THEORETICAL CONFORMATIONAL ANALYSIS OF THE METHYLAMIDES OF N-ACETYL-L-ALANYL-L-PROLINE AND N-ACETYL-L-PROLYL-L-ALANINE. I.

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To develop a method for calculating the stable conformations of oligopeptides it is necessary to determine the possibility of the a priori prediction of the set of low-energy forms of a tripeptide fragment (n − 1, n, n + 1) on the basis of the completely known conformational states of the corresponding dipeptide fragments (n − 1, n and n, n + 1). In the case of a satisfactory answer to this question, real prospects are opened up of investigating the spatial structure of the peptide chain by studying the interactions between neighboring residues in the sequence.

The number of binary combinations of natural residues is comparatively small — 400 — and at the present time the complete conformational analysis of a dipeptide fragment is a comparatively simple task. The results of the calculation of dipeptides can be used in a study of the structure of any amino-acid sequences. The method may be of practical importance under two conditions. In the first place when the interactions between two adjacent residues lead to a substantial energy differentiation of the optimum forms of each of them and, in the second place, when the most preferred conformations of the tripeptide consist of combinations of the most preferred forms of the corresponding dipeptides. Encouraging results have already been obtained in relation to the first condition. The investigation was begun with an analysis of all the potentially possible conformations of molecules of the type Ac-X-X-NHMe (where X is Gly, L-Ala, or L-Val) [1]. Calculation showed the mutual conditionality of the conformational states of the two neighbouring residues. In the molecules where X = Gly and Ala it is caused mainly by the interaction of the main chains. Deviations from additivity appeared both in a considerable change in the geometric parameters and in the larger difference between the energies of the optimum forms than in the monopeptides. It was found that in the regular and irregular sections of proteins in the overwhelming majority of cases those linkages of the conformations of two residues are found that are predicted by calculating the isolated dipeptides as their most preferred conformations.

A complete conformational analysis of the Ac-L-Phe-L-Phe-NHMe molecule has recently been performed [2]. If the conformational states of the Phe residues were independent, the energies of the 36 optimum forms of the dipeptide should fall in the range between 0 and 1 kcal/mole. If interactions between the residues are taken into account, however, only two* come into this range, and nine conformations in the 0-2 kcal/mole range; the overall scatter of the energies amounted to 6 kcal/mole, with the energy being in the 3-6 kcal/mole range for half the conformations. An important role in the energy differentiation of the forms is due to the interaction of the side chains with one another and with the main chains of neighboring residues. Thus, even in the dipeptide fragment there is a considerable determinacy of the conformational states, i.e., the isolation in the residues of those low-energy forms that are best complemented by one another.

*One of these forms coincide with the structure realized in the crystal, according to x-ray structural analysis [3].

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The main task of the present investigation was to determine the possibility of describing the most favorable conformational states of a tripeptide on the basis of the known dipeptide conformations. With this aim, we have performed an analysis of the Ac-L-Ala-L-Pro-NHMe and the Ac-L-Pro-L-Ala-NHMe molecules, which have enabled us to evaluate separate influences of the preceding and following Ala (or Pro) residues on the conformational state of Pro (or Ala). Then we considered independently the conformational possibilities of the tripeptide Ac-L-Ala-L-Pro-L-Ala-NHMe in which an action on the state of the central Pro residue is exerted by Ala residues simultaneously from both sides.

The calculation of all the molecules was performed as applied to the conditions both of a polar and of a nonpolar medium. In the latter case, a considerable role in the tripeptide may also be played by hydrogen bonds of the 3→1, 4→1, and 5→1 types, and in the dipeptides by those of the 3→1 and 4→1 types.

As is well-known, in a protein chain a tertiary peptide group preceded by Pro is present in the trans configuration in the overwhelming majority of cases. However, this form possesses only a slight advantage in comparison with the cis configuration. Realization of the latter is extremely likely in linear [4-9], and particularly, cyclic [10-14] oligopeptides and polypeptides. Consequently, we performed the conformational analysis of the dipeptide and tripeptide molecules in two variants — with the trans and with the cis configuration of the peptide group preceding the proline.

