THE SPACE STRUCTURES OF α-MELANOTROPIN

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1. Introduction

The study of conformation–function relationships in biologically active peptides requires a detailed knowledge of their space structure. Semi-empirical conformational analysis is one of the methods providing the necessary information [1–4]. This communication describes the set of low-energy structures of α-melanotropin (α-MSH) peptide backbone determined by that method. α-MSH (Ac-Ser_1–Tyr_2–Ser_3–Met_4–Glu_5–His_6–Phe_7–Arg_8–Trp_9–Gly_{10}–Lys_{11}–Pro_{12}–Val_{13}–NH_2) is the natural oligopeptide which in many respects can be regarded as a natural analogue of corticotropin (ACTH).

2. Methods and results

The intramolecular conformational energy U involved the non-bonded, electrostatic and torsional potentials along with the hydrogen bond potentials [4]. The ionogenic side chains of the molecule (Glu, Arg, Lys) are assumed completely ionized [5]. The sets of local energy minima of the peptide backbone, i.e., B ($\varphi \sim -140°$, $\psi \sim 140°$), R (φ $-60°$, $\psi \sim -60°$), L ($\varphi \sim 60°$, $\psi \sim 60°$) and H (for the Gly_{10} residue; $\varphi \sim 80°$, ψ $-80°$) conformations and all the $\chi_1 \sim 60°$, $180°$, $-60°$ angle rotamers were considered as possible molecule conformations. The values of dihedral angles χ_2–χ_4 were chosen in accordance with the calculation results obtained for tha appropriate monopeptides [6]. The principal steps involved in the selection of low-energy backbone structures are as follows:

(1) Determination of the set of low-energy backbone structures for molecule fragment 1–6 using the conformational energy U calculations for all possible di- and tripeptide conformations and consecutive estimation of 'near-neighbouring' interaction energies in tetra-, penta- and hexapeptide fragments (see [2]). The final stage involves the refinement of side chain spacing for each of the selected hexapeptide backbone structures using an algorithm for the selection of energetically optimal dihedral angles χ [7]. As a result, 46 backbone structures of fragment 1–6 were found to meet the requirement $\Delta U = U - U_{min} \leqslant 10$ kcal/mol.

(2) The preliminary evaluation of the ionized group electrostatic interaction energy, E^{el}, and the energy of 'near-neighbouring' interactions in the backbone, E^{b}, resulted in ~750 structures of the fragment 5–11 backbone for which $\Delta(E^{b} + E^{el}) \leqslant 20$ kcal/mol. At the same time, only 84 of them appear to satisfy the criterion $\Delta U \leqslant 15$ kcal/mol, as judged by the results of energy U calculations for the structures of the 'model fragment': Glu–Ala–Ala–Arg–Ala–Gly–Lys. The optimal backbone conformations of fragment 12–13 have been determined for each of the 84 structures based on the calculation results for the fragment 7–13 (selection of the backbone structures satisfying the criterion $\Delta U \leqslant 10$ kcal/mol according to the scheme: 8–11 → 8–13 → 7–13 accompanied by the refinement of the side chain spacing at each step). This was followed by the determination of 34 backbone structures for the fragment 5–13 which meet the requirement $\Delta U \leqslant 15$ kcal/mol when the side chains are optimally spaced.

(3) All the possible variants of the fragment 1–4 backbone contained in the earlier selected set of fragment 1–6 backbone structures were examined for each of 34 backbone structures of fragment 5–13 at the level of complete α-MSH molecule. The final step of the calculations including the refinement of side chain spacing led to the selection of 36 (out of > 200 calculated) types of low-energy backbone structures of α-MSH ($\Delta U \leqslant 12$ kcal/mol). Table 1 demonstrates

structures characterized by the optimal backbone conformation of fragment 1 4 with respect to backbone structure of fragment 5–13. Structure 1 from table 1 is depicted in fig.1.

