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Modeling of the Amino Acid Side Chain Effects on Peptide Conformation

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Semiempirical AM1 calculations were carried out for quantum-chemically optimized minimum energy conformations of peptides $(Ala)_4$-X-$(Ala)_4$, where X stands for different L-α-amino acids (Ala, Arg, Asn, Asp, Cys, Gln, Glu, Gly, His, Ile, Leu, Lys, Met, Phe, Pro, Ser, Thr, Trp, Tyr, and Val). The effect of these variable amino acids on the conformation of the model peptide was quantified in terms of the conformational "strain energy" (ΔH_{strain}), and also analyzed in terms of spatial compatibility of the peptides. The ΔH_{strain} corresponds to the energy of transformation from the minimum conformation of the alanine-containing peptide into the conformation, optimized for the X-containing peptide. The results of calculations revealed that variation of the amino acid X influences the conformation of the model peptide and determines the value of the "strain effect." As the ΔH_{strain} values characterize interaction between the amino acid side group and the surrounding peptide fragment, an attempt was made to derive a set of parameters that would quantify the influence of a single amino acid on the conformation of a peptide/protein molecule. These parameters could be used as structure-dependent molecular descriptors in developing the quantitative structure–activity relationships for peptides.

INTRODUCTION

The three-dimensional structure of proteins and large peptides is believed to be determined by the primary structure of these molecules (*1,2*). However, even in the case of short peptides, the relationship between the sequence of amino acids and the three-dimensional structure of the molecule has not been resolved (*3,4*). Furthermore, several experimental studies indicate the absence of a single peptide conformation in aqueous solutions (*5,6*) or in other polar solvents (*7,8*). It has been suggested that the decrease in the polarity of medium should lead to the formation of fixed conformations, even in the case of comparatively short peptides (*7*). Consequently, the bioactivity of peptides, as related to their interaction with enzyme or receptor molecules is expected to be significantly influenced by their spatial structure, because the solvation of ligands in the low polarity binding sites could be substantially different from those in aqueous medium. Evidently, the related changes in the peptide conformation should be taken into account in the analysis of the bioactivity of these molecules.

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In the present report, an attempt is made to quantify the influence of the side groups of different amino acids on the conformation of a peptide chain by using the results of the quantum chemical modeling. The alanine containing nonapeptide $(Ala)_9$ was selected as a model compound for these calculations. The conformation of this peptide, defined as a standard helical structure (*9*), was perturbed by replacement of the central (fifth) alanine residue by other L-α-amino acids, yielding nonapeptides $(Ala)_4$-X-$(Ala)_4$, where X stands for Arg, Asn, Asp, Cys, Gln, Glu, Gly, His, Ile, Leu, Lys, Met, Phe, Pro, Ser, Thr, Trp, Tyr, and Val. The geometrical structure of each of these peptides was optimized and the respective heats of formation were calculated. The effect of different amino acids X on the structure of the model peptide was quantified in terms of the "conformational strain energy," corresponding to the energy needed for the transformation of nona-alanine from the minimum energy conformation to the optimized conformation of X-containing peptide. The principles of this approach were initially suggested in our previous study (*10*), where the influence of proline residues on peptide conformation was analyzed. Proceeding from the "strain energy" values for particular amino acids, a new scale of correlation parameters was designed for quantitative structure–activity analysis of peptides.

COMPUTATIONAL METHODS

The peptide molecules studied were built up by using the program package *PC Model* for *Windows* (Version 1.0). Also, a preliminary molecular mechanical optimization was performed by the same program using the MMX method. All possible combinations of the *cis* and *trans* peptide bonds were considered and the conformation with the lowest energy minimum was selected. The final quantum-chemically optimized structures were obtained by using the AM1 methods (*11*) within the *MOPAC* (Version 6.0) program package (*12*). The geometry optimization termination criterion GRAD $\leq$ 0.01 kcal/mol was used in the energy gradient minimization.

