THEORETICAL CONFORMATIONAL ANALYSIS OF CYCLIC OCTADEPSIPEPTIDES

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The investigation of the spatial structure of cyclic depsipeptides with regularly alternating α-amino and hydroxy-acid residues is of interest in connection with their biological activity and, in particular, with the specific influence on the transport of ions through cell and mitochondrial membranes [1, 2]. Previously, by means of a theoretical analysis, the conformational possibilities of a series of di- [3, 4], tetra- [5, 6], hexa- [7], and dodecadepsipeptides [8] containing respectively, 6, 12, 18, and 36 atoms in the ring were studied, and the geometric and thermodynamic parameters of the optimum forms were determined. For these compounds, the most preferred spatial forms were found and the states of the conformational equilibrium in polar and nonpolar media were deduced. The conformations of a number of methyl esters of N-acetyl-α-amino acids and of methylamides of O-acetyl-α-hydroxy acids were also calculated [9], and the same applies to a number of more complex linear depsipeptides [10] modeling fragments of the cyclic compounds mentioned above. The investigation of the stereochemical interactions between the closest members of the depsipeptide chain permitted the selection of a set of optimum forms describing the conformational states of the simplest linear depsipeptides. It was shown that the canonical forms found for these compounds can be considered as a conformational code in the analysis of the structure of more complex compounds. The results of a calculation of conformations [3-8] agree well with the experimental results obtained by the ORD, NMR, IR, dipole moment, and x-ray structural analytical methods [4, 8, 11, 12].

The present paper gives the results of a theoretical study of the conformational states of cyclic N-methylated octadepsipeptides consisting of eight regularly alternating L-α-amino and D-α-hydroxy acid residues (24 atoms in the ring). Some compounds of this series, such as $[\overline{(L\text{-MeVal-}D\text{-Hylv})_4}]$,* show a high antimicrobial activity and a capacity for binding alkali-metal ions [1].

As the model for calculation we selected the cyclooctadepsipeptide $[\overline{(L\text{-MeAla-}D\text{-Lac})_4}]$ with methyl groups on the C^{α} atoms. In the series of cyclic octadepsipeptides, this molecule possesses the greatest conformational freedom (with the exception of derivatives having Gly and Glyco residues). As follows from previous work [9], the introduction of more voluminous side chains does not lead to qualitatively new conformations of the main chain but, in the main, affects only the values of the thermodynamic parameters, i.e., the position of the equilibrium of the optimum forms. The approach to the analysis of the spatial structure of the cyclooctadepsipeptides, the procedure for calculation, the values of the bond lengths and valence angles, and the potential functions of the atom–atom interactions used in the present investigation were similar to those which we have described in the analogous study of the cyclohexadepsipeptides [7].

The formula of the cyclooctadepsipeptide considered is shown in Fig. 1. The calculation of the optimum conformations of the molecule was performed by minimizing the potential energy, taking into account the nonvalent interactions of the atoms, the electrostatic interactions, and the torsional energy.

*Hylv, Lac, and Glyco are the symbols used for residues of α-hydroxyisovaleric, lactic, and glycolic acids.

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TABLE 1. Optimum Conformations of $[\overline{(L\text{-MeAla-}D\text{-Lac})_4}]$

