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Is the parallel or antiparallel β-sheet more stable? A semiempirical study

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Summary

The geometry and energy of parallel and antiparallel peptidic β-sheets have been calculated using AM1. β-Sheets composed of two peptide chains of up to 11 amino acid residues (Ala and Gly) and the dimers of cyclooctapeptides are used as model systems. The enthalpic difference between the parallel and the antiparallel arrangement is calculated to be very small, as it is found experimentally for the cyclic systems. The coordinates of the calculated structure of the cyclooctapeptide dimer **1** (cyclo-D,L-$(Ala)_8$) have an rms deviation of only 0.223 Å to the coordinates of the corresponding cyclopeptide obtained by X-ray analysis.

Introduction

Proteins, containing large regions of β-sheets, play an important functional role in various regulation and recognition processes of living organisms. Examples are electron transport processes, transport of vitamins and hormones in the serum or the transcription of DNA [1]. Even the quaternary structure of complex proteins is determined by intermolecular β-sheet arrangements. The transformation of α-helix domains of prion proteins into β-sheets is potentially causing the Scrapie and BSE disease [2]. Depending on the orientation of neighbouring strands, β-sheets are found either parallel or antiparallel (Fig. 1).

Force field energy minimization studies suggest that the antiparallel β-sheets are slightly more stable than their parallel counterparts [3]. This work reports the semiempirical approach to the problem using the quantum mechanical method AM1 [4,5]. Is there a significant energetic difference between parallel and antiparallel β-sheets when they are calculated with quantum mechanical programs?

Method and models

The β-sheet secondary structures were modelled using three different systems. To meet the requirements of a realistic model system, β-strands with protection groups at both ends of the peptide chain were used. A single β-strand with fixed dihedrals $\Phi = -109.4°$ and $\Psi = 151.9°$ was used to reflect the computational trends within one chain. Two single strands dimerize, forming parallel or antiparallel β-sheets. These β-sheets were optimized in all degrees of freedom including the Φ and Ψ angles. The dimerization energies allow one to estimate the relative stabilities of the parallel and the antiparallel system. All these calculated structures are, however, artificial and are not found as isolated units in biological systems. Recently [6–8], it was reported that cyclic peptide structures made of an even number of D,L-alternating amino acid residues tend to form β-sheet-like dimers (Fig. 2). These are excellent model systems for pure parallel and antiparallel β-sheets without the disturbance of end groups.

To compute β-sheet forming energy of single strands or cyclopeptides, we have chosen the following procedure. First, the heats of formation for the dimers of Ac-$(Gly)_n$-NHMe, Ac-$(Ala)_n$-NHMe (n = 1–11), cyclo[-(D-Ala-N^2-Me-L-Ala)$_4$-] and cyclo[-(L-Ala-N^2-Me-D-Ala)$_4$-] were computed with AM1. The optimized dimers were then separated and the single point energies for the resulting monomers were also calculated with AM1. The difference between the heat of formation of the dimeric and monomeric

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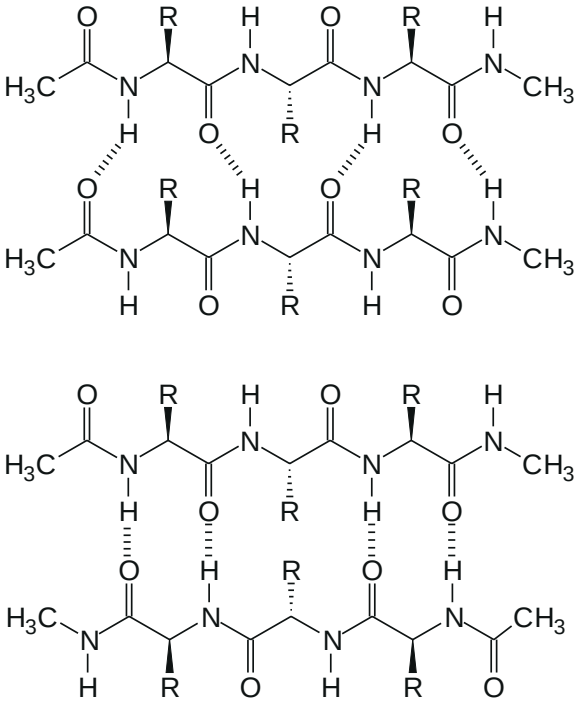

Fig. 1. Examples of a parallel (top) and an antiparallel (bottom) peptidic β-sheet formed by adjacent protected amino acids.