The pyrrolidine ring of proline makes rotation round the N–C^{α} bond (φ) impossible. Numerous experimental results nevertheless show that the angle φ possesses some freedom and may assume various values according to the configuration of the Pro and of its environment [15]. In order to evaluate the dependence of the energy on the size of the angle φ of the Pro residue, all the calculations were performed with the variation of from −55 to −70° every 5°.

The present paper gives and discusses the results of a calculation of the Ac-L-Ala-L-Pro-NHMe and Ac-L-Pro-L-Ala-NHMe molecules.

Molecular Models and Potential Functions. Models of the dipeptide molecules with the symbols of the variable dihedral angles of rotation and an indication of the possible methods of forming intramolecular hydrogen bonds are given in Fig. 1. The length of the bonds and the valence angles have been taken as in the calculations of the methylamide of N-acetyl-α-methylalanine [16] and actinomycin [14].

In the calculation of the conformational energy of the molecules, contributions from nonvalent and electrostatic interactions, from frozen rotation round the valence bonds, and from the hydrogen bonds were taken into account. In the investigation of the conformational states in a polar medium, the formation of intramolecular hydrogen bonds was not considered.

The nonvalent interactions were calculated from the Lennard–Jones potential with Scott and Scheraga's parameters [17]. The methyl groups at the ends of the main chain were approximated by spheres with a diameter of 3.7 Å; the values of the parameters of the potential functions of the Lennard–Jones type describing the nonvalent interactions of these groups with other atoms were obtained in our laboratory.

The electrostatic energy was evaluated from the Coulomb law with the charges on the atoms suggested by Yan et al., [18] and by Momany et al., [19]; the dielectric constant ε in the calculation of the conformations with hydrogen bonds (nonpolar medium) was taken as 4, and in the calculation without hydrogen bonds (polar medium) as 10 [20]. The energy of the hydrogen bond was calculated from a potential of the Morse type with the parameters $D \approx 4$ kcal/mole and $r_0 = 1.8$ Å [21]. The torsional potentials and the values of the barriers to rotation around the bonds C^{α}–N (φ), C^{α}–C' (ψ), C'–N (ω), and C^{α}–C^{β} (χ) were taken as in a previous paper [21].

The parameters of the optimum forms were obtained by the minimization of the energy with respect to the angles of internal rotation ω_0, φ_1, ψ_1, ω_1, χ_1, ψ_2, ω_2 (Ac-L-Ala-L- Pro-NHMe) and ω_0, ψ_1, ω_1, φ_2, ψ_2, ω_2, χ_2 (Ac-L-Pro-L-Ala-NHMe). As the zero approximation we took all the combinations of the optimum forms of the free Ala and Pro residues known from the calculation of the Ac-L-Ala-NHMe, Ac-L-Ala-NMe_2, and Ac-L-Pro-NHMe [22, 23].

The symbols for the variables and the reckoning of the angles of rotation are in accordance with the IUPAC-IUB nomenclature [24].

