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How many hydrogen-bonded α-turns are possible?

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Abstract

The formation of α-turns is a possibility to reverse the direction of peptide sequences via five amino acids. In this paper, a systematic conformational analysis was performed to find the possible isolated α-turns with a hydrogen bond between the first and fifth amino acid employing the methods of *ab initio* MO theory in vacuum (HF/6-31G*, B3LYP/6-311+G*) and in solution (CPCM/HF/6-31G*). Only few α-turn structures with glycine and alanine backbones fulfill the geometry criteria for the i←(i+4) hydrogen bond satisfactorily. The most stable representatives agree with structures found in the Protein Data Bank. There is a general tendency to form additional hydrogen bonds for smaller pseudocycles corresponding to β- and γ-turns with better hydrogen bond geometries. Sometimes, this competition weakens or even destroys the i←(i+4) hydrogen bond leading to very stable double β-turn structures. This is also the reason why an "ideal" α-turn with three central amino acids having the perfect backbone angle values of an α-helix could not be localized. There are numerous hints for stable α-turns with a distance between the C_α-atoms of the first and fifth amino acid smaller than 6-7 Å, but without an i←(i+4) hydrogen bond.

Keywords Secondary structure · α-Turns · Conformational analysis · *Ab initio* MO theory · Protein design

Introduction

Reverse turns and loops, which allow the reversal of the direction of peptide sequences, are important secondary structure elements for the formation of globular protein structures [1-10]. In the simplest way, chain reversal could formally be organized via two amino acids connected by a cis-peptide bond. However, such an arrangement brings the arriving and leaving strands, which are often α-helices or β-strands, in too close contact. Turns via three amino acids, which are connected by trans-peptide bonds, are more realistic. Such γ-turns have a stabilizing intramolecular hydrogen bond between the CO group of the first and the NH group of the third amino acid. They occur in proteins and in linear and cyclic peptides [1, 3, 4, 10], but are still relatively rare because of sterical reasons. Much more frequent are β-turns realized via four amino acids. They are well examined and classified into various families [11-22]. The most important types of β-turns, the βI- and βII-turns and their approximate backbone mirror images βI´ and βII´, are characterized by hydrogen bonds between the CO group of the first and the NH group of the fourth amino acid. In comparison to β-turns, the so-called α-turns over five consecutive amino acids with a hydrogen bond between the first and fifth amino acid are not so frequent. Therefore, they attracted less attention, although this hydrogen bond pattern corresponds to one turn of the famous α-helix. A systematic search for hydrogen-bonded α-turns, which are not part of an α-helix, in 193 not structurally related proteins in the Protein Data Bank (PDB) by Pavone et al. [23] provided 349 isolated trans-configured α-turns, which could be clustered into four types with their approximate backbone mirror images. These structures were essentially confirmed in a more extended analysis of the Protein Data Bank by Dasgupta et al. [24], who considered also structures without the i←(i+4) hydrogen bond, but with distances smaller than 7 Å between the C_α atoms of the amino acids i and (i+4) in a peptide sequence as potential α-turn structures. Such a criterion is also valid for the distance between the C_α atoms of the amino acids i and (i+3) in β-turns [13, 15, 16, 20].

In a systematic conformational search on a blocked α-turn model on the basis of molecular mechanics employing a force field suggested by Ramachandran and Sasisekharan [25], Ramakrishnan and coworkers [26, 27] looked for all possible hydrogen-bonded α-turns. They found 23 minimum energy conformations, which they assigned to 13 different families of hydrogen-bonded α-turns. Our detailed inspection of the geometry and the assignment of

these α-turns on the basis of quantum chemical calculations showed some inconsistencies, probably caused by the shortcomings of the empirical force field. This made us to revisit this conformational problem on the basis of the more sophisticated methods of *ab initio* MO theory.

Computational details

The blocked tripeptide **1** was chosen as a model compound for an α-turn. The backbone angles φ and ψ of all amino acids were systematically varied in intervals of 30° resulting in 12^6 = 2,985,984 conformations.

<Structure formula **1**>

These conformations were checked for the existence of a hydrogen bond between the first and fifth amino acids (distance criterion CO···HN: 1.8-2.5 Å). The energy of all conformations fulfilling the hydrogen bond criteria were calculated employing the CHARMM c32b1 force field [28] keeping the backbone torsion angles fixed. All structures within an energy range of 100 kcal mol^{-1} referred to the most stable one were selected for further studies. This analysis provided 2418 candidate structures for α-turns. Since amino acid side chains are missing in the model peptide **1**, only 1209 conformations had to be considered in the full geometry optimizations at the HF/6-31G* level of *ab initio* MO employing the program package Gaussian 03 [29] (keyword: opt) to find all minimum conformations. The Gaussian 03 program package was also used for all other quantum chemical calculations. All optimized structures were checked for maintenance of the α-turn hydrogen bond and for their minimum character by calculation of the vibration frequencies (keyword: freq). Changing the sign of the backbone torsion angles of all conformers leads to their mirror images as energetically equivalent turn structures. In order to estimate the influence of correlation energy and basis set, all turn conformers obtained at the HF/6-31G* level were reoptimized at the DFT//B3LYP/6-311+G* level of *ab initio* MO theory to confirm the turn structures and their energy order at a higher level of theory.

The turn structures obtained for model compound **1** were also the starting point for the study of side chain influence. For this purpose, L-alanine residues were substituted for the glycine residues followed by complete geometry optimization. Since the mirror image structures are

not longer equivalent, they have to be additionally optimized at the same approximation levels as given for the glycine turns. To estimate the influence of a polar solvent, the resulting alanine α-turns were also subject to complete geometry optimization in an aqueous environment employing a conductor-like polarizable continuum model (keyword: scrf=cpcm; dielectric constant ε = 78.4, CPCM/HF/6-31G* [30-32]).

Results and discussion

Glycine α-turns (Gat)

The geometry optimization of the 1209 candidate structures from the conformational search at the HF/6-31G* level provided 33 stationary points on the potential hypersurface for model compound **1**. One of these structures proved to be a transition state, the other 32 were conformers according to the calculated vibration frequencies. Only three conformers strictly fulfill the criterion of 1.8-2.5 Å for the CO···HN distance of the α-turn hydrogen bond. Another two conformers show a bit longer distances of about 2.7 Å. Thus, the five structures **Gat1**-**Gat5** and their mirror images could be considered as hydrogen-bonded α-turns. They are visualized in Fig. 1. The energy and free enthalpy differences between the various α-turns and their backbone torsion angles are listed in Tables 1 and 2. The most stable structures **Gat1** and **Gat2** show additional hydrogen bonds which are independent of the i←(i+4) α-turn hydrogen bond. They correspond to the classic and inverse γ- and γ´-turns, respectively (Tables 2 and 3). Additional hydrogen bonds corresponding to γ-turns also occur in **Gat4** and **Gat5**. In contrast to **Gat1** and **Gat2**, they are bifurcated with the α-turn hydrogen bond. Turn structure **Gat-3** shows a weak hydrogen bond corresponding to a hydrogen-bonded C_5 pseudocycle. The hydrogen bond geometries and types of the five turns are given in Table 3. Obviously, the stability order of the α-turns is determined by the type of the additional hydrogen bond. The competition of two hydrogen bonds to realize optimum geometries leads to deviations from ideal values, which are larger for the α-turn hydrogen bond than for the additional one (Table 3). This situation makes the search for isolated α-turns in protein structures difficult, since the search algorithms do not always adequately account for this problem.

