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Conformational properties of sulfonamido peptides

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Abstract

A systematic analysis of the conformation of the sulfonamide bond at various levels of ab initio MO theory shows distinct differences in comparison to the amide/peptide bond. Most important are (i) the different values of the torsion angle ω ($\angle C^{\alpha}SNC^{\alpha}$), which are about -100 and 60° in the two basic conformers of the sulfonamide bond, but about 180 and 0° for the peptide bond, (ii) the rotation barriers around the SN bond, which are distinctly lower than for the peptide bond, thus making sulfonamido peptides more flexible, and (iii) the pyramidal nature of the sulfonamide nitrogen in the conformers in comparison to a practically planar arrangement of the peptide bond.

Despite these differences, sulfonamido peptides are able to form a great number of characteristic elements of secondary structure, which can be derived from the conformer pool of the monomer constituents. Some of them correspond to typical elements of secondary structures in native peptides and proteins. Although these conformers agree in type with their native counterparts and show similar shapes, the values of the torsion angles φ and ψ in the α-aminosulfonic acid monomers differ due to the special conformational properties of the sulfonamide bond.

Keywords: Sulfonamide bond; Sulfonamido peptides; Peptidomimetics; Conformational analysis; Ab initio MO theory

1. Introduction

The direct application of physiologically important native peptides as drugs is often prevented by their poor bioavailability. Moreover, pharmacological use demands a better selectivity towards different receptor subtypes [1]. One way to change peptide properties with the aim of drug development is the structure modification of the proteinogenic amino acid constituents. In recent years, numerous possibilities were suggested for the change of amino acid side chains and the modification of the amino acid backbone. Interesting examples for side chain variations are the substitution of D-amino acids for their native L-configured counterparts [2,3], the use of dehydro amino acids with a double bond between the C^{α} backbone atom and the C^{β} atom of the side chain [4–6] and the shift of the side chain from the C^{α} atom to the peptidic nitrogen atom leading to N-substituted glycines, which are the constituents of peptoids [7–11]. A typical backbone modification is realised in azaamino acids [12–14], where the C^{α} atom is replaced by a nitrogen atom, which is still able to keep the amino acid side chain. Even the possibility of backbone elongation is considered. Thus, investigations on β- [15–18], γ- [19–22], and δ-amino acids [23,24] and their oligomers are of outstanding interest at present.

Independent of the type of structure modification, the modified compounds must be able to mimic the electronic and steric properties of their native counterparts, since the biological activity depends on a definite three-dimensional structure [25]. Among the various structural aspects, the investigation of the possibilities to form secondary structure elements in the modified compounds, which are at least similar to the typical helices, sheets, and turns in native peptides and proteins, is of special interest [26–29].

Here, we want to turn attention to a further possibility of structure modification in peptides, namely the replacement of the peptide bond itself by bioisosteric groups such as carbamate [30], phosphonamidate [31,32] and sulfonamide [33–40] groups. In particular the realisation of the amino acid ligation by a sulfonamide bond might be interesting, since the replacement of amide bonds by this bioisosteric bond is a frequently applied principle in several fields of drug development. There were also promising attempts to employ sulfonamide analogues of oligopeptides as inhibitors for proteases and lipases, which could be favoured by their structural similarity with the tetrahedral transition state in the proteolysis of amide bonds [36–43]. The syntheses of the rather stable α-aminosulfonic acids [44] and their

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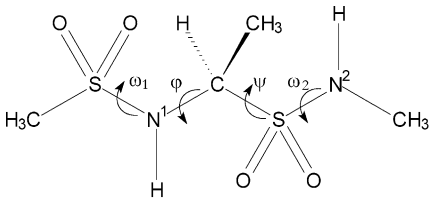
derivatives as for instance β-aminosulfonic acids [36,45] is possible and their introduction into α-amino acid sequences was successfully performed [40]. The oligomerisation of α-aminosulfonic acids to sulfonamido peptides is more difficult, but nevertheless possible [46].

At a first view, there seems to be considerable similarity between the amide bond and the sulfonamide bond, as it could be expected for bioisosteric groups. Thus, only the additional oxygen atom of the sulfone group might be responsible for the origin of novel and possibly more structure alternatives than in the corresponding α-amino acid sequences [47,48].



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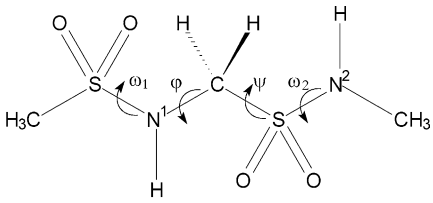

B

Some theoretical studies on the sulfonamide bond [43,49–51] provide interesting general information. It is the aim of this study to demonstrate structural similarities and differences between sulfonamido peptides and α-peptides arising from peculiarities of the sulfonamide bond on the basis of quantum chemical conformational analyses.

