structure Pro-*Xaa*-Aib (Figure 1). Whereas **1**, **3**, and **5** feature anthranilic acid (*Xaa* = Ant,

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an aromatic β-amino carboxylic acid) as the central residue of the tripeptide building block, **2**, **4**, and **6** feature 2-aminobenzenesulfonic acid (^{S}Ant, an aromatic β-amino sulfonic acid) as the central residue in the tripeptide building blocks.

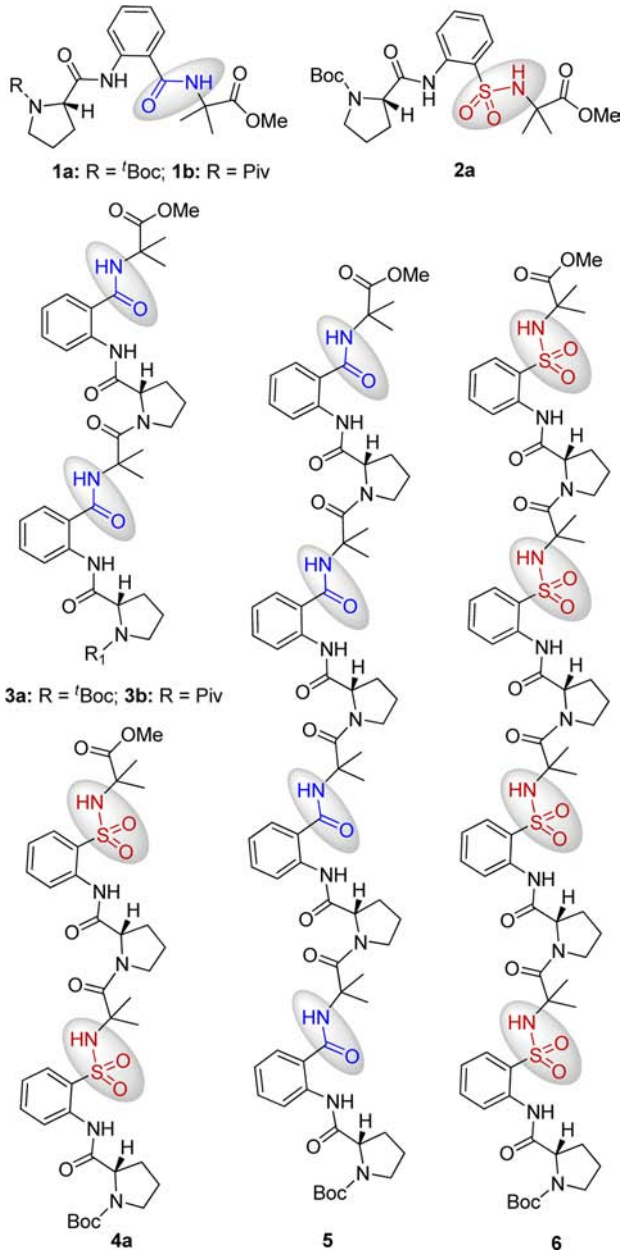

Figure 1. Designed α,β,α-hetero foldamers featuring carboxamide (Pro-Ant-Aib) and sulfonamide (Pro-^{S}Ant-Aib) building blocks.

Investigation of crystal data unambiguously revealed that the Pro-Ant-Aib oligomers **1b** and **3a** display six-membered intra-residual hydrogen bonding (C6 H-bonding) within the Ant rings (Figure 2). In stark contrast, their sulfonamide counterparts **2a** and **4a** display an inter-residual 11-membered ring intramolecular H-bonding (C11 H-bonding). The nature of these H-bonded interactions is persistent in the shorter segments as well as in their higher analogues (**1b** and **3a** feature only C6 H-bonding, whereas their sulfonamide analogues **2a** and **4a** feature C11 H-bonding). Oligomers **3a** and **4a** assume helical architecture containing different H-bonded networks, and the onset of helix formation can be seen from the tripeptide stage itself.