Angle, deg	Conformations									
	1	2	3	4	5	6	7	8	9	10
Φ_1	299	250	263	123	265	119	280	112	114	321
Ψ_1	93	234	229	129	228	124	234	87	128	268
Φ_2	69	249	240	81	240	29	235	41	122	263
Ψ_2	333	354	258	326	97	106	176	261	131	320
Φ_3	289	269	338	279	244	236	115	345	110	268
Ψ_3	21	14	7	13	54	228	135	26	20	279
Φ_4	70	71	66	53	85	245	63	65	69	249
Ψ_4	4	349	318	14	49	160	221	175	349	254
Φ_5	273	277	327	273	125	353	269	106	269	236
Ψ_5	17	233	23	16	116	112	56	33	19	25
Φ_6	62	238	77	93	55	78	102	75	87	105
Ψ_6	291	223	281	300	27	340	313	318	340	83
Φ_7	269	264	318	253	295	313	258	311	256	257
Ψ_7	22	62	138	25	30	122	352	167	57	71
Φ_8	259	257	265	253	60	349	245	232	162	80
Ψ_8	145	231	38	288	295	81	162	195	281	155
$\mu(D)$	6,8	8,9	5,5	9,1	8,4	7,7	11,8	10,6	10,9	12,4
U_{nv}	3,4	0	7,1	3,4	4,7	7,3	11,1	14,8	13,3	22,6
U_{el}	1,5	3,8	0	4,0	1,8	0,1	0,8	1,0	5,8	3,6
($\varepsilon = 4$) U_{tor}	0	1,6	1,1	1,5	1,4	2,0	2,2	1,7	1,8	2,3
U_{tot} $\varepsilon = 1$	1,2	8,6	0	12,7	5,1	1,5	7,9	12,3	30,1	31,1
$\varepsilon = 4$	0	0,5	3,3	4,0	3,0	4,5	9,2	12,6	16,0	23,6
$\varepsilon = 10$	0,9	0	5,1	3,4	3,7	6,3	10,4	13,7	14,3	23,2

Notes. The values of the angles of rotation Φ_i and Ψ_i with odd indices we ascribe to the hydroxy-acid residues and those with even indices to the amino acid residues; in order to compare the results obtained with those of preceding investigations, the angles have been represented by the 1966 notation [14]; the relative values of the total energy and of the individual energy contributions are given in kcal/mole.

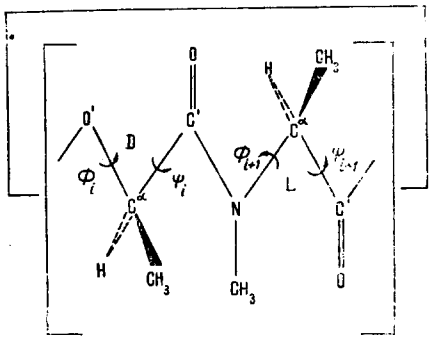

Fig. 1. Structural formula of the cyclic octadepsipeptide $[\overline{(L\text{-MeAla-D-Lac})_4}]$. The mutual positions of the bonds in the fragment illustrated correspond to the values $\Phi = \Psi = 0$.

The search for the local minima was performed by varying the 14 angles of rotation Φ_i ($C^\alpha - N$ and $C^\alpha - O'$) and Ψ_i ($C^\alpha - C'$), which were selected as independent variables (two angles dependent).

The initial null approximations for minimization were selected on the basis of the conformational charts of linear compounds modeling the fragments $[\overline{(L\text{-MeAla-}D\text{-Lac})_4}]$, namely: the methyl ester of N-acetyl-N-methyl-L-alanine (Ac-L-MeAla-OMe, I) and the dimethylamide of O-acetyl-D-lactic acid (Ac-D-Lac-NMe_2, II). The maps of compounds (I) and (II), which are shown in Fig. 2, form a set of equipotential sections (0, 1, 2, 3, 5, and 10 kcal/mole); they were obtained by varying the angles of rotation Φ ($C^\alpha - N$ or $C^\alpha - O'$) and Ψ ($C^\alpha - C'$) by intervals of 20° and calculating the nonvalent interactions of the atoms [9]. As can be seen from Fig. 2, compound (I) possesses considerably greater conformational possibilities than (II). This gives grounds for assuming that the forms of $[\overline{(L\text{-MeAla-}D\text{-Lac})_4}]$ with small energies of the nonvalent interactions in all the local sections of the ring are determined primarily by the conformational states of the fragments containing the hydroxy-acid residues. At the selected values of the angles Φ and Ψ of the hydroxy-acid residues (they are located mainly in the region of the minimum of P), the fulfillment of the condition for ring closure is ensured by a variation in the angles Φ and Ψ of the amino acid residues within the limits of the four approximately equivalent low-energy regions on the map of compound (I) – R, B, L, and P. With such an approach,