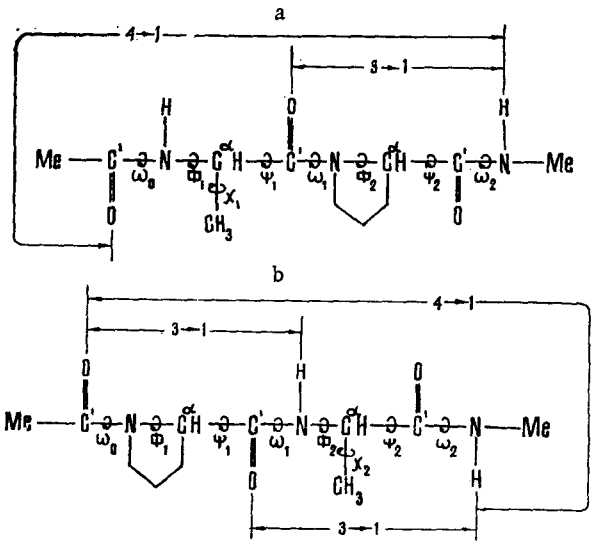

Fig. 1

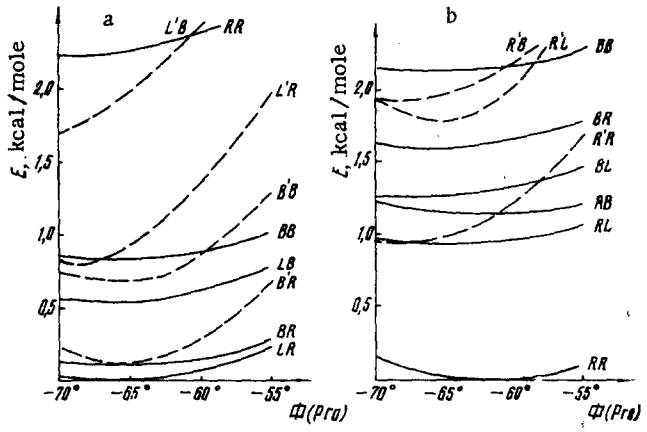

Fig. 2

Fig. 1. Calculation models of the methylamides of N-acetyl-L-alanyl-L-proline (a) and of N-acetyl-L-prolyl-L-alanine (b).

Fig. 2. Dependence of the energies of the conformations of Ac-L-Ala-L-Pro-NHMe (a) and Ac-L-Pro-L-Ala-NHMe (b) on the angle φ (Pro).

Methylamide of N-Acetyl-L-alanyl-proline. For the alanine monopeptide, the extended forms R and B located on the conformational map in the first quadrant ($\varphi = \psi = -180°$-$0°$) and in the second quadrant ($\varphi = -180°$-$0°$, $\psi = 0°$-$180°$), respectively, are the most suitable and approximately equivalent [22]. The optimum form L, the energy of which is approximately 1.5 kcal/mole greater than the energies of R and B, is located in the third quadrant ($\varphi = \psi = 0°$-$180°$). The form P from the first quadrant has an even higher energy. In the case of a tertiary group, according to a calculation of the dimethylamide of N-acetyl-L-alanine [23], the most preferred forms both with its trans and cis configurations are the B and L forms (the conformations with the cis configuration of the peptide group is denoted by the same letters with a prime: B' and L').

In the proline monopeptide there are only two extended conformations, R and B, with extremely close energies. But in the Ac-L-Ala-L-Pro-NHMe molecule with a fixed configuration

TABLE 1. Geometric and Energy Parameters of the Optimum Conformations of Ac-L-Ala-L-Pro-NHMe

Type of conformation	Angles of rotation, deg								Energy E_{tot}, kcal/mole	
	ω_0	φ_1	ψ_1	ω_1	χ_1	φ_2	ψ_2	ω_2	polar medium	nonpolar medium
				$\omega_1 \sim 180°$ (trans-)						
L—R	180	53	65	180	60	−65	−48	180	0	0
B—R	180	−66	152	178	59	−65	−43	180	0.1	−0.1
L—B	180	53	65	180	60	−65	115	180	0.6	0.2
B—B	180	−67	152	178	60	−65	127	180	0.9	0.5
R—R	−179	−57	−50	−178	25	−70	−38	180	2.3	2.1
R—B	180	−52	−44	176	59	−70	124	180	4.4	4.2
L—M	180	52	64	−179	60	−70	72	177	—	1.1
B—M	180	−66	151	180	60	−70	72	177	—	1.3
$\overbrace{\text{R—R}}$	−178	−49	−51	180	26	−55	−29	−178	—	2.1
R—M	180	−60	−49	−175	37	−70	74	177	—	4.0
				$\omega_1 \sim 0°$ (cis-)						
B′—R	−179	−167	89	2	58	−65	−43	−179	0.2	−0.1
B′—B	−178	−168	91	2	58	−65	140	177	0.7	0.3
L′—R	−180	53	86	7	60	−70	−39	−179	0.8	0.7
L′—B	−178	51	83	1	60	−70	147	179	1.7	2.0
R′—R	179	−48	−42	−33	30	−70	−24	179	7.3	6.9
R′—B	179	−47	−43	−32	32	−70	162	180	7.6	7.7
$\overbrace{\text{B′—R}}$	−179	−46	145	−3	59	−70	−7	−172	—	3.7
$\overbrace{\text{B′—B}}$	−172	−153	92	−4	59	−70	129	165	—	4.6
$\overbrace{\text{L′—R}}$	161	24	84	−5	59	−70	−33	−167	—	7.2

(trans or cis) of the central peptide group and with a constant value of the angle φ_2 of the proline, the number of initial approximations for minimization without taking hydrogen bonds into account was eight. In the first case, these are the R—R, R—B, B—B, etc., forms, and in the second case the R'—R, R'—B, B'—B, etc., forms.