2. Methods

To get a first idea of the conformational behaviour of sulfonamido peptides, the conformation of the sulfonamide bond was examined in detail. For this purpose the model compounds methylsulfonamide ($CH_3-SO_2-NH_2$) and methylsulfon-*N*-methylamide ($CH_3SO_2-NHCH_3$) were selected. The energy profile for the rotation around the SN bond was determined at various levels of ab initio MO theory (HF/6-31G*, HF/6-311++G**, DFT/B3LYP/6-31G*, DFT/B3LYP/6-311++G**, MP2/6-31G*, MP2/6-311++G**). The selection of the approximation levels considered both possible electron correlation effects and influences of the high electron density in the sulfone group by inclusion of diffuse functions. The rotation profiles were determined in 15° steps. As a further structure aspect of the sulfonamide bond, the possibility of nitrogen inversion was also examined. The search for the rotation and inversion transition states was based on the synchronous transit-guided quasi-Newton (STQN) [52] method as it is implemented in the GAUSSIAN98 program package (keyword: QST3). For higher precision, geometry optimisations and transition state searches were performed with the opt = tight convention.

Several studies show that the most important secondary structure elements in α-peptides can be derived from the conformational properties of blocked monomer constituents (monomer approach), even if typical hydrogen bonds cannot be formed at the monomer level [53–61]. Starting point for the determination of the conformer pool of an α-aminosulfonic acid constituent were energetic Ramachandran plots for the disulfonamides **A** and **B**.

Model compound **A** is the formal analogue to an L-alanine residue in an α-peptide sequence and, thus, the prototype of an L-configured amino acid, whereas compound **B** is the formal analogue to a glycine residue. The Ramachandran plots were calculated in steps of 30° for the torsion angles φ and ψ at the HF/6-31G* level of ab initio MO theory. Reoptimisation of grid point structures near the minima in the Ramachandran plots led to the conformer pool of the model compounds. The HF/6-31G* minimum conformations were subjected to DFT/B3LYP/6-31G* calculations to estimate the influence of correlation energy effects. Due to the importance of environmental effects for the structural properties of peptides, an estimation of solvent influence was performed on the basis of the polarisable continuum model (PCM) [62] at the HF/6-31G* level. An aqueous medium with a dielectric constant of $\varepsilon = 78.4$ was assumed. Continuum models are not able to consider specific solute–solvent interactions, which might play an important role in structuring of peptides. Thus, the solvation data should not be overestimated in a quantitative sense. They should be more considered as an estimation of the general trend of solvent influence.

Following the monomer approach, some possibilities of the formation of higher secondary structures in oligomers of α-aminosulfonic acids were examined at the trimer level. These calculations were also realised at the HF/6-31G* approximation level.

The quantum chemical calculations were performed using the GAUSSIAN98 (Gaussian Inc., Pittsburgh, PA, USA) and Spartan (Wavefunction Inc., Irvine, CA, USA) program

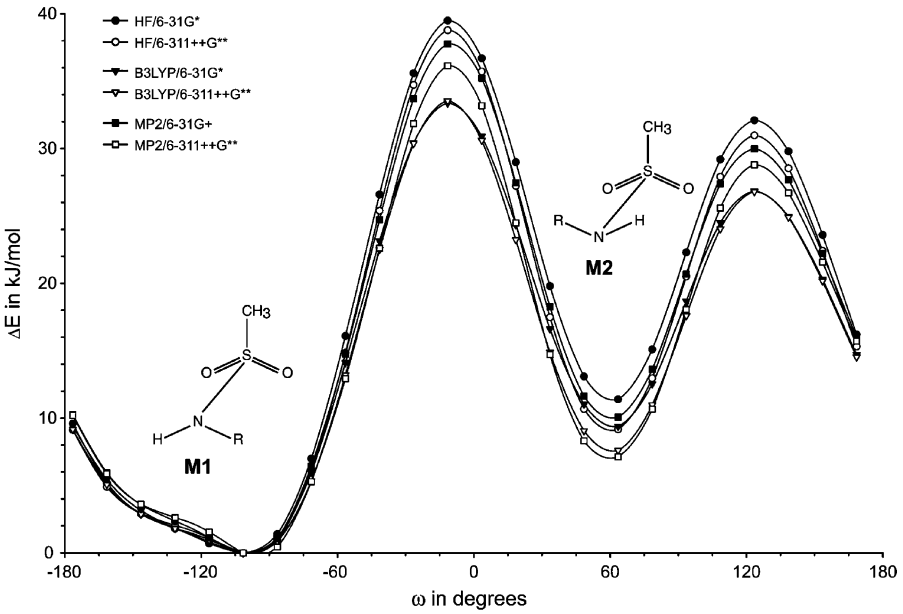

Fig. 1. Potential curves for methylsulfon-*N*-methylamide calculated at various levels of ab initio MO theory.

packages, respectively, with exception of the PCM calculations, which the Gamess-US program package [63] was employed for.