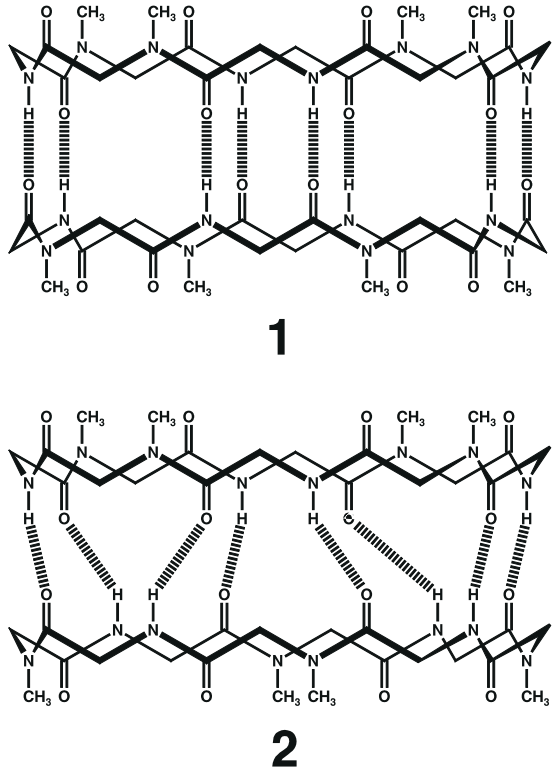

Fig. 2. Dimeric, partially N-methylated cyclooctapeptides cyclo-D,L-$(Ala)_8$, model systems for antiparallel **1** and parallel **2** β-sheets. The alanine side chains are not shown for clarity.

species is taken as a probe for the stabilization energy due to the formation of the intermolecular hydrogen bonds.

All calculations were carried out on a CONVEX C220 and an SGI-RX4 workstation using the VAMP 5.0 package [4] for the AM1 calculations [5]. (The default EF optimizer implemented in VAMP 5.0 stops at 0.4 kcal mol^{-1} $Å^{-1}$ as gradient.) The geometry of the amide bonds was optimized and not restrained to planarity by a molecular mechanic potential (as it is implemented in MOPAC [9]).

Results

A single peptidic chain in β-sheet conformation

The heat of formation of a single peptide chain increases linearly, when the number of amino acid residues fixed in β-sheet conformation at the angles Φ and Ψ is increased. The energy gain per amino acid remains con-

TABLE 1
DIMERIZATION ENERGIES (ΔH_{dim}) AND DIMERIZATION ENERGIES PER HYDROGEN BOND ($\Delta H_{dim}/m$) FOR PARALLEL (p) AND ANTIPARALLEL (ap) β-SHEETS FORMED BY TWO ADJACENT AMINO ACID STRANDS (PROTECTED GLYCINE OR ALANINE STRANDS)

Number of residues per strand	Number of hydrogen bonds	ΔH_{dim} (kJ/mol)				$\Delta H_{dim}/m$ (kJ/mol)			
		Gly ap	Gly p	Ala ap	Ala p	Gly ap	Gly p	Ala ap	Ala p
1	2	–43.63	–43.35	–44.39	–43.56	–21.82	–21.69	–22.20	–21.78
2	3	–55.22	–55.26	–54.63	–54.93	–18.39	–18.43	–18.22	–18.31
3	4	–78.96	–74.24	–75.20	–70.56	–19.73	–18.52	–18.81	–17.64
4	5	–93.55	–93.72	–86.94	–90.25	–18.73	–18.73	–17.39	–18.06
5	6	–115.58	–114.57	–102.12	–108.60	–19.27	–19.06	–17.01	–18.10
6	7	–134.47	–129.87	–111.31	–123.77	–19.19	–18.52	–15.88	–17.68
7	8	–129.87	–147.51	–142.04	–140.82	–16.22	–18.43	–17.77	–17.60
8	9	–166.82	–163.77	–158.17	–157.29	–18.52	–18.18	–17.56	–17.47
9	10	–190.50	–185.73	–[a]	–[a]	–19.26	–18.59	–[a]	–[a]
10	11	–202.85	–201.21	–[a]	–193.26	–18.42	–18.30	–[a]	–17.58
11	12	–221.94	–220.10	–210.42	–213.11	–18.46	–18.34	–17.54	–17.75

[a] Convergence not achieved.