<Figure 1>

<Tables 1 and 2>

<Table 3>

The calculations at the higher B3LYP/6-311+G* level of *ab initio* MO theory and the free enthalpy data essentially confirm the results obtained at the HF/6-31G* level. The most stable α-turns **Gat1** and **Gat2** are energetically equivalent now (Tables 1 and 2).

There are 10 structures among the 32 conformers of the conformational analysis without an α-turn hydrogen bond which can be considered as α-turns on the basis of the criterion for the distance between the C_α atoms of the amino acids i and (i+4) introduced above. The energy and geometry data and the hydrogen bonding patterns for these turns, which are denoted by an additional "d" in parentheses to the turn symbol, are given in the supplementary material (Tables S1 and S2). Turns of this type can be more stable than α-turns with an i←(i+4) hydrogen bond due to the formation of alternative hydrogen bonding patterns. There is no "ideal" α-turn fulfilling the hydrogen bond criterion and having the typical backbone torsion angle values of φ = -57° and ψ = -47° for an α-helix [1, 33] in the three central amino acids. This problem will be discussed in a later paragraph.

Obviously, the number of quantum chemically found hydrogen-bonded α-turns is much smaller than that arising from molecular mechanics [26, 27]. It is not unusual that empirical force fields find more minimum conformations than quantum chemical methods. Therefore, it was interesting to see which quantum chemical energy minima were reached from the 23 hydrogen-bonded α-turn minima resulting from molecular mechanics in geometry optimizations at the HF/6-31G* level. The data show that 14 of the 23 turns change into the quantum chemical α-turns **Gat1**, **Gat2**, **Gat4**, and **Gat5**, respectively (g2, g3, g5-9, g12-14, g16, g17, g22, g23 according to the nomenclature in Ref. [27]). Another seven structures (g1, g4, g10, g15, g18-20) correspond to quantum chemically predicted α-turns without an i←(i+4) hydrogen bond (Table S1 of the supplementary material), but fulfill the α-turn distance criterion. Finally, another two structures (g11, g21) will gain importance in the discussion on the possibility of "ideal" α-turns in a separate paragraph. Interestingly, turns grouped into the same family on the basis of molecular mechanics split into different quantum chemical minimum conformations.

Alanine α-turns (Aat)

In order to consider the effect of amino acid side chains, all 33 stationary points obtained for the glycine α-turn model **1** were transformed into the corresponding L-alanine derivatives. Because of chirality, 66 structures were subject to geometry optimization to obtain also the pseudo mirror images for each structure, which are denoted by a prime added to the turn symbol. Fifty-three conformers resulted from the optimizations since some of the 66 starting structures changed into the same minimum. This aspect concerns also hydrogen-bonded α-turns. Thus, the turn **Aat4** and its mirror **Aat4´** and the mirror image **Aat3´**can no longer be localized as minimum conformations. There are no additional hydrogen-bonded α-turns. Consequently, seven hydrogen-bonded α-turns were obtained for an alanyl backbone, showing the same hydrogen bond patterns as the corresponding glycine turns in Table 3. Their stabilities and backbone torsion angles are given in Tables 4 and 5. There is a fair agreement between the stability orders at the various approximation levels. Fig. 2 shows all hydrogen-bonded alanine α-turns. Twenty of the other conformers fulfill the distance criterion for α-turns without an i←(i+4) hydrogen bond. Their stability order, hydrogen bonding patterns and backbone torsion angles are given in Tables S3 and S4 in the supplementary material.

<Tables 4 and 5>

To estimate the influence of a polar solvent on the stability and geometry of the turns, the optimizations of the alanine turns were repeated employing a conductor-like polarizable continuum model. The results for energies and backbone torsion angles are given in Table 6.

There are no excessive changes of the vacuum data with exception of turn **Aat3**, which gains considerable stability, but opens its hydrogen bond. The CO···HN distance increases from 2.37 to 3.23 Å.

<Table 6>

The "ideal" α-turn

The calculated hydrogen-bonded α-turns should be compared with data from statistical analyses of the Protein Data Bank. The most comprehensive analysis for classical hydrogen-

bonded α-turns was performed by Pavone et al. [23]. The results of this study were essentially reproduced by another group which extended the subject to non-hydrogen-bonded α-turns fulfilling the criterion of 6-7 Å for the distance between the C_α atoms of the amino acids i and (i+4) [24]. Pavone and coworkers found four possible hydrogen-bonded α-turns and their approximate mirror images. Table 7 provides the average backbone angles for these turns. In Table 8, the frequency of their occurrence in the Protein Data Bank is given. The most stable structures **Aat1** and **Aat2** and their mirror images **Aat1´**and **Aat2´** from our quantum chemical study can immediately be assigned to the structures **II-α_{RS}**, **II-α_{LU}**, **IIα_{LS}**, and **IIα_{RU}** found by Pavone et al. (Table 7). Recently, turn **Aat1´** was designed in a peptide hairpin with a three-residue loop [34]. The theoretically determined turns **Aat5** and **Aat5´** are less stable. They find no counterparts in the data set of Pavone et al. This raises the question of the theoretical counterparts for the two other α-turn types **I-α_{RS}** and **I-α_{RU}** and their pseudo mirror images resulting from the data bank analysis, in particular the most frequently occurring **I-α_{RS}** turn.

<Tables 7 and 8>

It was already mentioned that the i←(i+4) hydrogen bond interaction corresponds to that in the α-helix. An ideal isolated α-helix turn with three central amino acids showing the typical backbone angle values of an α-helix was neither found in our systematic conformational search nor in the data bank analysis of Pavone et al. (Table 7). This is not surprising, since the formation of α-helices requires a critical sequence length. In shorter sequences, the formation of 3_{10}-helices with an i←(i+3) hydrogen bond interaction is favored [1, 33]. Therefore, we selected the "ideal" α-helix turn conformation as starting point of geometry optimization. The backbone torsion angle values of the minimum conformation obtained at the HF/6-31G* level for the alanine backbone are φ_{i+1} = -69.2°, ψ_{i+1} = -23.7°; φ_{i+2} = -69.2°, ψ_{i+2} = -12.9°; φ_{i+3} = -95.2°, ψ_{i+3} = 2.8°. These angles fairly agree with those determined by Pavone et al. for the **I-α_{RS}** turn. Therefore, we assigned this structure to **I-α_{RS}** with the notation **Aat6** in Table 7.