3. Results and discussion

3.1. Conformation of the sulfonamide bond

The potential curves for the SN rotation in the model compounds methylsulfonamide ($CH_3-SO_2-NH_2$) and methylsulfon-*N*-methylamide ($CH_3-SO_2-NHCH_3$) were calculated at various approximation levels of ab initio MO theory. They are shown for the more general case of the substituted model system methylsulfon-*N*-methylamide in Fig. 1. There is a fair agreement between all energy profiles. The global minimum conformation **M1** is characterised by an ecliptic arrangement of the sulfone oxygen atoms and the amino substituents, the local minimum **M2** corresponds to a staggered orientation of these atoms (Fig. 1). The lesser stability of **M2**, which is by about 9–12 kJ/mol above the global minimum for methylsulfonamide and by about 5–6 kJ/mol above **M1** in methylsulfon-*N*-methylamide (Table 1), dependent on the approximation level, is probably

Table 1
Energetic data for the conformers, inversion and rotation transition states of methylsulfonamide $CH_3-SO_2-NH_2$ and methylsulfon-*N*-methylamide $CH_3-SO_2-NHCH_3$ at the HF/6-31G* and MP2/6-311++G** levels of ab initio MO theory

Energy[a]	**M1/M4**[b]	**M2/M3**[b]	**TS1/TS1′**[b]	**TS2/TS2′**[b]	**TS3/TS3′**[b]
$CH_3-SO_2-NH_2$[c]					
ΔE_T	0.0 (0.0)	11.7 (9.0)	11.9 (10.5)	33.0 (29.7)	33.0 (29.7)
$\Delta E_T + \Delta$ZPVE	0.0 (0.0)	10.6 (8.7)	8.7 (8.1)	31.1 (27.7)	31.1 (27.7)
ΔG	0.0 (0.0)	10.9 (9.1)	9.1 (9.0)	32.3 (28.9)	32.3 (28.9)
$CH_3-SO_2-NHCH_3$[d]					
ΔE_T	0.0 (0.0)	6.1 (5.2)	6.6 (8.8)	30.9 (28.8)	40.0 (36.5)
$\Delta E_T + \Delta$ZPVE	0.0 (0.0)	5.3 (4.8)	3.7 (5.6)	28.8 (26.9)	39.6 (35.6)
ΔG	0.0 (0.0)	5.4 (4.5)	4.3 (3.8)	31.2 (29.2)	43.1 (38.6)

[a] Relative energies in kJ/mol; ΔE_T, total energy differences related to **M1**; ΔZPVE, zero-point vibration energy differences related to **M1**; ΔG, Gibbs free energy differences related to **M1**.

[b] See Fig. 2; **M1**–**4**, minimum structures; **TS1/TS1′**, inversion transition states; **TS2/TS2′** and **TS3/TS3′**, rotation transition states.

[c] HF/6-31G* data for **M1**: $E_T = -642.389174$ a.u.; ZPVE = 0.080855 a.u.; thermal enthalpy correction ΔH =0.087388 a.u.; entropy contribution ΔS =0.000118 a.u.; in parentheses MP2/6-311++G** data for **M1**: $E_T = -643.373063$ a.u.; ZPVE = 0.075520 a.u.; thermal enthalpy correction ΔH =0.082348 a.u.; entropy contribution ΔS =0.000120 a.u.

[d] HF/6-31G* data for **M1**: $E_T = -681.416575$ a.u.; ZPVE = 0.111335 a.u.; thermal enthalpy correction ΔH =0.119248 a.u.; entropy contribution ΔS =0.000130 a.u.; in parentheses MP2/6-311++G** data for **M1**: $E_T = -682.558256$ a.u.; ZPVE = 0.104395 a.u.; thermal enthalpy correction ΔH =0.112566 a.u.; entropy contribution ΔS =0.000131 a.u.

caused by the repulsion between the lone-pairs of the sulfone oxygen and the amino nitrogen atoms. Comparing with a peptide bond, it is most striking that the values of the torsion angle ω ($\angle C^{\alpha}SNC^{\alpha}$) of the sulfonamide bond minima are with about $-100°$ in the global minimum structure and about 60° in the second conformer far away from the familiar values of 180° for a *trans*- and 0° for a *cis*-peptide bond. Besides, the rotation barriers, which are 40.0 kJ/mol referred to the most stable conformer **M1** and 30.9 kJ/mol referred to the second minimum **M2** for methylsulfon-*N*-methylamide at the HF/6-31G* level (Table 1), are distinctly lower than those for peptide bonds, which are typically in between 65 and 90 kJ/mol dependent on the environment [64]. Thus, a higher flexibility of the sulfonamide bond could be expected in sulfonamidopeptide structures in comparison to the more rigid peptide bond in α-peptide sequences.

There is another structure aspect which makes the sulfonamide bond different from the amide/peptide bond. This is the pyramidal structure of the sulfonamide nitrogen atom, whereas the peptide bond shows planarity. Therefore, the possibility of nitrogen inversion in the sulfonamide bond has additionally to be considered. In fact, the potential hypersurface of the sulfonamide bond is characterised by four energy minima corresponding to the structures **M1**–**M4** in Fig. 2. The minimum structures **M3** and **M4** can be reached from the above-mentioned minima **M1** and **M2** by nitrogen inversion and are themselves related by rotation around the SN bond. The relationships between the various stationary points on the energy hypersurface are illustrated in Fig. 2. In the case of substitution, inversion leads to a change of the configuration at the nitrogen atom. The energy data in Table 1 show that the inversion barriers are very low. Thus, rapid interconversion between the corresponding minimum structures could be expected (Fig. 2). It is striking that the inversion transition states **TS1/TS1′** of both model compounds, which are characterised by a nearly planar arrangement at the nitrogen atom, and the corresponding local minima **M2** and **M3**, respectively, are close together in energy. Consideration of the zero-point vibration energies shows the inversion states even more stable. This tendency is still increased at the level of free enthalpies, which were obtained by the inclusion of thermal energies and entropies from a thermochemical analysis on the basis of the calculated force constants. Therefore, fixation of a special nitrogen configuration in the sulfonamide group should only be possible in the case of specific interactions between the hydrogen atoms of the amino group in this arrangement and other functional groups in a molecule.