In a conformational analysis of the dipeptide in relation to nonpolar media, the number of initial approximations rises because of the forms with intramolecular hydrogen bonds. However, with the trans configuration of the tertiary amide group, Pro can form the convoluted conformation M (second quadrant) with a hydrogen bond of the 3→1 type closing a seven-membered ring (Fig. 1a). This leads to the appearance of the R—M, B—M, etc., forms. In addition, in the case of the trans configuration of the peptide group in the dipeptide, 4→1 hydrogen bonds closing ten-membered rings of the forms $\overbrace{\text{R—R}}$, $\overbrace{\text{R—B}}$, and $\overbrace{\text{P—R}}$ are theoretically probable. With the cis configuration of the peptide group, the formation of the M form in the case of Pro becomes impossible, but the number of local minima with a hydrogen bond of the 4→1 type ($\overbrace{\text{L'—R}}$, $\overbrace{\text{B'—B}}$, $\overbrace{\text{B'—R}}$) rises. In the general case, the number of initial approximations including forms with hydrogen bonds is 15 for the trans and 15 for the cis configuration of the tertiary peptide group.

Table 1 gives the values of the geometrical and energy parameters characterizing the conformational possibilities of the Ac-L-Ala-L-Pro-NHMe molecule under the conditions of polar and nonpolar media. The top part of the table corresponds to the conformation of the dipeptide with the trans configuration of the peptide group ($\omega_1 \sim 180°$) and the bottom part to the cis configuration ($\omega_1 \sim 0°$). For each conformation the most preferred value of the angle φ_2 of the Pro residue (−55°, −60°, −65°, or −70° is given). Figure 2 a gives an idea of the sensitivity of the conformational energy of the molecule to the value of φ_2 for the case of the most favorable extended forms. Calculation shows that all the conformations of the dipeptide with the P form of the Ala residue have a very high energy (more than 20 kcal/mole), and they are therefore not included in Table 1.

The calculation of the methylamide of N-acetyl-L-alanyl-L-proline led to the conclusion that under the conditions of a polar medium forms having both the trans and the cis configuration of the central peptide group must be represented in considerable force. This result is confirmed by the experimental facts; the existence of forms with a cis-peptide group has

TABLE 2. Geometrical and Energy Parameters of the Optimum Conformations of Ac-L-Pro-L-Ala-NHMe

Type of conformation	Angles of rotation, deg								Energy E_{tot}, kcal/mole	
	ω_0	φ_1	ψ_1	ω_1	φ_2	ψ_2	ω_2	χ_2	polar medium	nonpolar medium
					$\omega_0 \sim 180°$ (trans-)					
R—R	180	—60	—48	—176	—61	—41	180	60	0	0
R—L	180	—65	—47	180	54	36	180	57	0.9	0.9
R—B	180	—65	—48	—178	—66	40	180	60	1.1	1.1
B—L	180	—70	111	—179	54	38	—179	57	1.2	0.8
B—R	180	—65	135	—179	—59	—41	180	60	1.6	1.5
M—M	—179	—70	72	178	—70	65	179	60	—	1.6
B—B	180	—70	114	180	—63	43	180	60	2.1	1.8
$\overline{\text{R—R}}$	—179	—55	—33	—177	—54	—32	—179	60	—	—0.5
B—L	179	—55	112	—177	54	32	—179	57	—	—0.2
R—M	180	—60	—51	178	—72	61	180	60	—	—0.2
$\overline{\text{R—B}}$	—178	—55	—43	175	—98	32	180	58	—	0
R—H	180	—65	—45	179	69	—66	—179	50	—	0.2
B—H	180	—65	114	—178	70	—63	180	48	—	0.6
B—M	180	—65	110	180	—71	64	179	60	—	0.7
M—L	—179	—70	72	179	56	34	—179	57	—	2.0
M—R	—179	—70	72	177	—62	—45	180	60	—	2.1
M—B	180	—70	72	177	—63	122	180	60	—	3.4
					$\omega_0 \sim 0°$ (cis-)					
R′—R	0	—70	—46	—176	—62	—40	180	60	1.0	0.9
R′—L	1	—65	—45	180	54	36	180	57	1.8	1.7
R′—B	0	—70	—46	—178	—67	53	180	60	1.9	1.8
B′—R	10	—70	156	—178	—58	—41	180	60	2.5	1.7
B′—L	1	—70	149	180	54	43	179	58	2.7	2.8
B′—B	0	—70	145	—179	—63	139	180	60	3.1	3.1
R′—M	0	—70	—48	180	—71	63	180	60	—	0.8
R′—H	0	—70	—45	180	69	—66	—179	50	—	1.0
B′—H	—1	—65	138	—177	69	—64	180	49	—	1.9
B′—M	—2	—70	135	180	—71	64	179	60	—	2.1