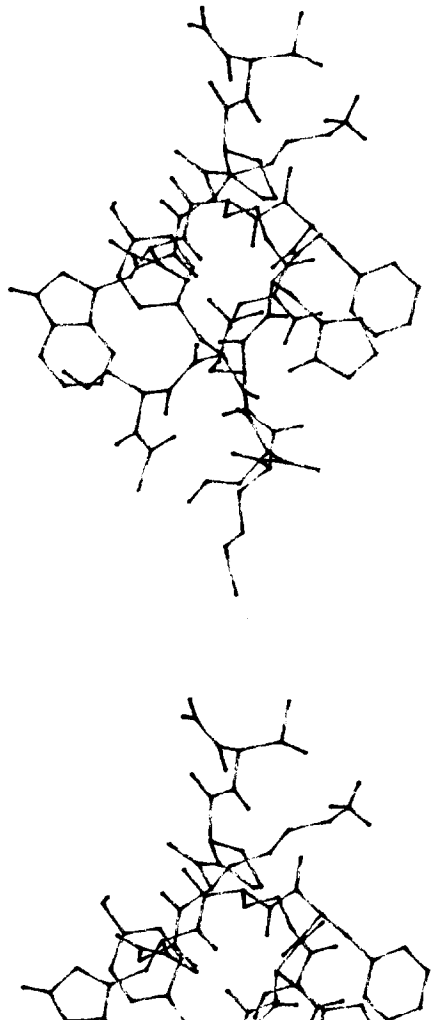

Fig.1. The α-melanotropin structure with lowest energy.

3. Discussion

The most remarkable feature of the structures presented in table 1 is the close spacing of the side chains of Glu_5 and Arg_8 residues. At the same time,

Table 1
The set of low-energy α-MSH structures

Residue	Angle	Backbone structures 1	2	3	4	5	6	7	8	9	10	11	12	13
Ser	φ	-106	-128	-124	-99	-126	-119	-133	-133	-118	-121	-111	-119	-123
	ψ	145	126	120	142	118	155	142	136	154	111	-42	154	132
	χ_1	61	-64	-62	61	-63	177	-178	-179	176	179	176	176	-179
	χ_2	179	180	175	179	176	162	180	180	161	178	172	162	180
Tyr	φ	52	-136	-140	49	-142	-128	-132	-145	-118	-139	48	-121	-132
	ψ	30	-55	-53	31	-53	11	142	166	10	-56	31	12	108
	χ_1	-57	-42	-60	-58	-58	-81	-162	59	-78	-57	-61	-80	-40
	χ_2	89	96	97	101	97	93	79	88	90	97	97	92	96
	χ_3	-86	-97	-93	-84	-93	-83	-88	84	-83	-97	-95	-83	87
Ser	φ	-151	-107	-97	-144	-107	-114	-128	-101	-115	-130	-142	-114	-160
	ψ	-53	-34	-35	-50	-33	-37	142	-32	-30	-48	-53	-31	-53
	χ_1	50	58	57	51	58	47	-178	57	52	55	180	50	54
	χ_2	180	179	178	180	178	179	-175	179	179	177	180	179	180
Met	φ	-102	-127	-124	-113	-121	-105	-137	-143	-104	-127	-142	-105	-127
	ψ	-49	158	153	-47	110	-36	132	149	-41	156	101	-40	141
	χ_1	-83	-160	-160	-81	-156	-83	-101	-160	-64	-81	-80	-61	-80
	χ_2	80	-178	-161	81	178	81	180	-160	161	81	180	160	80
	χ_3	-177	173	168	-177	178	-178	180	175	-177	-178	-179	-178	171
Glu	φ	-119	-105	-109	-135	-152	-114	-133	-133	-113	62	-140	-114	65
	ψ	128	145	120	132	144	131	122	127	134	152	150	133	133
	χ_1	-126	-122	-168	-136	57	-161	-156	-160	-159	-74	-76	-161	-172
	χ_2	-71	-73	169	-66	-67	-94	-99	-101	-98	-175	-177	-97	-150
	χ_3	75	92	80	89	104	85	86	91	92	85	84	86	80
His	φ	-166	-150	-113	-153	-71	-131	-148	-150	-136	-102	-94	-135	-104
	ψ	39	43	-36	59	-22	116	49	39	107	-32	-33	110	-28
	χ_1	40	-39	-41	40	75	-44	-58	40	-42	60	60	-40	60
	χ_2	-82	85	81	-80	80	-61	81	-80	-81	-80	-81	-80	80
Phe	φ	-122	-137	-138	-144	-53	31	-116	-110	34	-142	-141	34	-37
	ψ	-46	-54	143	-49	-35	78	-41	-41	83	140	136	83	-44
	χ_1	-58	-76	42	-76	-74	-61	-42	-40	-57	179	-177	-58	-80
	χ_2	99	93	87	100	97	92	101	104	91	81	81	97	96
Arg	φ	-117	-112	-96	-118	-92	-140	-103	-105	-135	-134	-136	-137	-123
	ψ	-49	-44	-10	-47	-53	-54	-46	-40	-60	144	144	-55	140
	χ_1	-70	-78	-66	-73	-73	-78	-67	-73	-70	-76	-76	-71	-78
	χ_2	145	143	-165	143	-174	-177	161	170	-173	174	171	-174	153
	χ_3	-80	-81	171	-81	-154	-139	-151	-78	-160	170	173	-159	-78
	χ_4	104	109	-84	105	145	140	89	111	143	126	144	144	-90
Trp	φ	-116	-114	-107	-81	-154	-128	-153	-141	-135	-133	-136	-130	-117
	ψ	146	152	129	-47	144	150	145	143	-54	140	132	127	-49
	χ_1	178	-175	40	178	-178	178	180	-79	-41	59	61	-19	-60