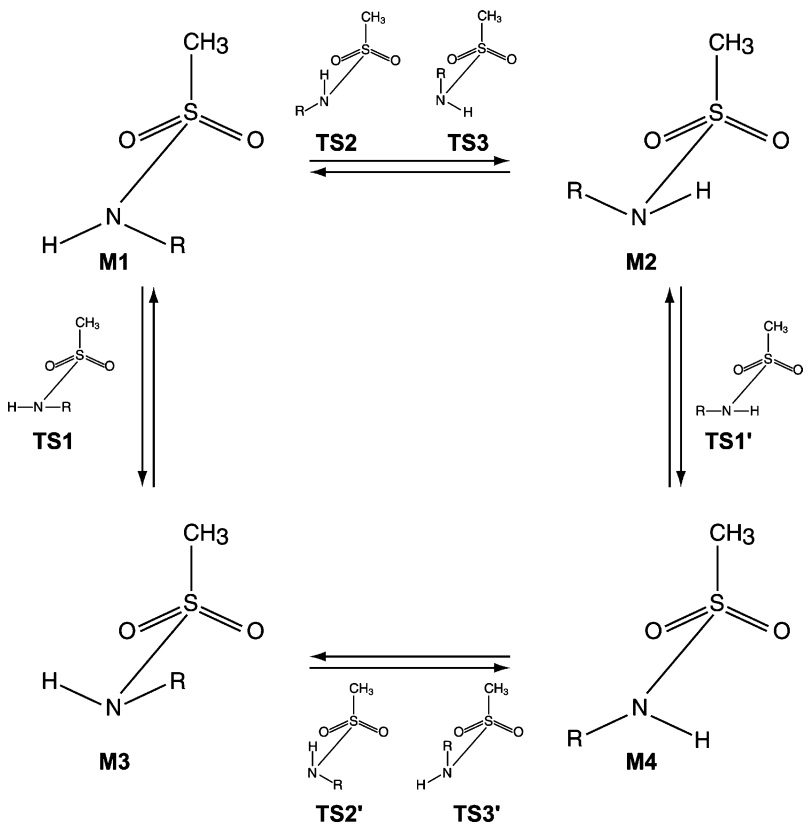

Fig. 2. Stationary points on the potential energy hypersurface of the sulfonamide bond models $CH_3–SO_2–NH_2$ (R = H) and $CH_3–SO_2–NHCH_3$ (R = CH_3) and their relationships (**M1**–**M4**, minimum conformations; **TS1/TS1′**, inversion transition states; **TS2/TS2′** and **TS3/TS3′**, rotation transition states).

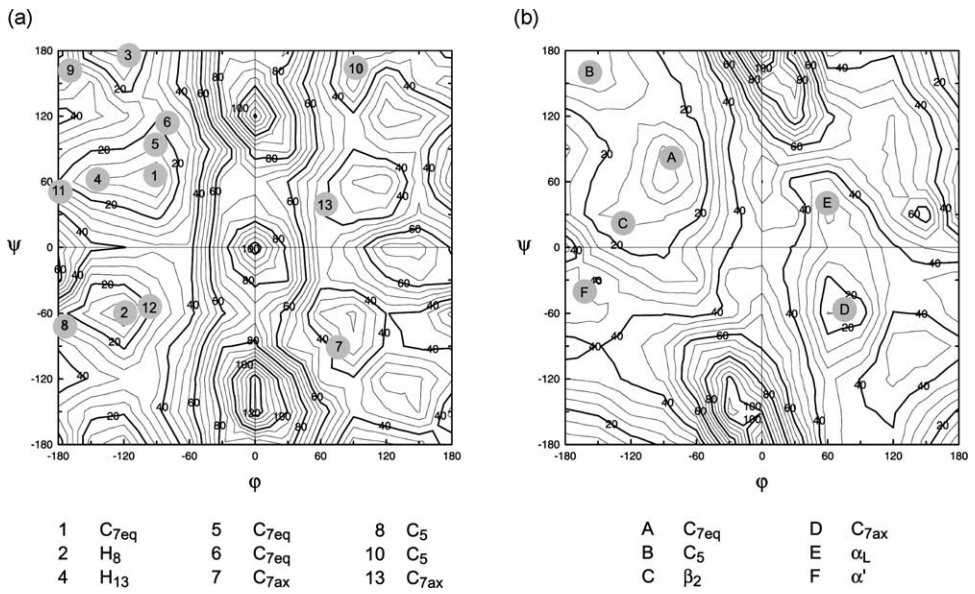

Fig. 3. Comparison of the HF/6-31G* Ramachandran plots for the disulfonamide **A** (a) and the diamide Ac-L-Ala-NMe (b) and the obtained minimum conformations (conformers of **A** with hydrogen-bonded pseudocycles or relations to helical structures are indicated).