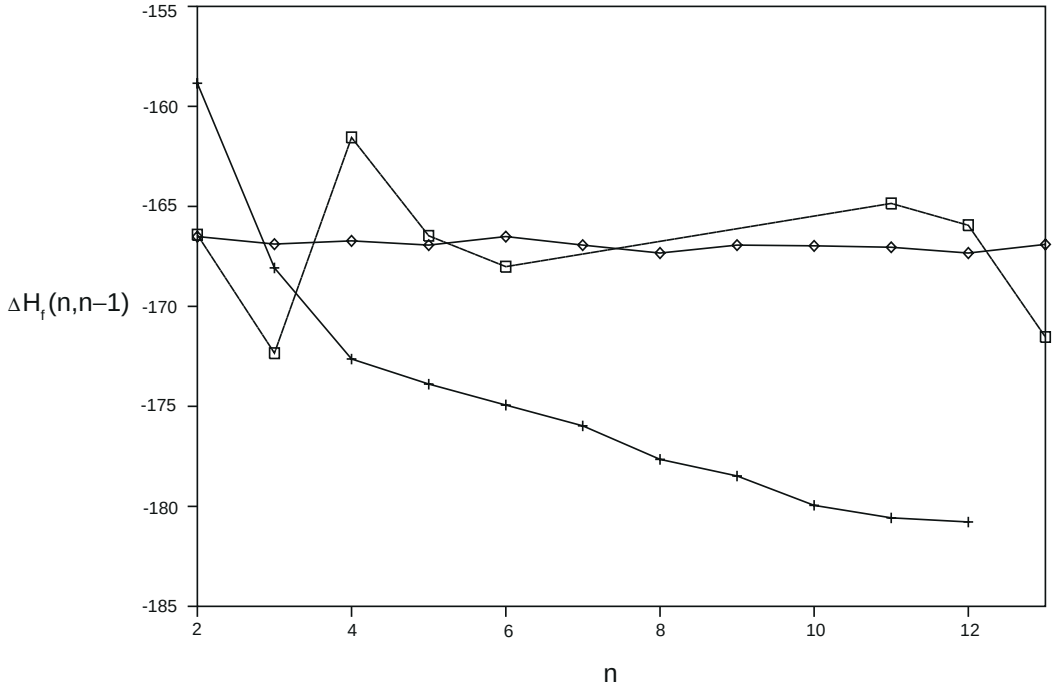

Fig. 3. $\Delta H_f(n,n-1)$ (kJ/mol) versus alanine chain length n; $\Delta H_f(n,n-1) = H_f(n) - H_f(n-1)$. $H_f(n)$: heat of formation of Ac-$(Ala)_n$-NHMe; $\Delta H_f(n,n-1)$: difference in the heat of formation between $(Ala)_n$ and $(Ala)_{n-1}$. Cross: chain in a fixed α-helix conformation; diamond: chain in a fixed β-sheet conformation; square: chain in β-sheet conformation, completely optimized.

stant at longer chains (Fig. 3). Complete geometry optimization gives some scattering of the dashed line in Fig. 3. The systems are optimized to local minima with different Φ and Ψ angles. However, systems in an α-helical conformation show strong stabilization at longer chain lengths due to the formed intramolecular hydrogen bonds [10].

Two peptide chains forming parallel or antiparallel β-sheets

The dimerization of two single chains in β-sheet conformation gives a β-strand. To get a realistic model system, we investigated model β-sheets (Fig. 1) with optimization of all degrees of freedom. Glycine and alanine polypeptides with up to 11 amino acid residues per strand were used. The obtained systems match the geometrical properties of naturally occurring systems quite well. AM1 even reproduces the well-known 'twist of the β-sheet' (Fig. 4). Table 1 summarizes the energies of the dimerization reaction (ΔH_{dim}).