	χ_2	77	83	85	-100	68	83	-101	-78	-76	98	97	101	-81
Gly	φ	56	82	63	-73	-45	56	-66	-54	-59	47	44	88	-82
	ψ	51	-65	51	-38	103	32	99	-27	-31	46	53	-43	76
Lys	φ	-109	-130	-105	-124	-135	-146	-123	-111	-125	-132	-131	-86	-143
	ψ	135	102	130	113	136	143	111	146	140	142	121	137	133
	χ_1	-163	-70	-162	-67	-72	-71	-62	-76	-61	-73	-72	-55	54
	χ_2	179	175	-171	162	162	147	163	180	94	170	178	156	-171
	χ_3	-172	-173	166	-169	-171	-162	-169	180	-139	-173	-175	-157	-177
	χ_4	167	177	-175	165	172	175	164	180	171	179	-177	164	-169
Pro	φ	-32	119	-32	128	-30	-31	-39	110	140	-28	-35	129	-40
Val	φ	-109	-137	-106	-123	-120	-110	-124	-134	-118	-106	-109	-119	-117
	ψ	129	132	132	132	137	143	137	134	133	138	129	133	129
	χ_1	-178	176	180	-179	-179	-177	-178	178	-176	-177	-179	-175	-178
ΔU, kcal/mol		0.0	4.4	5.0	5.0	5.4	6.6	6.7	7.0	8.0	9.3	9.8	10.9	11.2
Interatomic distances, Å	C^{α}_{Glu}-C^{α}_{Arg}	3.3	3.3	3.8	3.4	3.1	5.3	4.4	3.4	5.5	4.0	4.1	5.5	3.7
	C^{ϵ}_{Glu}-N^{ζ}_{Lys}	8.8	10.9	3.5	8.5	4.4	2.9	3.8	12.4	3.4	3.5	3.5	3.0	3.6
	C^{β}_{Tyr}-C^{β}_{Trp}	9.5	9.9	10.7	9.3	6.5	7.3	13.7	7.6	7.6	9.7	5.7	7.5	10.3
Structure of fragment 6-9 backbone		BRRB	BRRB	RBRB	BRRR	RRRB	BLRB	BRRB	BRRB	BLRR	RBBB	RBBB	BLRB	RRBR

Dihedral angle values in accordance with [14]

the side chain of lysine is in many cases directed 'outside' the fragment 6–9 (e.g., fig.1) which can acts as the 'active centre' of the molecule and allegedly provides direct binding to specific receptors [8]. This peculiarity of the molecule's space organization agrees well with the high melanotropic activity of α-MSH analogues, where Lys_{11} is substituted by Nle, Ser or even Gly [9,10]. Furthermore, it can elucidate the reasons for the drop in lipolytic activity found for ACTH 2–19 analogues with cystine bridges of (2,10), (3,10) or (5,10) type [11]. Typically, the data in table 1 frequently imply the retention of BRRB or BRRR structures for the fragment 6–9 backbone, thus indicating considerable conformational rigidity of this 'active centre'.

The data given in table 1 are also in keeping with the results of physico–chemical studies on the ACTH space structure which indicate the presence of α-helix elements [12] in the peptide backbone as well as with the estimation of experimental values (~10 Å) found for the distance between the side chains of Tyr_2 and Trp_9 residues [13]. Consequently, it can be assumed that the set of low-energy conformations found in this study contains sufficient information concerning the main features of α-MSH space organization and can be therefore applied to the study of conformation–function relationships for α-melanotropin and adrenocorticotropin.

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