been found experimentally in a considerable number of linear [4-9] and cyclic [10-14] oligopeptide and polypeptide compounds containing proline and N-methylated residues. An investigation of the ^{13}C NMR spectra of the alanylprolyl dipeptide in D_2O solution [7] estimated the amount of the trans form as 57% and of the cis form as 43%. These figures agree well with our calculations which predict the proportions of these forms as 65 and 35%, respectively.

Among the extended forms of the dipeptide with $\omega_1 \sim 180°$ (trans-), the most suitable conformations, with energies in the range from 0 to 1 kcal/mole, are L—R, B—R, L—B, and B—B. In these conformations, the Pro residue is present in two states — R and B, the only possible ones — and practically equivalent — in the monopeptide; the Ala residue is in the L and B states which are also the most favorable forms of the dimethylamide of N-acetyl-L-alanine [23]. The structures R—R and R—B in which the Ala residue is in the R form have greater energies. In the dimethylamide of N-acetyl-L-alanine, this form is practically impossible, since it is about 7 kcal/mole less advantageous than B [23]. The loss of energy of the R—R form in the dipeptide as compared with R—B is considerably smaller because of the stabilization of the dispersion interaction between the terminal peptide groups [25]. However, the realization of the R form in the residue preceding the Pro nevertheless remains less likely than the B and L forms.

Among the extended conformations of the dipeptide $\omega_1 \sim 0°$C (cis-), as in the case with $\omega_1 \sim 180°$, four structures, in which the Pro residue has the B and R forms and the Ala residue the B′ and L′ forms, prove to be favorable. The energy of the two conformations of the dipeptide with the R′ form of the alanine is so high that their realization is practically out of consideration. These conclusions are in complete agreement with the results of theoretical [23, 26-28] and experimental [10-14] investigations performed previously.

On passing to a nonpolar medium, the conformational equilibrium of Ac-L-Ala-L-Pro-NHMe both at $\omega_1 \sim 180°$ and at $\omega_1 \sim 0°$, does not undergo fundamental changes. As a rule, under these conditions the stability of the low-energy extended forms considered above rises still

TABLE 3. Conformational Distribution in Proteins of Dipeptide Fragments with the Pro Residue

Type of conformation	Fragment	
	-X-Pro-	-Pro-X-
B—R	8	5
B—B	12	6
R—R	2	8
R—B	—	2
B—L	—	1

further (see Table 1). The formation of hydrogen bonds does not lead to a decrease in energy but, conversely, is accompanied by considerable nonvalent repulsions. In actual fact, not one of the calculated conformations with 3→1 and 4→1 hydrogen bonds is found in -X-Pro- fragments in proteins (where X is an amino-acid residue).

