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The path of a protein chain can be approximated by the conformation dictated by interpeptide ionic bridges

Valery I. Lim, Česlovas Venclovas* and Natalya A. Kurochkina

Institute of Protein Research, Russian Academy of Sciences, 142292 Pushchino, Moscow Region, Russia

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A stereochemical simulation of the formation of ionic bridges between adjacent peptide groups along the polypeptide chain has been made. Such ionic bridges constrain the amino-acid residues into eight conformations. It is shown that the path of any protein-chain fragment 10–15 residues long can be approximated well by these conformations. This suggests that the conformations dictated by the ionic bridges can be used as blocks in the formation of the spatial protein structure.

Ionic bridge; Bridge conformation; Protein structure

1. INTRODUCTION

The attainment of the native conformation of proteins both in vivo and in vitro occurs in the presence of ions. At the same time it is known that a wide variety of metals form complexes with amides, by interacting with their oxygen and nitrogen atoms [1–4]. X-ray data also indicate the existence of interactions between ions and the polar atoms in the native structure of proteins [5–7]. The question arises as to the role of interactions between ions and the polypeptide chain during the formation of the spatial structure of proteins.

2. BRIDGE CONFORMATIONS

We have begun consideration of this question with a stereochemical simulation of the formation of ionic bridges between neighbouring peptide groups along a polyglycine chain. The ionic bridges O–I^+–O, O–I^+–N, N–I^+–O and N–I^+–N were considered. Here I^+ indicates a monovalent or divalent cation of radius 0.7–1.3 Å (Na^+, K^+, Mg^{2+}, Ca^{2+}), and O and N are the oxygen and nitrogen atoms of a peptide group serving as ligands. The nitrogen of a peptide group was considered as a ligand because there are indications that this atom can form complexes with cations. For example, a complex of Ag^+ linked to the nitrogen of *N,N*-dimethylacetamide actually exists in aqueous solutions [3]. The ab initio computations [4] also show the possibility of the existence, besides the classical cation–oxygen adduct, of a second relatively stable product in which the cation assumes a bridged position between the two heteroatoms of the peptide bond.

Since the nitrogen atom of a peptide group can serve as a ligand only in the pyramidal state [4], the I^+–N bond was oriented approximately at right angles to the plane of a peptide group. Small departures from planarity of a peptide group induced by the pyramidalization of the nitrogen atom were ignored. Only those variants of ionic bridges were considered in which dehydration of the peptide NH-group is not observed, and where the ion can be tetrahedrally and octahedrally coordinated by ligands.

The ionic bridges satisfying the above requirements are given in Table I. These ionic bridges constrain the amino acid residues into eight different possible conformations which can be divided into the symmetric groups $\alpha, \beta, \tau, \rho$ and $\alpha', \beta', \tau', \rho'$. The structure of the polypeptide chain will be called the **'bridge'** structure or **bridge** conformation if each residue is in one of these eight conformations.

Analysis of the bridge conformations led to an unexpected result. It appears that the path of a protein chain (the positioning of the C^α atoms and orientations of their C^α–C^β bonds) can be approximated by the bridge conformations, for the most part composed of conformations of the α, β, τ and ρ group (Figs. 1 and 2). It may be seen from Fig. 2 that the path of a chain fragment 10–15 residues long in bovine pancreatic trypsin inhibitor [8] (a popular protein with researchers, containing a wide variety of amino-acid conformations) is well approximated by the bridge conformation. As a rule, the distances between the C_i^α atoms of the native structure and the C_i^α atoms of the bridge structure do not exceed

Permanent address: Institute of Applied Enzymology, Fermentu 8, Vilnius, 232028, Lithuania. Fax: (7) (0122) 642 624.

Correspondence address: V.I. Lim, Institute of Protein Research, Russian Academy of Sciences, 142292 Pushchino, Moscow Region, Russia. Fax: (7) (095) 975 2014.

	ρ	τ	τ	τ	τ	β	ρ	β	β	α	ρ′	τ	β	τ
φ	-61	-63	-64	-65	-92	-79	-60	-63	-121	-72	89	-82	-84	-108
ψ	148	-28	-23	-16	-8	147	155	145	110	-40	179	-3	155	21
ARG	PRO	ASP	PHE	CYS	LEU	GLU	PRO	PRO	TYR	THR	GLY	PRO	CYS	LYS
				5					10					15
ρ	β	β	ρ	ρ′	β	β	β	β	α	α	β	α	ρ	β
-76	-129	-109	-83	-129	-102	-136	-86	-96	-66	-71	-94	66	-141	-87
168	86	117	122	168	149	155	121	99	-24	-38	-18	33	157	133
ALA	ARG	ILE	ILE	ARG	TYR	PHE	TYR	ASN	ALA	LYS	ALA	GLY	LEU	CYS
				20					25					30
β	β	ρ	β	β	ρ	α	ρ	α′	β	ρ	τ	τ	β	β
-134	-89	-151	-98	-95	-81	105	-146	61	-56	-105	-75	-90	-159	-134
164	156	166	115	136	-9	-7	158	41	150	180	-30	71	115	153
GLN	THR	PHE	VAL	TYR	GLY	GLY	CYS	ARG	ALA	LYS	ARG	ASN	ASN	PHE
				35					40					45
α	β	α	α	α	α	α	α	α	τ	β	β			
-88	-141	-62	-67	-66	-58	-65	-60	-82	-114	-88	-164			
-17	151	-33	-46	-39	-52	-43	-37	-42	-16	-167	-138			
LYS	SER	ALA	GLU	ASP	CYS	MET	ARG	THR	CYS	GLY	GLY	ALA		
				50					58					