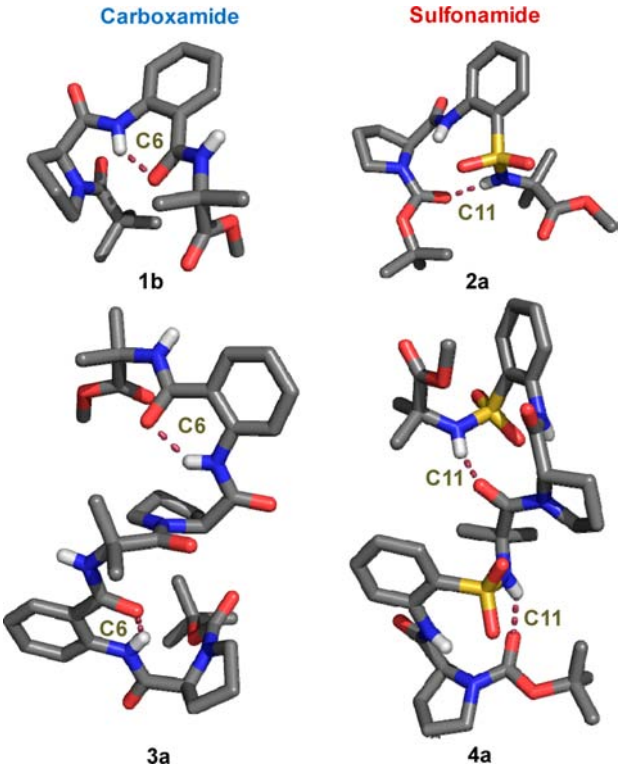

Figure 2. PyMOL-rendered crystal structures of carboxamide oligomers **1b** and **3a** and sulfonamide oligomers **2a** and **4a**. Hydrogens, other than the polar amide hydrogens, have been removed for clarity.

Analysis of the torsion angles and hydrogen-bonding parameters of all of the crystal structures reveals the following characteristic features, as detailed in Tables 1 and 2, respectively. In the (Pro-Ant-Aib) oligomers **1b** and **3a**, proline adopts preferential torsional angles ϕ and ψ around $\pm 60°$ and $\pm 35°$, while in the case of (Pro-^{S}Ant-Aib) oligomers **2a** and **4a**, the Pro ϕ and ψ values are $\pm 80°$ and $\pm 10°$, respectively (Table 1). The Ant ϕ ranges from a minimum value of 160.4° (**3a**) to a maximum value of 169.3° (**1b**); on the other hand, ^{S}Ant ϕ ranges from a minimum value of $-133.9°$ (**4a**) to a maximum value of $-143.3°$ (**2a**). However, significant differences in ψ value of Ant (-154.6 to $-166.8°$) and ^{S}Ant (64.3 to 70.8°) have been noted. It is noteworthy that, among all torsion angles, the amide dihedral angle ω of Ant and ^{S}Ant differs the most. In the (Pro-Ant-Aib) oligomers, Ant displays ω values about 178°. In stark contrast, ^{S}Ant displays ω value ranging from 58.3° (**4a**) to 86.4° (**2a**). A closer look at the ω

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Table 1. Backbone Torsion Angles Observed in Crystals **1b**, **2a**, **3a**, and **4a**

			torsion (deg)								
			Pro		Ant/^{S}Ant				Aib		
compd no.		type of amide	ϕ	ψ	ϕ	θ	ψ	ω	ϕ	ψ	(NH...O=C)
1b		carboxamide	−61.8(4)	−34.2(4)	169.3(3)	−3.0(4)	−155.9(3)	−178.6(3)	49.7(4)		8.72
3a	1st seg	carboxamide	−65.5(4)	−41.6(4)	165.8(3)	0.9(5)	166.8(3)	179.0(3)	46.6(4)	45.5(4)	−40.70
	2nd seg		−67.1(4)	−32.3(4)	160.4(3)	1.7(5)	−154.6(3)	177.7(3)	−59.5(4)		9.84
2a		sulfonamide	−89.9(3)	−0.9(3)	−143.3(2)	2.0(3)	64.3(2)	86.4(2)	65.5(3)		3.13
4a	1st seg	sulfonamide	−87.9(3)	−6.9(4)	−138.8(3)	4.5(4)	68.0(2)	58.3(2)	41.7(3)	71.3(3)	−83.84
	2nd seg		−69.9(3)	−21.3(4)	−133.9(3)	4.1(4)	70.8(3)	69.4(3)	−62.6(3)		−116.78