A detailed inspection of this structure shows correspondence with a double β-turn structure with i←(i+3) and (i+1)←(i+4) hydrogen bonding interactions (Fig. 3). Despite the close agreement of the backbone torsion angles of **I-α_{RS}** and **Aat6**, the α-turn hydrogen bond is not adequately realized in **Aat6** and the distance between the C_α atoms of the amino acids i and

(i+4) is with 7.6 Å a bit above the upper limit of the distance criterion. The tendency to favor the formation of hydrogen bonds with smaller pseudocycles was already observed in the other α-turn structures for the additional hydrogen bond, which is generally better realized than the i←(i+4) hydrogen bond. In **Aat6**, this tendency is even strengthened due to the possibility of the formation of two β-turns. It could well be possible that additional factors in longer peptide and protein sequences, as for instance special side chain effects, may support the formation of the i←(i+4) hydrogen bond for an α-helix-like backbone. However, the intrinsic stability is in favor of the double β-turn structure, which was obtained at all approximation levels both for glycine and alanine backbones. Structure **Aat6** is distinctly more stable than the other turn structures (Table 8). This finding correlates with the highest frequency of occurrence of this turn type in the Protein Data Bank (Table 8).

A similar situation exists for the theoretical counterparts of the α-turns **I-α_{RU}** and **I-α_{LU}**. The backbone torsion angles of these structures agree satisfactorily with those of two other theoretically predicted double β-turn structures **Aat(d)5** and its pseudo mirror image **Aat(d)5´** (Table 7 and Table S2 in the supplementary material). Both structures are relatively stable and clearly fulfill the α-turn distance criterion. The turn **Aat(d)5** is visualized in Fig. 4. Thus, the average backbone angle values for the four basic α-turn types and their mirror images derived by Pavone et al. from the data bank analysis correspond to two distinct types of theoretically predicted α-turns. The turns **II-α_{RS}** and **II-α_{LU}** and their pseudo mirror **II-α_{LS}** and **II-α_{RU}** images correspond to the theoretically predicted α-turns **Aat1**/**Aat1´** and **Aat2**/**Aat2´** with an i←(i+4) hydrogen bond. The other two turn types **I-α_{RS}** and **I-α_{LU}** and their pseudo mirror images find their theoretical equivalents in structures with a strong tendency to double β-turn structures (**Aat6**/**Aat6´**, **Aat(d)5**/**Aat(d)5´**).

The theoretically estimated free enthalpy data of the turns in Table 8 show an acceptable correlation with the frequency of their occurrence in the proteins of the Protein Data Bank.

Conclusions

Our systematic conformational analysis employing quantum chemical methods at various approximation levels provides several possibilities for α-turns as a possibility to reverse the direction of a peptide sequence via five amino acids. Only few structures realize a hydrogen

bond between the amino acids i and (i+4) satisfactorily. More stable are structures with a strong tendency to double β-turn structures without this hydrogen bond, but with a distance smaller than 6-7 Å between the C_α atoms of the amino acids i and (i+4). None of the predicted turns agrees with the ideal backbone angles of an α-helix. There is a fair correlation of the theoretical data with the results of statistical analyses on the basis of the Protein Data Bank.

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Electronic supplementary material available

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Tables

Table 1 Relative energies ΔE (in kJ mol^{-1}) and free enthalpies ΔG (in kJ mol^{-1}) for hydrogen-bonded α-turns of model compound **1** with glycine backbone at the HF/6-31G* and B3LYP/6-311+G* levels of *ab initio* MO theory

α-turn	HF/6-31G*		B3LYP/6-311+G*
	ΔE	ΔG	ΔE
Gat1	**0.0**[a]	**0.0**[b]	0.2
Gat2	2.2	2.7	**0.0**[c]
Gat3	5.7	9.9	6.3
Gat4	8.6	8.6	6.2
Gat5	12.8	6.8	6.2

[a] E_T = -867.457489 a.u.
[b] G_T = -867.215068 a.u.
[c] E_T = -872.810124 a.u.

Table 2 Backbone torsion angles (in degrees) for hydrogen-bonded α-turns of model compound **1** with glycine backbone at the HF/6-31G* (first line) and B3LYP/6-311+G* (second line) levels of *ab initio* MO theory

α-turn	φ_{i+1}	ψ_{i+1}	φ_{i+2}	ψ_{i+2}	φ_{i+3}	ψ_{i+3}
Gat1	-65.7	146.2	85.5	-61.9	-118.4	7.0
	-65.7	142.7	83.1	-60.8	-108.5	1.7
Gat2	-75.4	-20.8	-85.3	62.4	119.0	-12.1
	-76.2	-17.6	-82.6	62.7	117.7	-13.4
Gat3	-61.5	-34.7	-106.7	137.9	102.3	-27.3
	-67.3	-27.2	-107.9	121.0	111.0	-30.6
Gat4	-84.7	75.7	123.3	-26.5	-125.8	9.2
	-81.3	76.2	119.7	-24.7	-121.3	7.5
Gat5	-85.1	52.9	-141.9	28.4	135.2	-13.4
	-82.1	70.4	-112.4	10.1	117.5	-15.9

Table 3 Hydrogen bonding geometries and patterns (distances R in Å, angles in degrees) in hydrogen-bonded α-turns at the HF/6-31G* level of *ab initio* MO theory

α-turn	α-turn hydrogen bond: i←(i+4)			Additional hydrogen bond		
	$R_{O\cdots HN}$	∠O···NH	$R_{C\alpha\cdots C\alpha}$ [a]	$R_{O\cdots HN}$	∠O···NH	Type
Gat1	2.42	33.2	4.40	2.20	26.4	(i+1)←(i+3) = γ
Gat2	2.37	29.2	5.37	2.23	26.9	(i+1)←(i+3) = γ´
Gat3	2.24	21.1	4.77	2.37	57.7	(i+2)←(i+2) = C_5
Gat4	2.71	35.3	4.07	2.20	31.6	i←(i+2) = γ´
Gat5	2.68	27.5	5.76	2.07	21.4	i←(i+2) = γ´

[a] Distance between the C_α-atoms of the amino acids i and (i+4)

Table 4 Relative energies ΔE (in kJ mol^{-1}) and free enthalpies ΔG (in kJ mol^{-1}) for hydrogen-bonded α-turns of model compound **1** with alanine backbone at the HF/6-31G* and B3LYP/6-311+G* levels of *ab initio* MO theory

α-turn	HF/6-31G*		B3LYP/6-311+G*
	ΔE	ΔG	ΔE
Aat1	**0.0**[a]	**0.0**[b]	**0.0**[c]
Aat2	1.1	3.2	2.0
Aat3	5.3	8.1	7.5
Aat2´	9.5	8.2	8.2
Aat1´	10.4	13.2	11.0
Aat5	13.5	11.3	12.4
Aat5´	15.9	15.2	13.1

[a] E_T = -984.565125 a.u.
[b] G_T = -984.236825 a.u.
[c] E_T = -990.778720 a.u.