The dimerization energy per hydrogen bond (ΔH_{dim}/m in Table 1) is nearly identical in the parallel and in the antiparallel geometry. For example, Ac-$(Gly)_{11}$-NHMe-parallel yields an energy gain of –18.34 kJ/mol per hydrogen bond and Ac-$(Gly)_{11}$-NHMe-antiparallel gives –18.46 kJ/mol. The dimerization of the alanine strands is slightly less exothermic than that of the corresponding glycine residues.

Dimeric cyclopeptides as models for parallel and antiparallel β-sheets

The heats of formation for the partially N-methylated cyclo-D,L-$(Ala)_8$ peptide dimers (Fig. 2) were also calculated optimizing all degrees of freedom. The difference ΔH_{dim} between the heat of formation of the dimeric and

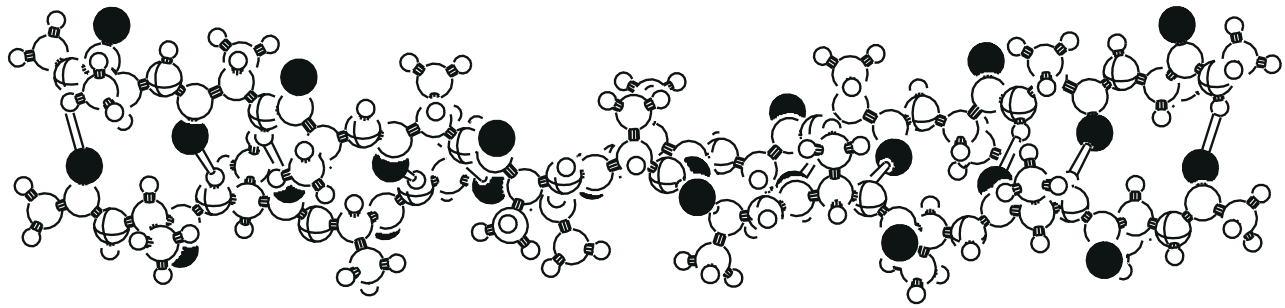

Fig. 4. β-Sheet formed by two adjacent Ac-$(Ala)_{11}$-NHMe strands, optimized with AM1 using the VAMP 5.0 package illustrating the twist of larger β-sheets.

TABLE 2
AM1 CALCULATED ENERGETIC DATA FOR THE β-SHEET MODELS **1** AND **2**

Compound	H_{fd} (kJ/mol)	H_{f2} (kJ/mol)	H_{f1} (kJ/mol)	ΔH_{dim} (kJ/mol)	$\Delta H_{dim}/8$ (kJ/mol)
1	−2472.47	−1175.29	−1175.25	−121.97	−15.26
2	−2472.60	−1175.08	−1174.74	−121.81	−15.34

H_{f1}, H_{f2}: single point energies of the isolated cyclopeptides; H_{fd}: heat of formation of the hydrogen bonded dimer; ΔH_{dim}: reaction energy for the dimerization; $\Delta H_{dim}/8$: stabilization energy per hydrogen bond.

the monomeric cyclopeptide (Table 2) is a probe for the stabilization energy due to the formation of intramolecular hydrogen bonds and may be compared with the hydrogen bonding increments in Table 1. The dimerization energy of parallel arrangements is again nearly identical to the dimerization energy in antiparallel systems (the parallel β-sheet **2** is favoured by only 0.13 kJ/mol (Table 2, Fig. 5)). The heat of formation H_{fd} is also identical for the two different ensembles. Experimental data suggest that the energy difference between the two types of β-sheets is very small. NMR studies of partially N-methylated derivatives of cyclo-D,L-$(Ala)_4(Phe)_4$ peptide in $CDCl_3$ solution favour the antiparallel structure by 3.36 kJ/mol [6].