Table 2. Backbone Hydrogen-Bonding Parameters Observed in Crystals **1b**, **2a**, **3a**, and **4a**

		hydrogen-bonding parameters									
		1st segment					2nd segment				
		distances (Å)		angles (deg)			distances (Å)		angles (deg)		
compd no.	type of amide	(O···H)1	(N···O)1	(C=O···H)1	(C=O···N)1	(NH···O)1	(O···H)2	(N···O)2	(C=O···H)2	(C=O···N)2	(NH···O)2
1b	carboxamide	1.89	2.63	99	87	140					
3a	carboxamide	1.95	2.61	100	89	133	1.95	2.65	98	86	137
2a	sulfonamide	2.04	2.90	119	119	179					
4a	sulfonamide	2.18	2.95	116	115	148	2.072	2.826	114	118	146

values of all crystal structures unambiguously confirms the disparity of the geometrical preferences of carboxamides ($\omega \sim 180°$) and sulfonamides ($\omega \sim 90°$).[5]

The hydrogen-bonding distances [d(N−H···O=C)] of **1b** and **3a** have been found to range from 1.89 to 1.95 Å, respectively, suggesting a strong C6 H-bonded network (Table 2). The C11 H-bonded network in the sulfonamide counterparts **2a** and **4a** were also found to range from 2.04 to 2.18 Å, respectively. The H-bonding angles [Δ(C=O···N)] of Pro-Ant-Aib and Pro-^{S}Ant-Aib oligomers are ∼87 and 117°, respectively.

The conformational characteristics of the oligomers in the solution state were investigated by extensive NMR studies. All oligomers were readily soluble in nonpolar organic solvents (≫100 mM in $CDCl_3$, CD_3CN) at ambient conditions. The results obtained from NMR dilution studies of **3b** and **4a** ($\Delta\delta$(NH) < 0.33, Supporting Information, S43−S44) suggest absence of aggregation caused by intermolecular hydrogen bonding. The signal assignments of all oligomers have been done using a combination of 2D COSY, NOESY, HMBC, HSQC, and TOCSY (concentration = 80−100 mmol). Some of the characteristic NOE patterns observed for **3b** and **4a** are given in Figure 3, which is consistent with the helical conformation observed in the crystal structure (detailed signal assignments in Supporting Information S54−S73). It is noteworthy that multiple NMR signals, due to rotamer formation, are observed for the carboxamide oligomers having the N-terminal Boc-Pro residue. This is a well-known phenomenon associated with Pro having the N-terminus Boc carbamate group causing *cis*−*trans* isomerization at the N-terminal carbamate carbonyl.[6] This problem could be efficiently circumvented by attaching a pivaloyl group at the N-terminus, resulting in a sharp single set of signals (Supporting Information, S26−S29). Interestingly, the sulfonamide counterparts did not experience the rotamer problem arising from the slow rotation of the N-terminus Boc-carbamate group, primarily due to the fact that the Boc-carbamate carbonyl is locked in intramolecular C11 H-bonding. Two-dimensional NOESY study of the hexapeptide **3b** exhibited inter-residual nOes between Piv-CH_3 (C36H) versus Aib_1-CH_3 (C15H), supporting the folded conformation, similar to the one found in the crystal structure. Similarly, the 2D NOESY data of hexapeptide **4a** revealed several inter-residual nOes, for instance, Boc-CH_3 (C34H) vs NH2, Boc-CH_3 (C34H) vs Pro1-C20H, Aib1-CH3 (C14H) vs NH4, and Pro2-C17H vs Aro C9H (Figure 3 and Supporting Information, S54−S73), supporting a folded conformation, as seen in the solid state. The existence of intramolecular hydrogen bonding in the oligomers was confirmed by DMSO-d_6 titration and

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(7) Crystallographic data for **1b** and **2a**−**4a** have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication no. CCDC-914493−914496, respectively.