Table 5 Backbone torsion angles (in degrees) for hydrogen-bonded α-turns of model compound **1** with alanine backbone at the HF/6-31G* (first line) and B3LYP/6-311+G* (second line) levels of *ab initio* MO theory

α-turn	φ_{i+1}	ψ_{i+1}	φ_{i+2}	ψ_{i+2}	φ_{i+3}	ψ_{i+3}
Aat1	-63.9	133.4	75.1	-51.7	-102.4	-4.1
	-63.7	133.1	74.1	-49.7	-100.4	-5.2
Aat2	-74.2	-22.7	-85.5	68.5	64.5	34.5
	-76.2	-18.2	-82.4	68.3	69.5	26.5
Aat3	-63.2	-31.6	-111.4	136.8	73.9	9.5
	-68.3	-24.3	-111.4	129.5	82.0	-7.3
Aat2´	63.4	34.8	74.6	-53.0	-115.4	4.6
	63.7	32.3	72.7	-52.7	-115.9	6.8
Aat1´	54.8	-138.5	-85.9	71.1	63.6	36.6
	56.2	-135.9	-83.6	69.3	65.4	33.0
Aat5	-88.6	49.2	-145.8	18.8	-171.9	-33.8
	-85.2	49.6	-142.4	17.2	-175.4	-34.9
Aat5´	75.0	-64.4	-158.9	-44.5	-145.4	21.3
	72.8	-63.0	-157.4	-49.6	-136.5	16.9

Table 6 Relative energies (in kJ mol^{-1}) and backbone torsion angles (in degrees) for hydrogen-bonded α-turns of model compound **1** with alanine backbone after geometry optimization at the CPCM/HF/6-31G* level of *ab initio* MO theory

α-turn	CPCM/HF/6-31G* [a]	Backbone torsion angles					
	ΔE	φ_{i+1}	ψ_{i+1}	φ_{i+2}	ψ_{i+2}	φ_{i+3}	ψ_{i+3}
Aat1	6.8	-63.0	138.8	74.8	-52.0	-94.1	-17.3
Aat2	2.9	-70.1	-33.6	-90.8	76.7	60.3	40.1
Aat3	**0.0**[b]	-70.5	-34.3	-117.8	119.4	58.9	41.0
Aat2´	11.7	57.5	42.4	76.3	-47.7	-101.4	-9.5
Aat1´	20.3	56.3	-129.4	-90.6	77.5	60.8	39.5
Aat5	37.9	-90.5	50.3	-143.6	23.0	-175.3	-36.7
Aat5´	21.1	74.7	-59.1	-150.6	-50.5	-136.4	10.8

[a] Dielectric constant ε = 78.4
[b] E_T = -984.572356 a.u.

Table 7 Comparison of the backbone torsion angles (in degrees) of the corresponding hydrogen-bonded α-turns from Protein Data Bank analysis[a] and from theory at the HF/6-31G* level

α-turn	φ_{i+1}	ψ_{i+1}	φ_{i+2}	ψ_{i+2}	φ_{i+3}	ψ_{i+3}
I-α_{RS}	-60 ± 11	-29 ± 13	-72 ± 14	-29 ± 15	-96 ± 20	-20 ± 17
Aat6	-69.2	-23.7	-69.2	-12.9	-95.2	2.8
I-α_{LS}	48 ± 22	42 ± 14	67 ± 9	33 ± 14	70 ± 11	32 ±12
Aat6´	61.9	32.1	58.4	26.5	63.3	25.9
II-α_{RS}	-59 ± 10	129 ± 15	88 ± 15	-16 ± 19	-91 ± 22	-32 ± 18
Aat1	-63.9	133.4	75.1	-51.7	-102.4	-4.1
II-α_{LS}	53 ± 15	137 ± 25	-95± 12	81± 23	57± 5	38 ± 8
Aat1´	54.8	-138.5	-85.9	71.1	63.6	36.6
I-α_{LU}	-61 ± 12	158 ± 15	64 ± 17	37 ± 21	62 ± 12	38 ± 8
Aat(d)5	-60.6	129.2	56.7	29.9	65.7	22.9
I-α_{RU}	59 ± 18	-157 ± 31	-67 ± 17	-29 ± 20	-68 ± 12	-39 ± 12
Aat(d)5´	55.6	-125.9	-67.7	-15.3	-94.4	2.8
II-α_{LU}	-65 ± 15	-20 ± 15	-90 ± 17	16 ± 44	86 ± 18	37 ± 27
Aat2	-74.2	-22.7	-85.5	68.5	64.5	34.5
II-α_{RU}	54 ± 8	39 ± 15	67 ± 13	-5 ± 31	-125 ± 11	-34 ± 32
Aat2´	63.4	34.8	74.6	-53.0	-115.4	4.6

[a] PDB-analysis by Pavone et al. [23]

Table 8 Comparison of the occurrence of hydrogen-bonded α-turns in the Protein Data Bank (PDB) with the relative free enthalpies ΔG (in kJ mol^{-1}) of α-turns theoretically predicted at the HF/6-31G* level of *ab initio* MO theory

α-turns (PDB)[a]		α-turns (theory)	
Type	Number	Type	ΔG
I-α_{RS}	238	**Aat6**	-9.3
II-α_{RS}	39	**Aat1**	0.0
I-α_{RU}	28	**Aat(d)5´**	0.5
I-α_{LU}	14	**Aat(d)5**	6.2
II-α_{RU}	9	**Aat2´**	8.2
II-α_{LS}	8	**Aat1´**	13.2
II-α_{LU}	8	**Aat2**	3.2
I-α_{LS}	5	**Aat6´**	16.4

[a] Classification by Pavone et al. [23]

Figure captions

Fig. 1 Hydrogen-bonded glycine α-turns at the HF/6-31G* level of *ab initio* MO theory

Fig. 2 Hydrogen-bonded alanine α-turns at the HF/6-31G* level of *ab initio* MO theory