The AM1 calculations reproduce the geometries of the X-ray data of Ghadiri et al. [6] quite well. The mean distances ($r_{N\cdots O}$(exp) = 2.90 Å; $r_{N\cdots O}$(calc) = 2.96 Å) of the hydrogen bonded atoms are similar and the root-mean-square (rms) deviation between the coordinates of the backbone atoms of the calculated and the experimental structure, which was calculated using MacroModel, is only 0.223 Å [11]. To compare the calculated and the experimental structure, we used the RIGSA option. All backbone atoms, as well as all N-methyl groups, have been considered. The carbonyl oxygens not involved in hydrogen bonding have been ignored, because their coordinates are disordered in the X-ray structure [6]. The close similarity between experiment and calculation is surprising as solvent, side-chain effects and entropic contributions have not been considered in the computations. Test calculations on the complexation properties of systems **1** and **2**, which were proposed as models for ion channels as well [12], indicate that there is no disruption of the β-sheet-like structure owing to complexation. However, there are significant differences in the complexation energies ΔH_c for **1** and **2** encapsulating organic molecules: [host]/[guest]//ΔH_c (kJ/mol) = **1**/pyridine//−7.02; **2**/pyridine//−5.89; **1**/triazine//−10.87; **2**/triazine//−12.58; **1**/1,3-cyclopentadion//−14.25; **2**/1,3-cyclopentadion//−12.96; **1**/imidazol//−22.11; **2**/imidazol//−21.69; **1**/imidazol anion//−30.10; **2**/imidazol anion//−32.06; **1**/nicotin//−8.41; **2**/nicotin/−6.44.

Discussion and Conclusions

The calculations of model systems provide a stabilization energy per hydrogen bond of about −18 kJ/mol for a parallel β-sheet as well as for an antiparallel β-sheet. The calculations give, however, no final answer to the question whether the parallel or the antiparallel β-sheet structure is more stable. Gas-phase structures of parallel and antiparallel model systems were calculated and were found to be very close in energy. The computed energy differences of less than 4 kJ/mol are not significant when one attempts to predict the behaviour of real β-sheets. Nevertheless, AM1 is a powerful tool to reproduce experimental geometries. The coordinates of the calculated structure of the cyclooctapeptide dimer **1** have an rms deviation of only 0.223 Å to the coordinates of a corresponding cyclopeptide obtained by X-ray analysis.

The free energy difference including entropic contributions is unknown; the size of the systems prevents any

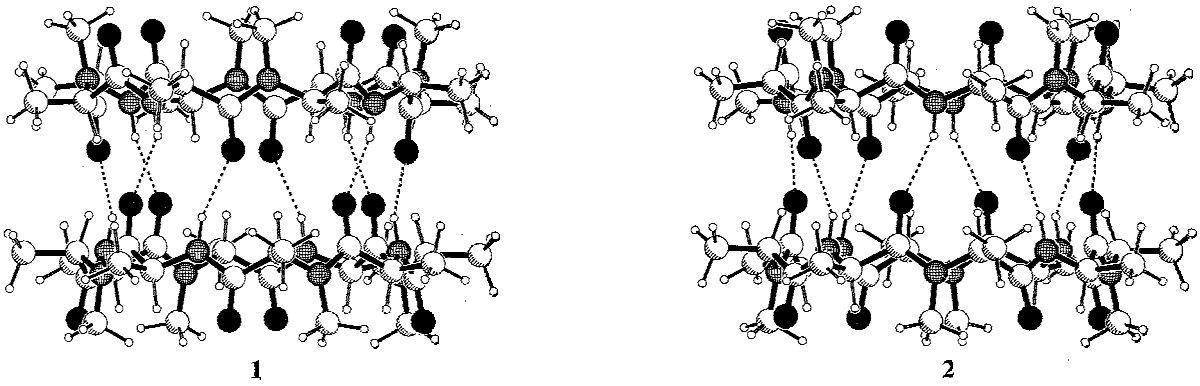

Fig. 5. Ball and stick models of the calculated structures of **1** and **2**; hydrogen bonds dashed.

quantum mechanical frequency calculations with the capacity resources available today. The authors of Ref. 5 demand a 100-fold increase in the speed of computers to be able to describe large organic ensembles. Another problem is that solvent effects on our systems cannot be studied even in the continuum approximations with the present versions of semiempirical programs. The major limitation is again the size of the model system. However, the present study shows that AM1 is well suited to describe the geometric properties of large polypeptidic systems, especially the formation and fixation of the hydrogen bonds in β-sheet conformation.

It is therefore wise to use AM1 in studying the complex peptidic units of enzymes and other amino acid containing natural products. The quantum mechanical treatment of large peptidic systems will be necessary if one attempts to describe chemical reactions within enzymes. AM1 may be a good compromise, providing a quantum mechanical treatment and a reasonable description of large hydrogen bonded systems at affordable computational requirements.

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