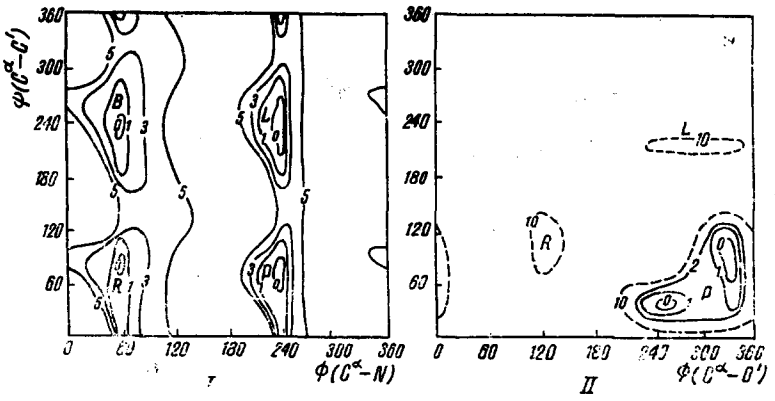

Fig. 2. Conformational charts of the methyl ester of N-acetyl-N-methyl-L-alanine (Ac-L-MeAla-OMe) (I) and of the dimethylamide of O-acetyl-D-lactic acid (Ac-D-Lac-NMe_2) (II).

the amino acid residues fulfill the role of peculiar hinges with a limited freedom of rotation. Fixing the angles Φ and Ψ of the four hydroxy-acid residues largely predetermines the region of permitted values for all the pairs Φ, Ψ of the amino-acid residues, i.e., their quadrants on the conformational chart of (I).

As the initial approximations for the search for the optimum conformations we took structures in which the parameters Φ and Ψ of not less than two hydroxy-acid residues were present in the map of compound (II) in the most energetically favorable region P. A total of ten null approximations most favorable from the point of view of the closest interactions and ensuring the formation of a closed system were taken for minimization.

Table 1 gives the values of the potential energy (U_{tot}), the dipole moments (μ), and the values of the angles Φ and Ψ of the optimum conformations of $\overline{[(L\text{-MeAla-}D\text{-Lac})_4]}$ with trans-amide and trans-ester groups and also contributions to U_{tot} of the energy of nonvalent interactions (U_{nv}), of the torsional energy (U_{tor}), and of the electrostatic interactions (U_{el}). The values of U_{el} were calculated at three values of the effective dielectric constant, $\varepsilon_{eff} = 1$, 4, and 10. The change in U_{tot} due to the different contributions of the energy U_{el} may show a tendency to a shift of the conformational equilibrium on passing from an inert to a polar medium [7, 13]. The figures in the table show that for the compound $\overline{[(L\text{-MeAla-}D\text{-Lac})_4]}$ the most favorable are the first two forms, N_1 and N_2.

A characteristic feature of the N_1 conformation is that the parameters Φ and Ψ of all the hydroxy-acid residues are in the most favorable region from the point of view of nonvalent interactions, P. The carbonyl groups of the amino- and hydroxy-acid residues in this form have the opposite pseudoaxial orientations with respect to the mean plane of the ring. The side groups occupy the pseudoequatorial positions.

In the N_2 form (apparently preferred in a polar medium), two hydroxy-acid residues are present in the P state and two in the L state. Structure N_2 possesses a somewhat elongated ellipsoidal form. The carbonyl groups of the third and seventh hydroxy-acid residues are directed to opposite sides of the plane of the ring as compared with the eight remaining C=O groups; the carbonyl groups of all the residues are inclined in some degree or other from the pseudoaxial orientation towards the center of the molecule. The side chains, deviating in pairs in different directions, occupy an intermediate position between the pseudoaxial and pseudoequatorial orientations. The preferential nature of this conformation as compared with the N_1 conformation is due mainly to the nonvalent interactions of the atoms of the different residues. The energy difference of the N_1 and N_2 forms, taking into account the contributions of U_{nv} and U_{tor}, is 1.8 kcal/mole. However, the advantage of the N_1 structure in relation to U_{el} ($\Delta U_{el} = 2.3$ kcal/mole at $\varepsilon_{eff} = 4$) makes it the most probable one in a nonpolar medium.

If the assumptions adopted in the calculation [7] are taken into account, then in a further consideration and experimental investigation of the spatial structures of the cyclooctadepsipeptides the N_3–N_5 conformations cannot be completely ignored. The realization of the other optimum forms (N_6–N_{10}) is extremely unlikely.

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