3.2. Conformer pool of the monomer constituents of sulfonamido peptides

A good information on the conformational properties of monomer constituents in peptide sequences is available from Ramachandran plots. Fig. 3 shows the Ramachandran plot for the disulfonamide **A**, the prototype for an L-configured amino acid. For comparison, the corresponding Ramachandran plot for the blocked L-alanine residue Ac-L-Ala-NMe [53] is also given. The minimum conformations of **A** are localised in the same regions as those of an L-alanine constituent. However, there are 13 conformers for **A** compared with only six for Ac-L-Ala-NHMe. This is mainly caused by the second oxygen atom in the sulfone group, which increases the number of interaction possibilities, in particular concerning the formation of hydrogen bonds. The torsion angles and the energies of the minimum conformations of **A** are given in the Tables 2 and 3. Numerous conformers of the disulfonamide show formal similarities to some well-known conformers in diamides of α-amino acids such as the C_{7eq}, C_{7ax} and C_5 conformers with hydrogen-bonded pseudocycles (Fig. 4). However,

Table 2
Geometry data for the conformers of **A** obtained at the HF/6-31G* level of ab initio MO theory

Conf.[a]	ω_1	φ	ψ	ω_2	N[b]	Type[c]
A1	−140.2	−89.1	65.4	76.3	RR	C_{7eq}
A2	99.0	−116.6	−60.4	108.2	RR	H_8
A3	101.2	−113.2	175.0	114.6	RR	
A4	103.0	−141.9	61.5	−109.3	RS	H_{13}
A5	−90.4	−88.9	93.3	165.4	SR	C_{7eq}
A6	122.0	−78.0	113.2	161.8	RR	C_{7eq}
A7	95.6	78.0	−91.7	−156.9	RS	C_{7ax}
A8	−102.7	−171.7	−72.6	102.0	SR	C_5
A9	−105.2	−167.1	161.2	−95.6	SS	C_5
A10	−76.8	94.3	163.7	−102.9	SS	C_5
A11	−102.9	−176.0	50.2	−128.6	SS	
A12	−119.3	−94.2	−54.6	−111.8	SS	
A13	150.8	66.8	38.7	137.4	RR	C_{7ax}

[a] Torsion angles in degrees.
[b] Pseudoconfiguration at the sulfonamide nitrogen atoms N^1 and N^2.
[c] C_x, hydrogen-bonded pseudocycle with x atoms. H_x, monomer of a helix with x-membered hydrogen-bonded pseudocycles.

Table 3
Relative energies of the conformers of **A** at the HF/6-31G*, DFT/B3LYP/6-31G* and PCM//HF/6-31G* levels of ab initio MO theory

Conf.	ΔE[a]		
	HF/6-31G*	B3LYP/6-31G*	PCM//HF/6-31G*[b]
A1	0.0[c]	0.0[d]	3.2
A2	4.0	8.3	0.0[e]
A3	5.0	10.2	0.2
A4	7.0	12.8	4.1
A5	13.4	10.5	8.7
A6	18.4	17.0	13.1
A7	18.6	16.4	13.8
A8	19.5	22.1	15.6
A9	20.4	22.6	14.5
A10	22.6	21.6	18.5
A11	24.0	25.1	19.1
A12	24.1	22.0	8.1
A13	35.5	28.7	24.7

[a] Relative energies in kJ/mol.
[b] Dielectric constant $\varepsilon = 78.4$.
[c] $E_T = -1361.678680$ a.u.
[d] $E_T = -1366.300176$ a.u.
[e] $E_T = -1361.689285$ a.u.

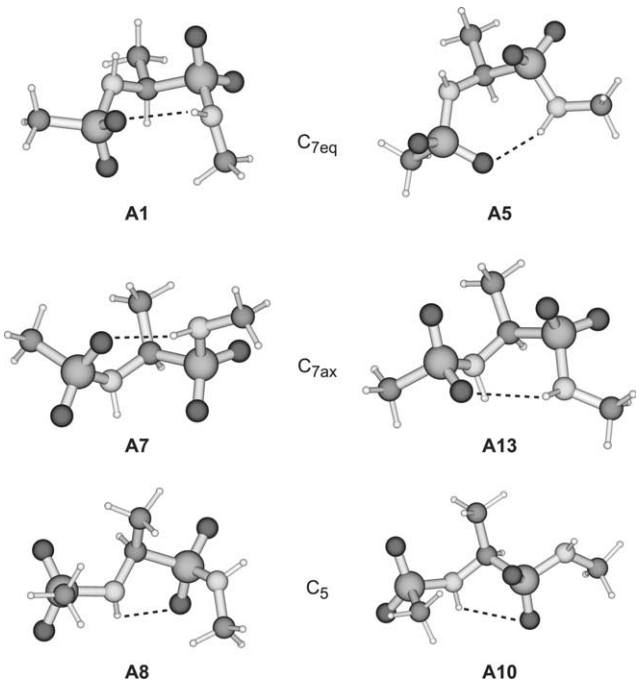

Fig. 4. Selected conformers of the disulfonamide **A** with hydrogen-bonded pseudocycles C_x.