Methylamide of N-Acetyl-L-prolyl-L-alanine. The conformational states of the Ac-L-Pro-L-Ala-NHMe molecule in a polar medium are described as in the preceding case by combinations of the optimum forms of the monopeptides — R and B (Pro) and R, B, L, and P (Ala). In a nonpolar medium, the realization of a considerable number of other forms with intramolecular hydrogen bonds is also possible. Thus, bonds of the 3→1 type may be present in the convoluted forms M in Pro and M and H in Ala. Within the limits of the dipeptide fragment and only at $\omega_0 \sim 180°$ can hydrogen bonds of the 4→1 type in the $\overline{R—R}$, $\overline{R—B}$, and $\overline{B—L}$ conformations be formed. The results of calculation are given in Table 2. Because of their high energies, it does not include any of the conformations with the P form of alanine. The dependence of the energy of the most favorable forms on the angles φ_1 of Pro is given in Fig. 2b.

In the Ac-L-Pro-L-Ala-NHMe molecule with the trans configuration of the peptide groups the relative energies of all the forms without hydrogen bonds fall into the range between 0 and 2 kcal/mole. The most suitable in this series is the R—R conformation, and the least suitable the B—B conformation (we may note that in the free monopeptides Pro and Ala the R and B forms have the same energy). The enthalpy preference of the α-helical form is due to the stabilizing dispersion interactions of the peptide groups [25]. However, this form is greatly inferior to the B—B form in entropy. Consequently, it may be assumed that the difference in the values of the free energy for R—R and B—B is less considerable.

In a nonpolar medium conformations with hydrogen bonds, particularly of the 4→1 type, become favorable for Ac-L-Pro-L-Ala-NHMe, in contrast to Ac-L-Ala-L-Pro-NHMe. Such forms in -Pro-X- fragments are actually found in proteins.

The conformations with the cis configuration of the peptide group ($\omega_0 \sim 0°$) are less preferred as compared with the trans configuration. Their amount both in a polar and in a nonpolar medium for Ac-L-Pro-L-Ala-NHMe should be considerably less than in the case of Ac-L-Ala-L-Pro-NHMe.

We compared the forms calculated for the two peptides with the conformational types of the main chains of the -X-Pro- and -Pro-X- fragments found in proteins, where X is any amino-acid residue with the exception of Gly. The conformational states of these fragments are affected by many other factors than those considered in our calculation — the interaction of the side chains, long-range interactions, etc. As a result, the comparison made shows only the role of the interactions of the main chains of two neighboring residues, one of which is Pro.

We have used x-ray structural results on six proteins (myoglobin [29], lysozyme [30], α-chymotrypsin [31], carboxypeptidase [32], cytochrome C [33], and insulin [34]) which contain 22 -X-Pro- and -Pro-X- fragments. As can be seen from Table 3, the conformational distribution of the fragments agrees fully satisfactorily with the calculated values of the energies of the dipeptides. In the case of -X-Pro-, the B—B and B—R conformations, which are among the lowest-energy forms of the Ac-L-Ala-L-Pro-NHMe molecule (see Table 1) are found most frequently; R—B is absent and R—R, having a comparatively high energy in the dipeptide, is rare. In fragments of the -Pro-X- type, in agreement with the calculation of Ac-L-Pro-L-Ala-NHMe, the R—R conformation has the greatest frequency, and this is followed by B—B and B—R; the comparatively small number of conformations of the B—B and B—R types is due to the stabilizing action of interchain hydrogen bonds in the protein chain and a number of other factors such as the entropy preference of B over the other forms. The absence (with a single exception) of conformations including L is connected with the unsuitability of the incorporation of this form of the residue into a peptide chain. Thus, none of the other forms of interactions of the residues present in the protein fragments X-Pro- and Pro-X are in contradiction to the interactions of their main chains.

SUMMARY

1. The most preferred forms of the compounds Ac-L-Ala-L-Pro-NHMe participating in a conformational equilibrium are characterized by both the trans and the cis configurations of the tertiary amide group.

2. The formation of intramolecular hydrogen bonds in the conformations of Ac-L-Ala-L-Pro-NHMe realized is unlikely.

3. The conformational states of the compounds Ac-L-Pro-L-Ala-NHMe with the trans configurations of the tertiary amide group are most probable. In nonpolar media a probability of the formation of structures with hydrogen bonds is high.

4. The conformational distribution of the fragments -X-Pro- and -Pro-X- in proteins agrees satisfactorily with the calculated values of the energy of the optimum forms of the corresponding dipeptides, Ac-L-Ala-L-Pro-NHMe and Ac-L-Pro-L-Ala-NHMe.

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