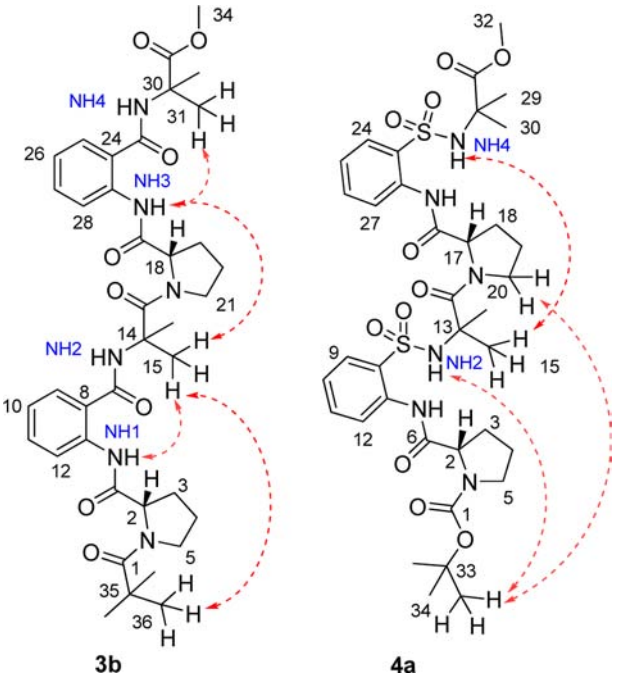

Figure 3. Selected NOE extracts from the 2D NOESY data of **3b** ($CDCl_3$) and **4a** [$(CD_3)_2CO$] (500 MHz). Detailed analysis given in Supporting Information.

variable-temperature studies. The amide NHs of carboxamide oligomers **1b** [$\Delta\delta$(NH) < 0.11 ppm] and **3b** [$\Delta\delta$(NH1) < 0.23 ppm and $\Delta\delta$(NH3) < 0.34 ppm] involved in the six-membered intramolecular H-bonding show negligible shift in DMSO titration experiments (Supporting Information, S45−S46). The amide NHs of the sulfonamide counterparts **2a** [$\Delta\delta$(NH) < 0.09 ppm] and **4a** [$\Delta\delta$(NH2) < 0.22 ppm and $\Delta\delta$(NH4) < 0.18 ppm] involved in 11-membered H-bonding also show negligible shift in DMSO titration experiments (Supporting Information, S47−S48). Variable-temperature studies of **1b**, **3b**, **2a**, and **4a** further support intramolecular hydrogen bonding wherein the NHs involved in the intramolecular H-bonding show a temperature coefficient ($\Delta\delta/\Delta T$) > −5 ppb/K [for **1b** ($\Delta\delta/\Delta T$)NH1 = −3.6 ppb, for **3b** ($\Delta\delta/\Delta T$)NH1 = −2.7 ppb, ($\Delta\delta/\Delta T$)NH3 = −0.6 ppb, for **2a** ($\Delta\delta/\Delta T$)NH2 = −3.8 ppb, for **4a** ($\Delta\delta/\Delta T$)NH2 = −4.7 ppb, ($\Delta\delta/\Delta T$)NH4 = −2.2 ppb; Supporting Information, S49−S53].

In conclusion, this communication describes a striking case of conformational comparison between two closely resembling synthetic oligomers featuring strategically positioned carboxamide and sulfonamide bonds on the backbone. Whereas the carboxamide oligomers (Pro-Ant-Aib)$_n$ display a periodically repeating six-membered intramolecular hydrogen-bonded left-handed helical structure, the (Pro-^{S}Ant-Aib)$_n$ oligomers display an 11-membered intramolecular hydrogen-bonded right-handed helical architecture. The substantial difference in the torsional angles ψ and ω of the aromatic amino acids would explain their conformational differences. The structural differences, which could be learned from this study, would have a bearing in practical importance, particularly in the de novo design of novel sulfonamide-based synthetic peptides.

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Supporting Information Available. Experimental procedures, NMR data for all compounds, and cif file for **1b**, **2a**, **3a**. and **4a**. This material is available free of charge via the Internet at http://pubs.acs.org.

The authors declare no competing financial interest.