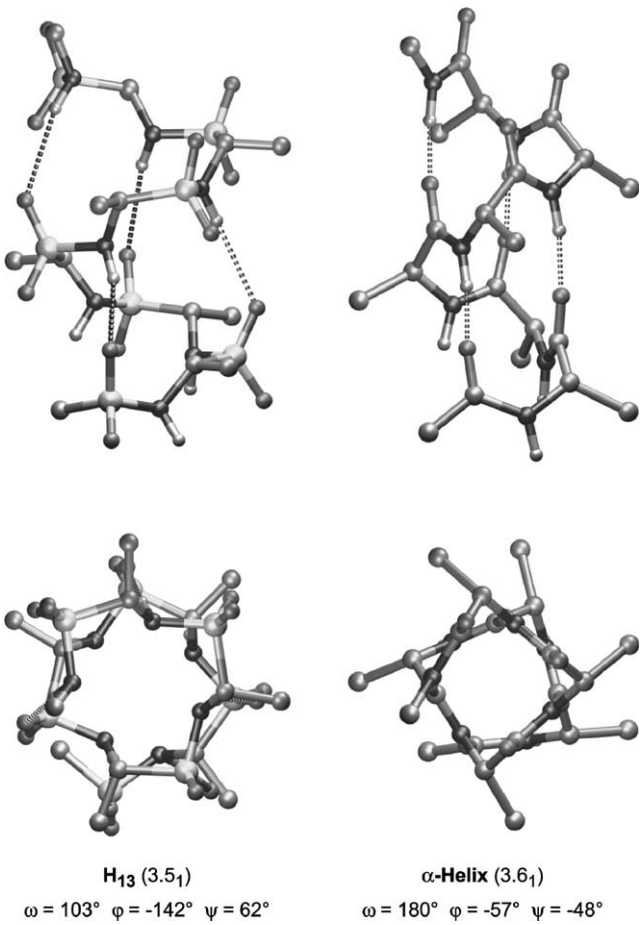

Fig. 5. Comparison of a hexamer model of the α-sulfonamido peptide helix H_{13} with the α-helix of native peptides.

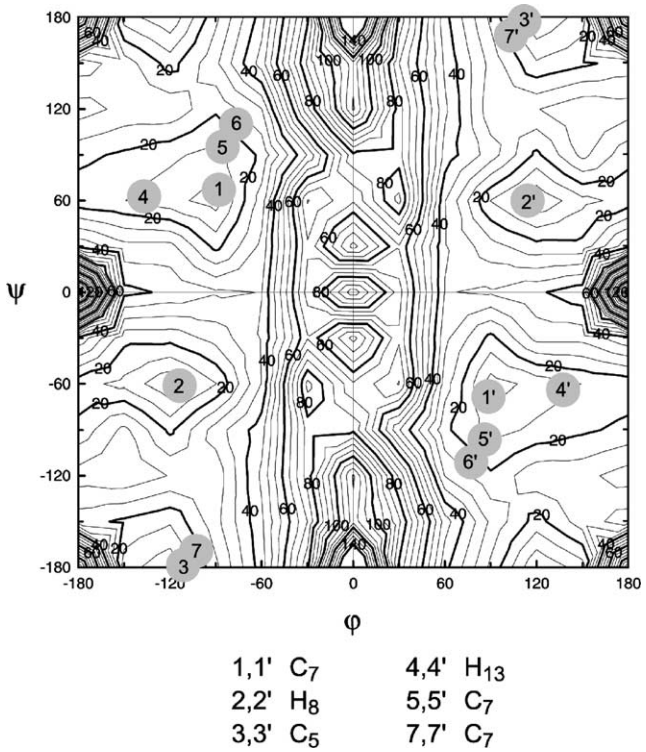

Fig. 6. HF/6-31G* Ramachandran plot for the disulfonamide **B** and the obtained minimum conformations.

a detailed inspection of the values of the torsion angles φ and ψ of the disulfonamide conformers in Table 2 shows partially considerable deviations from those in the formal analogues of α-peptides. This is caused by the above-described conformational differences between the sulfonamide and amide/peptide bonds documented by different values for the rotation angle ω in the minimum structures. A very impressive example for this situation provides conformer **A4**, which could be considered as the origin of a right-handed helix in sulfonamido peptides with 13-membered hydrogen-bonded pseudocycles (H_{13}), as it is typical for the α-helix in native peptides and proteins. The comparison of this helix with the α-helix in Fig. 5 illustrates a similar shape and the same hydrogen bond pattern, but

Table 4
Geometry data for the conformers of **B** obtained at the HF/6-31G* level of ab initio MO theory

Conf.[a]	ω_1	φ	ψ	ω_2	N[b]	Type[c]
B1	−142.2	−88.2	68.2	74.6	SS	C_7
B2	98.9	−113.9	−61.0	109.0	RR	H_8
B3	97.8	−111.6	−179.5	106.2	RR	C_5
B4	−105.8	137.1	−63.8	113.5	SR	H_{13}
B5	93.2	85.8	−96.5	−162.8	RS	C_7
B6	−120.3	76.9	−111.5	−160.6	SS	
B7	117.7	103.0	170.1	−102.8	RS	C_7

[a] Torsion angles in degrees.
[b] Configuration at the sulfonamide nitrogen atoms N^1 and N^2.
[c] See footnote b in Table 2.