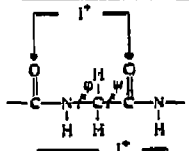
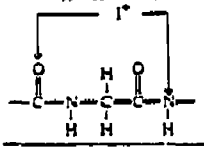
Fig. 1. Bridge structures for bovine pancreatic trypsin inhibitor. The native structure is represented by the angles φ (deg) and ψ (deg).

3 Å (the length of two C–C bonds), and the value $\Delta\alpha=|\alpha_n-\alpha_b|$ is less than 40°, where α_n is the angle between the bonds C_i^α–C_i^β and C_{i+1}^α–C_{i+1}^β in the native structure and α_b is the angle between these bonds in the bridge structure. A similar agreement has been observed for any chain fragment 10–15 residues long in all the proteins so far examined, regardless of their type. The following proteins (their Brookhaven Protein Data Bank codes [9] are given in parentheses) were considered: avian pancreatic polypeptide (1PPT), crambin (1CRN), lysozyme (1LYZ), ovomucoid third domain (2OVO), ribonuclease A (5RSA), rubredoxin (1RDG) and scorpion neurotoxin (1SN3). The bridge conformations for the fragments of the protein chains have been selected visually using a PS-390 computer graphics system (Evans and Sutherland).

As to the conformations of individual residues, a comparison of the angles φ and ψ of the native structures with the angles φ and ψ of the bridge structures showed that on the average they differ from one another by ±35°. However, all values of the angles φ and ψ in the bridge structures can be made equal or close to the native ones with a precision of $\Delta\alpha/2$, where $\Delta\alpha$ is less than 40° (see above). Achievement of this condition requires a synchronous rotation of the peptide group around the bonds C_i^α–C_i' (ψ_i angle) and N_{i+i}–C_{i+1}^α (φ_{i+1} angle), keeping the following rule: the changes in the angles ψ_i and φ_{i+1} should be equal in modulus but opposite in sign. Such a rotation will be called a $\psi_i\varphi_{i+1}$ rotation of a peptide group. Due to the parallelism of the bonds C_i^α–C_i', N_{i+1}–C_{i+1}^α and the small distance (~ 1 Å) between them, the $\psi_i\varphi_{i+1}$ rotation can be realized without a change in the angle between the bonds C_i^α–C_i^β and C_{i+1}^α–C_{i+1}^β and is accompanied by a displacement of the C_α atoms which does not exceed 1 Å, i.e. the $\psi_i\varphi_{i+1}$ rotation enables one to vary the angles φ and ψ over a wide range, with practically no change in the path of the polypeptide chain. It is precisely this property of the $\psi_i\varphi_{i+1}$ rotation that enables one to change the values of the angles ψ_i and φ_{i+1} in a bridge structure so that they only differ from the native ones, as a rule, by $\Delta\alpha/2<20°$. In particular, the angles φ and ψ in the bridge structures can be made close to the averaged ones given in the work of Rooman et al. [10].

Table I

Ionic bridges in the glycine dipeptide

Ionic bridges	Conformations of the glycyl residue which are maintained by the ionic bridges		
	φ (deg)	ψ (deg)	
	−60	−50	α
	+60	+50	α′
	−90 (−70)*	180	ρ
	+90	180	ρ′
	−90 (−70)*	0	τ
	+90	0	τ′
	−90 (−70)*	+120	β
	+90	−120	β′

*Proline can only adopt the bridge conformations α, β, τ, ρ with $\varphi=-70$ in ρ, τ and β.

3. DISCUSSION

The stereochemical stimulation shows that the native conformation of a protein chain can be obtained by selection of the appropriate bridge structure and subsequent $\psi_i\varphi_{i+1}$ rotations within it. It is evident that such a formal search for the native structure may will be close to the real process of formation of the spatial structure of a protein. Indeed, it would be expected that the protein chain will be in different bridge conformations as long as interactions between the amino acid residues (intramolecular hydrogen bonds, hydrophobic contacts, and others) are absent. The appearance of these interactions will be accompanied by $\psi_i\varphi_{i+1}$ rotations and destruction of ionic bridges in order to avoid dehydration of the polar atoms of peptide groups, immersion of cations in a hydrophobic core, or to form interpeptide hydrogen bonds, etc.