Fig. 3 Most stable double β-turn **Aat6** (left: front view, right: top view)

Fig. 4 Stable double β-turn **Aat(d)5**

Structure formula 1
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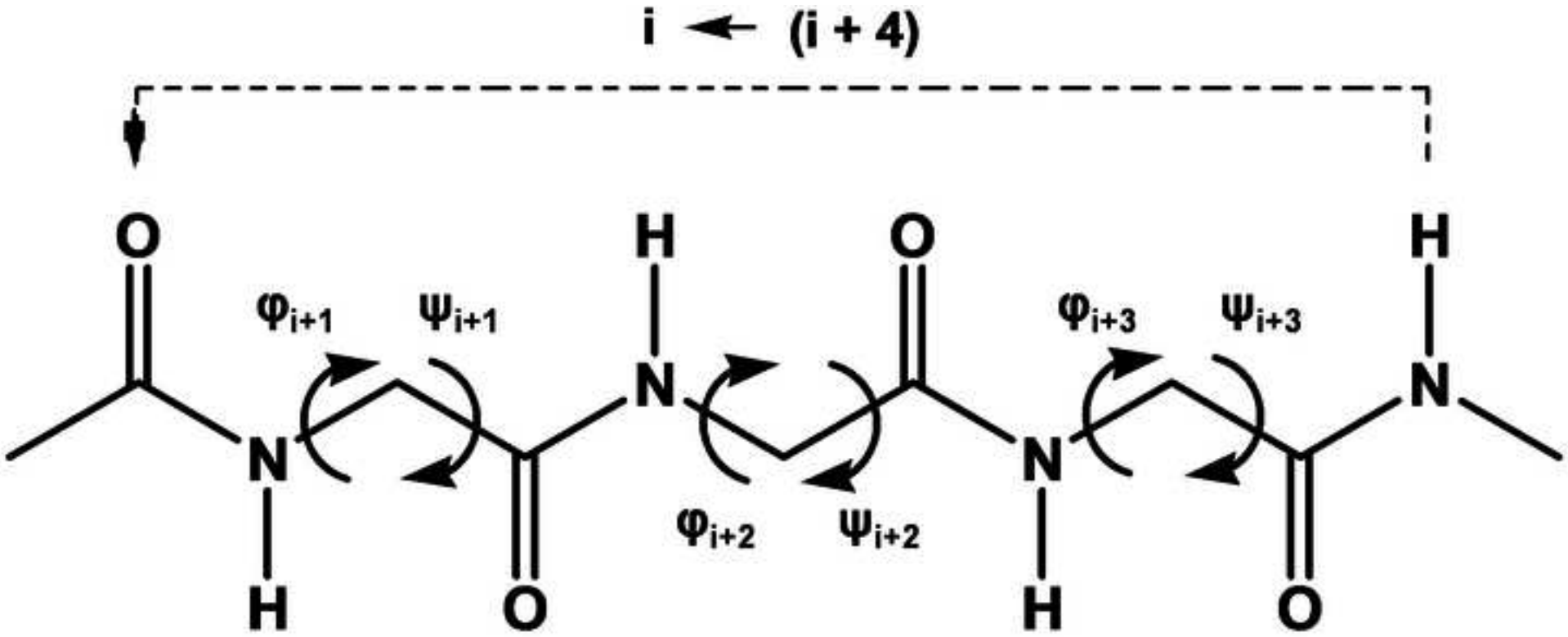

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Figure 1

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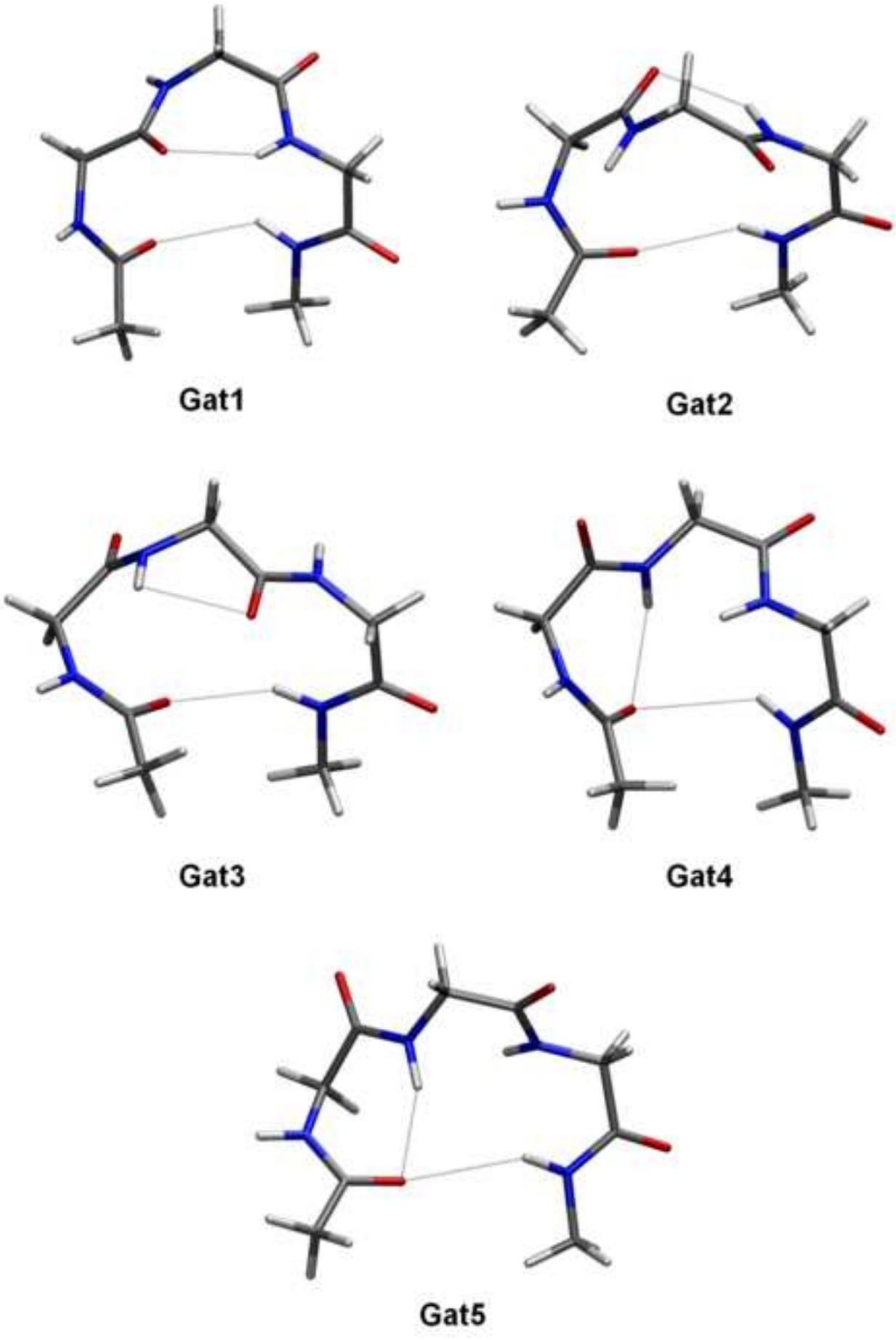