Table 5
Relative energies of the conformers of **B** at the HF/6-31G*, DFT/B3LYP/6-31G* and PCM//HF/6-31G* levels of ab initio MO theory

Conf.	ΔE[a]		
	HF/6-31G*	B3LYP/6-31G*	PCM//HF6-31G*[b]
B1	0.0[c]	0.0[d]	1.6
B2	5.1	10.1	0.0
B3	5.4	10.6	0.0[e]
B4	10.0	15.9	3.7
B5	10.5	9.5	6.0
B6	16.2	17.8	11.7
B7	21.8	22.1	8.0

[a] Relative energies in kJ/mol.
[b] Dielectric constant $\varepsilon = 78.4$.
[c] $E_T = -1322.640219$ a.u.
[d] $E_T = -1326.981661$ a.u.
[e] $E_T = -1322.654659$ a.u.

the values of the torsion angles φ and ψ are with -142 and 62° in **A4** and about -57 and -48° in an α-helix completely different. The stability relations between the most important conformers are not substantially changed when considering environmental effects (Table 3).

For completeness, the Ramachandran plot for the unsubstituted disulfonamide **B** is given in Fig. 6. The diamide of the amino acid glycine represents the counterpart in α-peptides. The geometry and energy data of the minimum conformations of **B** are given in the Tables 4 and 5. The plot and the conformation data confirm completely the conclusions which were drawn from the corresponding information on **A**. The monomer constituent **B** is also able to mimic typical conformers of the glycine analogue, but often with different torsion angle values for φ and ψ.

The H_{13} helix (Fig. 5) obtained by oligomerisation of the monomer **A4** (Table 2) was an interesting example to derive periodic structures in oligomer sequences from

Table 6
Structure parameters and relative energies for trimers derived from the conformers of compound **A** calculated at the HF/6-31G* and PCM//HF/6-31G* level of ab initio MO theory

Conf.[a]	ω	φ	ψ	N[b]	ΔE		Type[c]
					HF/6-31G*	PCM//HF/6-31G*	
(**A1**)$_3$	160.1	−117.6	58.5	S	40.6	57.5	
	166.3	63.9	25.1	R			
	109.7	−97.4	66.5	R			
(**A2**)$_3$	102.5	−117.6	−64.6	R	0.0[d]	0.0[e]	H_8
	100.5	−130.1	−68.1	R			
	99.1	−127.8	−63.3	R			
(**A3**)$_3$	104.4	−111.3	171.4	R	22.9	12.7	
	119.8	−142.6	178.6	R			
	114.8	−148.2	−178.0	R			
(**A4**)$_3$	138.4	−166.1	66.9	R	8.2	23.9	H_{13}
	105.3	−159.1	61.7	R			
	119.2	−162.2	66.5	R			
(**A5**)$_3$	−121.4	−100.2	69.4	S	32.9	35.5	C_5
	−106.5	−78.8	109.3	S			
	−116.9	−93.9	58.3	S			
(**A6**)$_3$	122.6	−76.9	105.3	R	36.5	38.6	C_7
	116.9	−70.2	103.5	R			
	115.2	−70.0	111.5	R			
(**A7**)$_3$	97.6	96.8	−70.4	R	70.2	72.0	
	118.7	98.1	−68.1	R			
	134.8	89.4	−69.1	R			
(**A8**)$_3$	−105.6	−171.5	−71.0	S	74.3	65.5	C_5
	−132.0	−166.2	−73.7	S			
	−129.2	−165.5	−75.0	S			
(**A9**)$_3$	−105.4	−170.3	163.3	S	62.4	53.6	C_5
	−103.9	−169.2	162.8	S			
	−104.2	−168.3	160.5	S			
(**A13**)$_3$	154.1	63.5	37.1	R	91.5	73.2	C_7
	150.6	65.2	38.9	R			
	144.6	69.2	42.3	R			

[a] For conformers of compound **A** see Table 2. Torsion angles in degrees, relative energies in kJ/mol.
[b] Configuration at the nitrogen atoms.
[c] See footnote b of Table 2.
[d] $E_T = -2722.201677$ a.u.
[e] $E_T = -2722.211070$ a.u.