Ionic bridges cannot be formed at the surface of α helices and β sheets. Cations at these surfaces cannot be tetrahedrally or octahedrally coordinated by ligands because of steric restrictions. Ion bridges should not occur in irregular protein regions either. Conformations of most residues in these regions considerably differ from the bridge ones. Therefore $\psi_i\varphi_{i+1}$ rotations which destruct ionic bridges must occur in these regions. We can thus presume that virtually all ionic bridges are destroyed in the course of the formation of the spatial protein structure.

The above arguments indicate that the interpeptide

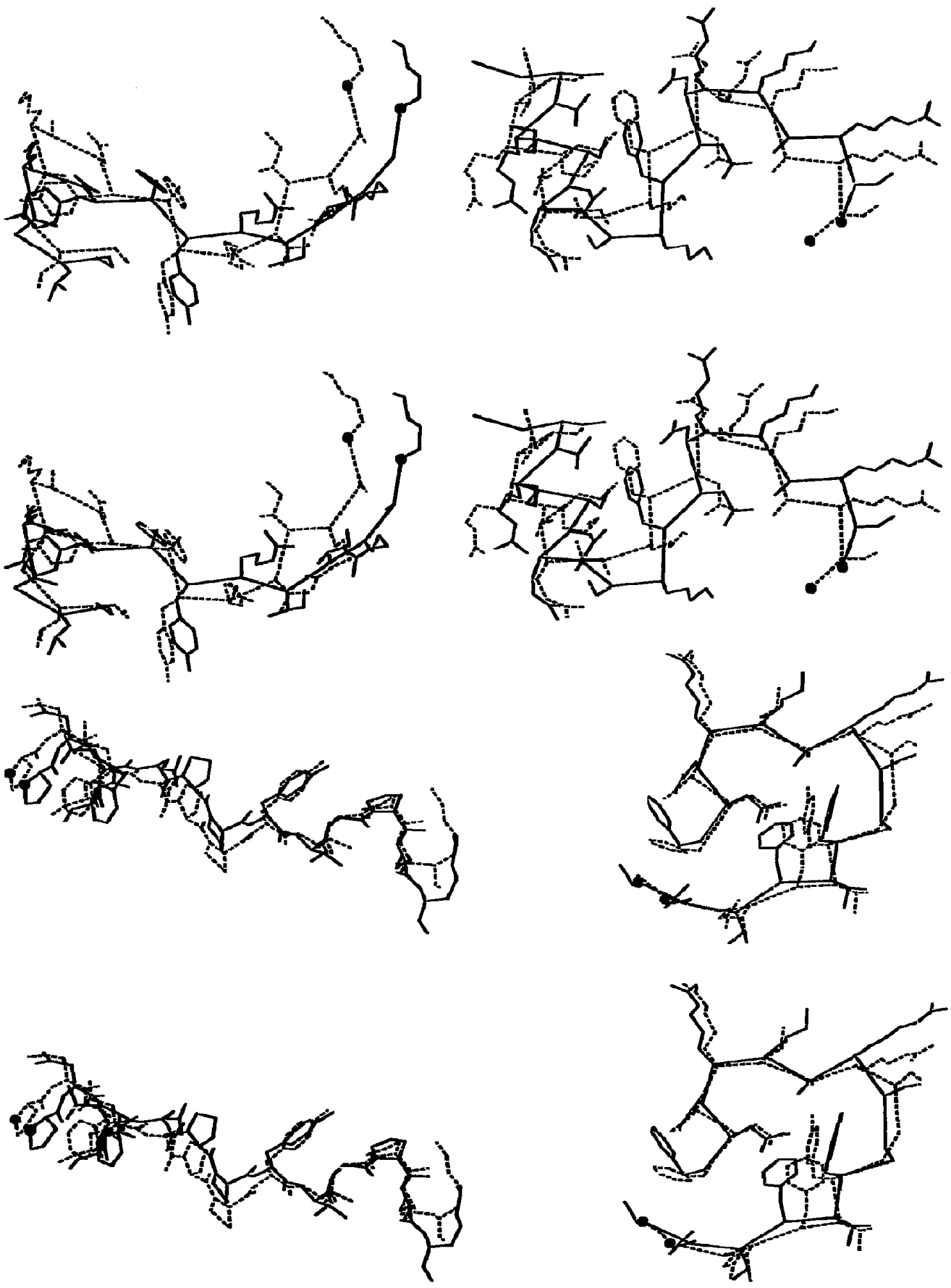


Fig. 2. Stereo views showing fragments of bovine pancreatic trypsin inhibitor in the native (solid lines) and the bridge (dashed lines) structures. Sport mark N ends of the fragments. The bond angles, ω angles, bond lengths, and conformations of side chains in both structures are the same. a, b, c, d are the fragments 2–15, 15–30, 30–45, and 37–57, respectively. Peptide groups are shown only in the fragment 2–15. In the other fragments only amino-acid residue side chains and C^{α} atoms joined with each other by straight lines are shown.

ionic bridges considered cannot be the elements stabilizing the protein 3D structure. Their main role is to form bridge structures which can be used as blocks in organization of this structure.

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