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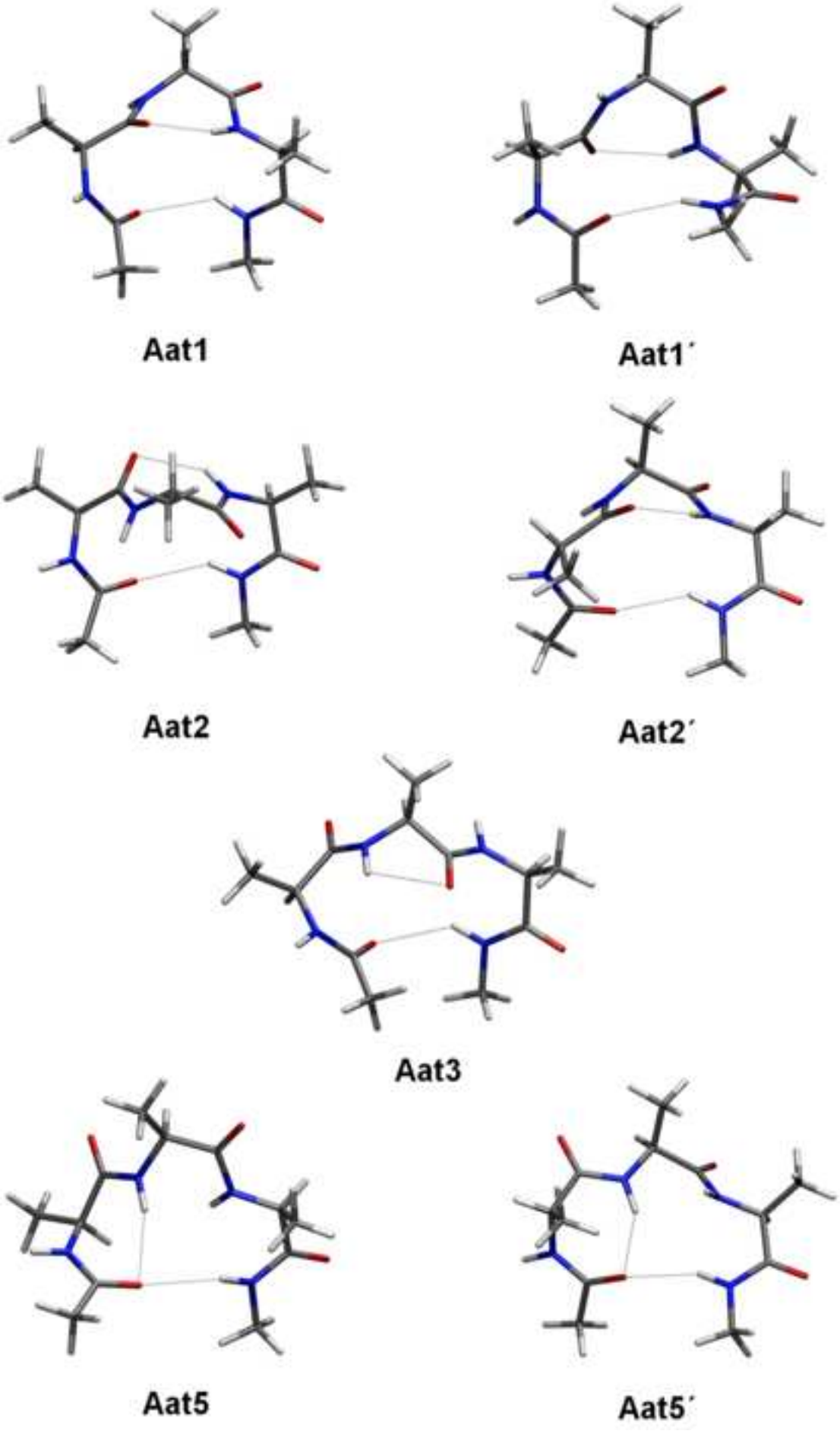

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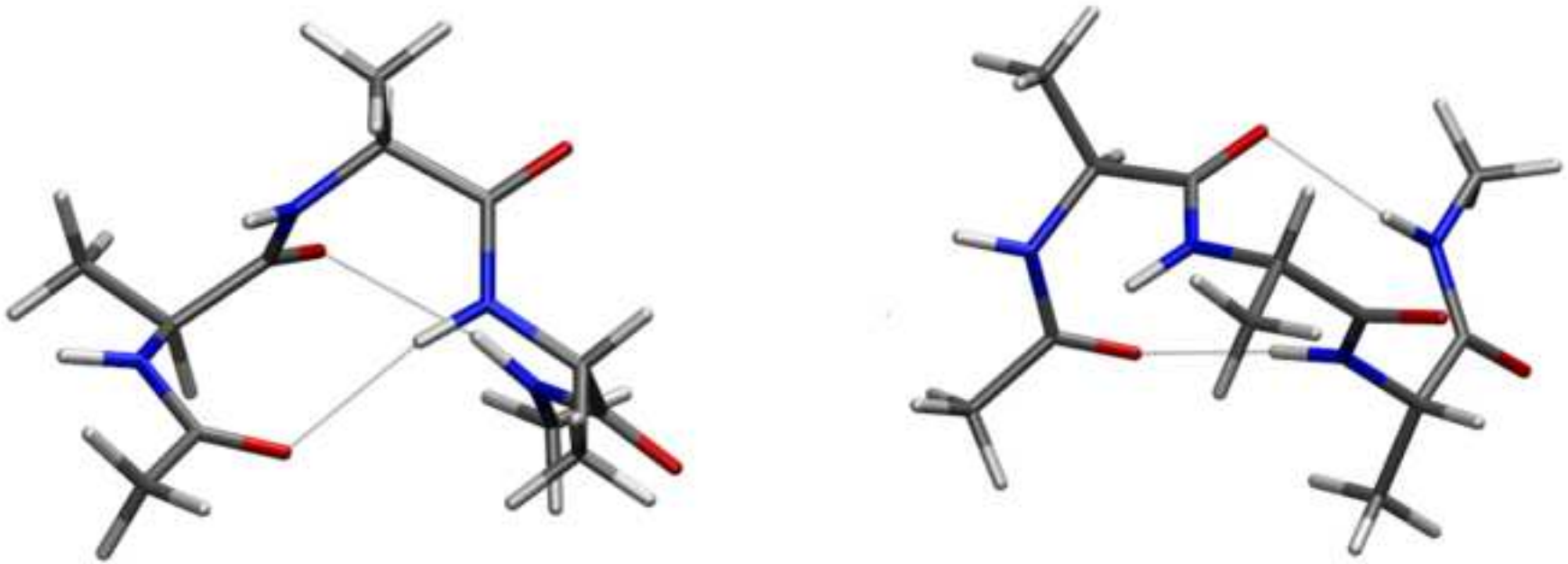