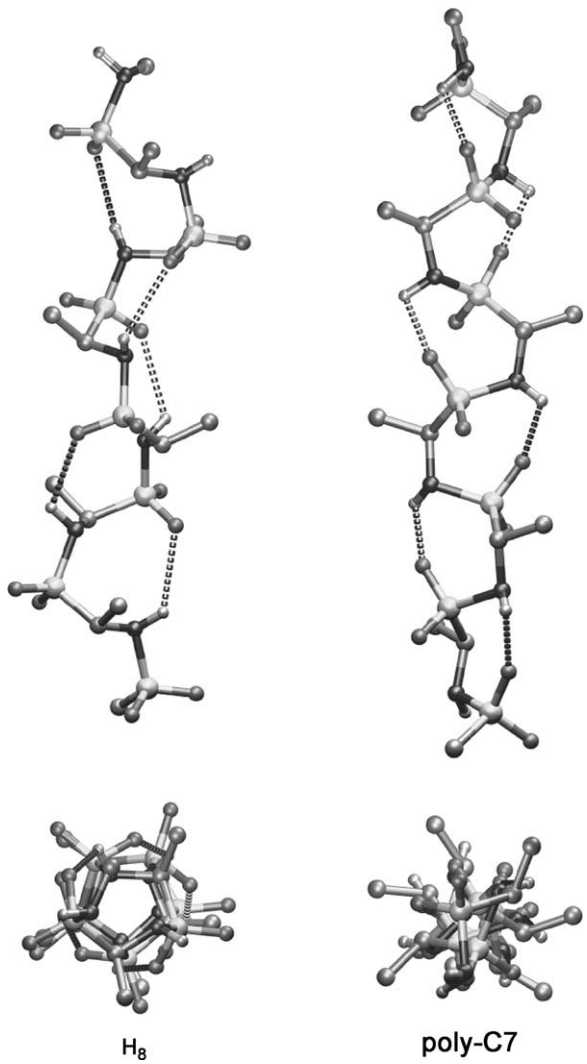

Fig. 7. Hexamer models of α-sulfonamido peptides showing the H_8 (derived from monomer **A2**) and poly-C_7 (derived from monomer **A6**) secondary structures.

the conformers of the constituents (monomer approach). The special note in this case was the fact that hydrogen bonding is impossible in the monomer and appears only in the blocked trimer between the NH group of residue *i* and one of the oxygen atoms of the sulfone group of residue $(i-4)$ in a sequence. It might be interesting to look for further characteristic oligomer conformations derived from the other minimum structures in Table 2. In fact, most of them can be confirmed at the trimer level (Table 6). However, there are remarkable changes of the stability order with elongation of the sequence. The global minimum conformation at the trimer level is a completely novel periodic secondary structure, which can be derived from the monomer **A2,** which was already most stable when solvent effects are considered. In this conformer, C_8 pseudocycles are formed in forward direction of the sequence by hydrogen bonds between the peptidic NH group of amino acid *i* and the peptidic CO group of amino acid $(i+1)$ (Fig. 7). This type of hydrogen bonding pattern deserves a special note, since the typical secondary structures in the native peptides and proteins are characterised by hydrogen bonding in backward direction. The next stable conformer is the above-mentioned H_{13}-helix of the sulfonamido peptides (Fig. 5), an analogue to the protein α-helix. The conformer **A1**, which was most stable at the monomer level, is not longer periodic and destabilised in comparison to other trimer structures. This is known from α-peptides, where for instance the 3_{10}- and α-helices get more stability with increasing chain length than poly-C_7 structures [65,66]. Here, even the trimer of another monomer with a C_7 pseudocycle $(\mathbf{A6})_3$ (Fig. 7) becomes more stable than the $(\mathbf{A1})_3$ trimer. The stability order of the trimers is not essentially changed when solvent influence is considered with exception of an inversion between $(\mathbf{A3})_3$ and $(\mathbf{A4})_3$.

Another point should be mentioned. In the case of L-substituted α-amino acids, a minimum conformation for right-handed helices appears in the energetic Ramachandran plot of a monomer constituent only if solvent influence is involved [58,67]. The values for the torsion angles φ and ψ correspond to those of a 3_{10}-helix with hydrogen bonds between the peptidic NH group of residues *i* and the peptidic CO group of residues $(i-3)$ in a sequence and not to those of an α-helix. In the sulfonamido peptides, the conformation for the realisation of an α-helical hydrogen bonding pattern is already among the conformers of the monomer constituents. Cooperative effects were indicated in the formation of α-helices by the determination of the residue energies that each amino acid constituent contributes to the stability of the growing helix [66]. The residue energies are defined by the differences between the energies of the peptides with *n* amino acids and that with $(n-1)$ amino acids. Contrary to the α-helix, the residue energies in the sulfonamido peptide analogue remain practically constant when adding amino acid constituents to the helix. Thus, cooperativity effects can be excluded in this case.

4. Conclusions

Comparing the conformational properties of the sulfonamide bond with those of the peptide bond, some peculiarities have to be stressed. Most striking are the differences of the values of the torsion angle ω ($\angle C^{\alpha}SNC^{\alpha}$) in the two conformers, which are about -100 and 60°, respectively, but 180 and 0° for the peptide bond. The barriers for the rotation around the SN bond are lower than that of the peptide bond. Therefore, sulfonamide groups are less rigid than peptide bonds. Finally, the sulfonamide nitrogen atom has a distinct pyramidal structure, whereas peptide bonds are planar. Both oxygen atoms of the sulfone group take part in specific interactions. Thus, the number of basic conformers in the monomers of sulfonamido peptides is greater than in the α-amino acid constituents of a peptide sequence. The minimum conformations of the monomers could be the origin of numerous elements of secondary

structure, which are able to mimic typical peptide and protein secondary structures. Some of these structures are of the same type and similar shape as their native counterparts, but the values of the torsion angles φ and ψ in the amino acid monomers differ due to the special conformational properties of the sulfonamide bond.

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