Aat6

Figure 4

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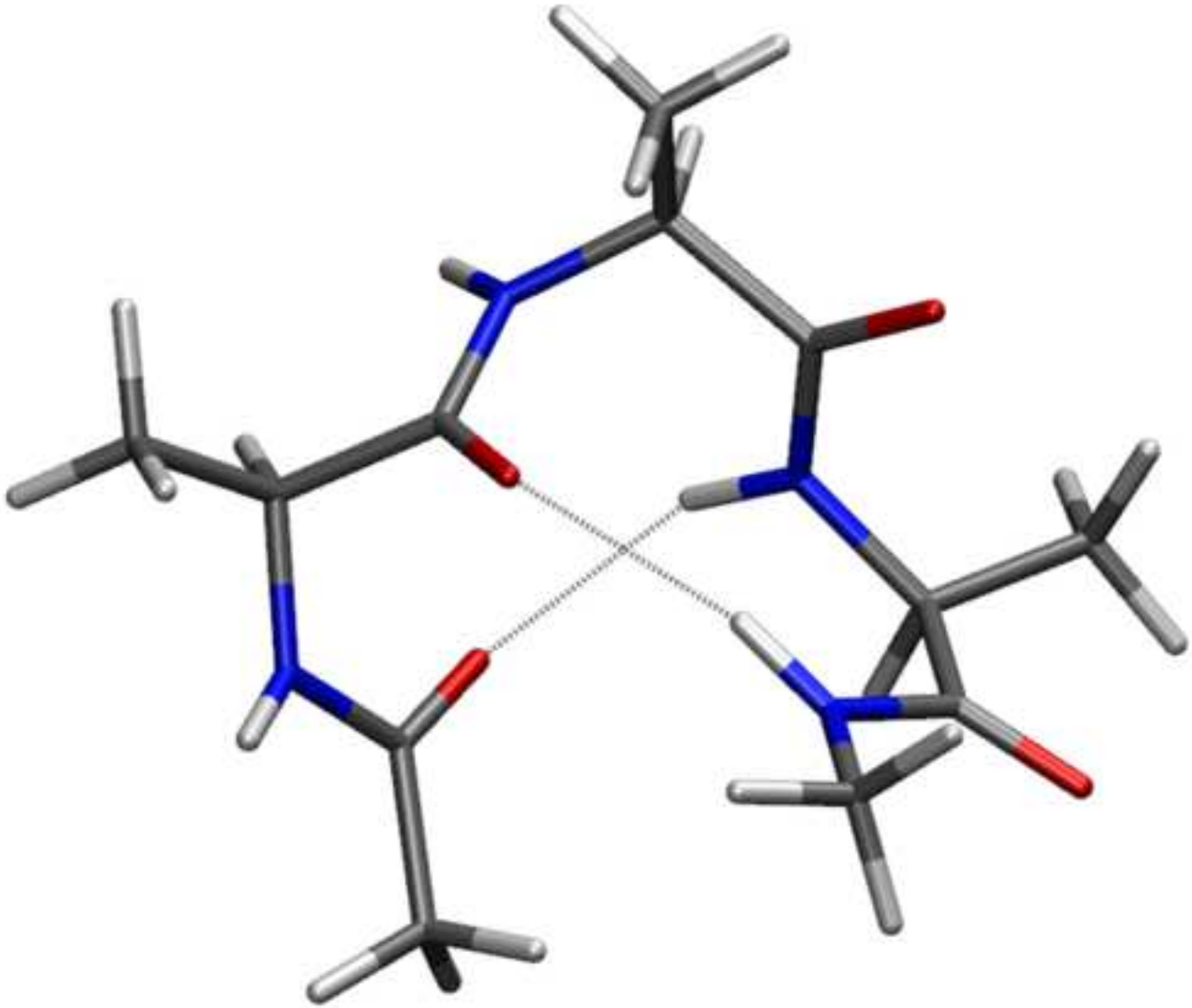

Aat(d)5

Supplementary material
Click here to download attachment to manuscript: Supplementary_material_Schreiber_et_al.pdf

Supplementary material

How many hydrogen-bonded α-turns are possible?

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Backbone torsion angles of alanine α-turns without i←(i+4) hydrogen bond S5

Table S1 Relative energies ΔE (in kJ/mol), free enthalpies ΔG (in kJ/mol) and hydrogen bonding patterns for α-turns of model compound **1** with glycine backbone without an i←(i+4) hydrogen bond, but fulfilling the distance criterion R < 7 Å for the distance between the C_α atoms of the amino acids i and (i+4) at the HF/6-31G* level of ab initio MO theory

α-turn	HF/6-31G*			
	ΔE	ΔG	$R_{C\alpha\cdots C\alpha}$	Hydrogen bonds
Gat(d)1	**0.0**[a]	**0.0**[b]	4.69	i←(i+2), (i+1)←(i+3), (i+1)→(i+3)
Gat(d)2	2.1	3.5	5.81	i←(i+2)/(i+3),[c,d] (i+2)←(i+4)
Gat(d)3	3.1	4.0	4.21	i←(i+2), (i+1)←(i+3), (i+2)←(i+4)
Gat(d)4	6.2	4.7	4.50	i←(i+3), (i+1)←(i+4)
Gat(d)5	8.9	6.3	5.49	i←(i+3)
Gat(d)6	10.0	10.8	6.02	i←(i+3), (i+2)←(i+4)
Gat(d)7	14.2	5.8	6.45	i←(i+2), (i+2)←(i+4)
Gat(d)8	16.6	3.3	6.54	(i+1)←(i+1)/(i+4)[c,d]
Gat(d)9	20.8	11.8	4.78	(i+2)←(i+2)/(i+4)[c,d]
Gat(d)10	44.5	37.6	4.36	(i+1)←(i+4)

[a] E_T = -867.462001 a.u.; for comparison: E_T(**Gat1**) = -867.457489 a.u. (see Table 1)

[b] G_T = -867.217159 a.u.; for comparison: G_T(**Gat1**) = -867.215068 a.u. (see Table 1)

[c] Bifurcated

[d] Weak

Table S2 Backbone torsion angles (in degrees) for α-turns of model compound **1** with glycine backbone without an i←(i+4) hydrogen bond but fulfilling the criterion for the distance R < 7 Å between the C_α atoms of the amino acids i and (i+4) at the HF/6-31G* level of ab initio MO theory

α-turn	φ_{i+1}	ψ_{i+1}	φ_{i+2}	ψ_{i+2}	φ_{i+3}	ψ_{i+3}
Gat(d)1	-86.7	65.0	79.1	-76.0	-72.6	156.6
Gat(d)2	-69.6	112.8	73.9	20.1	83.3	-81.0
Gat(d)3	-81.8	85.5	84.6	-61.6	-77.3	91.1
Gat(d)4	-61.8	128.9	68.0	12.9	95.8	-5.3
Gat(d)5	-71.5	-19.9	-119.0	37.5	70.7	-162.1
Gat(d)6	-67.6	-26.7	-114.7	28.4	81.7	-87.8
Gat(d)7	-81.6	77.5	72.0	-165.4	87.3	-67.1
Gat(d)8	-177.3	173.6	-61.3	139.8	96.1	-12.6
Gat(d)9	-70.9	158.4	89.4	-139.0	-86.8	55.9
Gat(d)10	-99.2	-81.8	-70.3	-19.8	-115.9	18.9

Table S3 Relative energies ΔE (in kJ/mol), free enthalpies ΔG (in kJ/mol) and hydrogen bonding patterns for α-turns of model compound **1** with alanine backbone without an i←(i+4) hydrogen bond, but fulfilling the distance criterion R < 7 Å for the distance between the C_α atoms of the amino acids i and (i+4) at the HF/6-31G* level of ab initio MO theory

α-turn	HF/6-31G*			
	ΔE	ΔG	$R_{C\alpha\cdots C\alpha}$	Hydrogen bonds
Aat(d)1	**0.0**[a]	**0.0**[b]	4.43	i←(i+2), (i+1)←(i+3), (i+1)→(i+3)
Aat(d)2	0.6	0.6	4.30	i←(i+2), (i+1)←(i+3), (i+2)←(i+4)
Aat(d)3´	1.8	2.8	5.59	i←(i+2)/(i+3),[c] (i+2)←(i+4)
Aat(d)4	5.6	4.5	6.97	i←(i+2), (i+1)←(i+4)
Aat(d)5´	7.1	6.3	4.47	i←(i+3), (i+1)←(i+4)
Aat(d)3	9.1	11.2	5.71	i←(i+3), (i+2)←(i+4)
Aat(d)6	11.3	9.8	5.64	i←(i+3), (i+2)→(i+3)
Aat(d)7	11.8	11.3	5.93	i←(i+3), (i+2)←(i+4)
Aat(d)5	12.1	12.0	4.97	i←(i+3), (i+1)←(i+4)
Aat(d)1´	13.7	16.3	4.43	i←(i+2), (i+1)←(i +3), (i+1) →(i+3)[d]
Aat(d)2´	14.8	18.0	4.13	i←(i+2), (i+1)←(i+3), (i+2)←(i+4)
Aat(d)8	16.9	4.9	6.84	(i+1)→(i+1),[d] (i+1)←(i+4)
Aat(d)4´	18.0	16.3	6.35	i←(i+2), (i+1)←(i+4)
Aat(d)9´	18.6	11.1	5.06	i←(i+2), (i+1)←(i+3), (i+2)←(i+4)
Aat(d)9	19.5	6.4	4.91	i←(i+2), (i+1)←(i+3)
Aat(d)8´	20.4	7.1	5.85	(i+1)→(i+1),[d] (i+1)←(i+4)
Aat(d)7´	21.4	21.5	5.88	i←(i+3), (i+2)←(i+4)
Aat(d)10	25.3	21.4	6.57	i←(i+2), (i+2)←(i+4)
Aat(d)11´	32.9	19.1	6.24	i←(i+2), (i+2)→(i+2), (i+2)←(i+4)
Aat(d)12	37.0	24.6	4.52	(i+1)←(i+4)

[a] E_T = -984.570085 a.u.; for comparison: E_T(**Aat1**) = -984.565125 a.u. (see Table 4)

[b] G_T = -984.239048 a.u.; for comparison: G_T(**Aat1**) = -984.236825 a.u. (see Table 4)

[c] Bifurcated

[d] Weak

Table S4 Backbone torsion angles (in degrees) for α-turns of model compound **1** with alanine backbone without an i←(i+4) hydrogen bond but fulfilling the criterion for the distance R < 7 Å between the C_α atoms of the amino acids i and (i+4) at the HF/6-31G* level of ab initio MO theory

α-turn	φ_{i+1}	ψ_{i+1}	φ_{i+2}	ψ_{i+2}	φ_{i+3}	ψ_{i+3}
Aat(d)1	-88.9	69.3	69.9	-69.1	-64.3	135.6
Aat(d)2	-82.8	86.3	74.7	-54.5	-77.9	93.5
Aat(d)3´	60.0	-114.1	-67.4	-26.4	-84.4	81.8
Aat(d)4	-81.4	78.9	50.3	-136.7	-91.2	6.1
Aat(d)5´	55.6	-125.9	-67.7	-15.3	-94.4	2.8
Aat(d)3	-66.1	117.4	55.7	36.3	72.2	-72.1
Aat(d)6	-70.6	-20.7	127.3	46.0	53.7	-145.2
Aat(d)7	-67.7	-25.8	-120.9	33.3	72.7	-77.0
Aat(d)5	-60.6	129.2	56.7	29.9	65.7	22.9
Aat(d)1´	75.6	-60.2	-80.8	77.0	53.9	-132.9
Aat(d)2´	72.4	-77.1	-87.3	64.6	66.7	-83.4
Aat(d)8	-155.8	152.0	-59.9	135.5	66.9	19.6
Aat(d)4´	72.0	-71.0	-55.8	138.9	65.9	19.9
Aat(d)9´	75.1	-60.9	-86.2	70.2	72.7	-61.0
Aat(d)9	-87.9	72.6	76.0	-49.3	-100.6	4.2
Aat(d)8´	-156.8	157.4	55.7	-133.4	-97.6	9.9
Aat(d)7´	59.0	41.7	97.4	-21.0	-83.4	88.1
Aat(d)10	-81.9	79.4	53.9	-142.4	78.8	-50.9
Aat(d)11´	77.7	-43.2	-151.6	147.6	76.3	-55.3
Aat(d)12	-103.9	-70.9	-71.7	-18.5	-124.5	22.1