The optimum conformation of the peptide backbone was characterized by the three torsional angles calculated for each amino acid residue: φ, the angle defined by C(O) - N - C_α - C(O); ψ, defined by N - C_α - C(O) - N; and the amide torsional angle ω, defined by C_α - C(O) - N - C_α (Fig. 1). The heats of formation (ΔH_f^0) were calculated for each peptide at the optimum conformation. In addition, the parameters of geometrical compatibility, i.e., the torsional angle between the N-C_α bond of the first amino

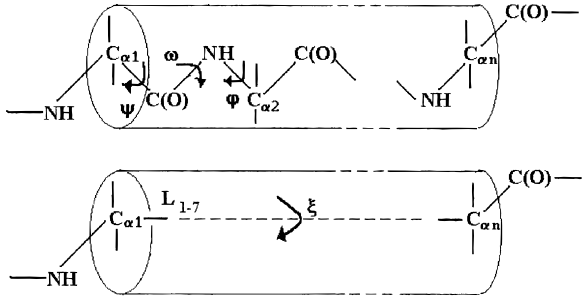

FIG. 1. Definition of the geometrical compatibility parameters of peptides ($L_{1\text{-}7}$ and torsional angle ξ) (*10*).

acid and the C_α-C(O) bond of the last amino acid of the peptide (ξ-angle) and the overall length of peptide L_{1-9} (the distance between the α-carbon atoms of the terminal amino acids in the nonapeptide) were calculated (Fig. 1). Also, the energies of "conformational strain" ΔH_{strain} (the transformation energy of nonaalanine from the minimum energy conformation into the conformation optimized for X-containing peptide) was calculated.

RESULTS AND DISCUSSION

Peptide Conformation

The torsional angles ω, φ, and ψ for optimized structures of $(Ala)_9$ and $(Ala)_4$-X-$(Ala)_4$ are listed in Table 1. These results show that the alanine homopolymer has indeed a regular structure with similar ω, φ, and ψ values along the whole peptide sequence. The only exceptions are the φ and ψ values at both terminal residues. This peptide has a regular structure and, therefore, it was used as a standard compound in the subsequent geometrical comparison of peptides.

The regular structure of polyalanine was significantly perturbed by the introduction of other genetically encoded amino acids into the fifth position of the alanine nonapeptide, corresponding to the series of compounds $(Ala)_4$-X-$(Ala)_4$ (Table 1). These perturbations are reflected by the deviation of the torsional angles φ and ψ from the respective angles for the alanine homopolymer. The amide torsional angle ω remained practically unchanged for all the peptides studied.

The data presented in Table 1 indicate that the φ and ψ values depend specifically on the chemical structure of the side chain of the amino acid X. Evidently, the effect of substitution was not localized only in the neighborhood of the variable amino acid, but spread along the peptide molecule. Again, these effects are highly specific for individual amino acids.

Thus, the variation of amino acid structure in just one position affects the conformation of the whole peptide. This can be quantified by examining the two parameters, L_{1-9} and ξ, which characterize the geometrical compatibility of peptides (*10*). The length L_{1-9} is calculated as the distance between the terminal groups of the nonapeptide $(Ala)_4$-X-$(Ala)_4$ at optimized conformation. The angle ξ is defined as a torsional angle between the N - C_α bond of the first amino acid and C_α - C(O) bond of the last amino acid of the same peptide. The respective AM1 calculated values of these parameters are listed in Table 2. The results also indicate that no strictly isosteric replacements of amino acids in peptides are possible. This means that two different peptides may have identical conformations only in the case when at least one molecule has the energetically unflavored "strained" structure.

Conformational "Strain" in Peptides

The influence of different amino acids on the three-dimensional structure of a peptide can be quantified by the energy of the "conformational strain," as demonstrated by us elsewhere (*10*). The "strain" energy (ΔH_{strain}) was defined as the energy of the transformation of the alanine-containing peptide $(Ala)_9$ from its optimal (regular) conformation into another conformation, optimized for peptide $(Ala)_4$-X$(Ala)_4$. In all cases, except glycine, the transformation of the minimum conformation of nonaalanine

TABLE 1

Torsional Angles (ω, φ, and ψ) and Heats of Formation (ΔH) for Quantum-Chemically Optimized Conformations of Peptide Series $(Ala)_4$-X-$(Ala)_4$

A_4XA_4, X:	ω_1	ω_2	ω_3	ω_4	ω_5	ω_6	ω_7	ω_8	φ_1	φ_2	φ_3	φ_4	φ_5	φ_6	φ_7	φ_8	ψ_1	ψ_2	ψ_3	ψ_4	ψ_5	ψ_6	ψ_7	ψ_8	**ΔH (kcal/mol)**
Ala	178.9	177.1	178.8	177.7	178.4	178.0	178.4	178.6	80.07	83.23	83.16	84.48	84.13	84.66	84.86	116.1	147.8	45.49	67.3	69.02	66.71	66.64	65.95	68.0	−433.66
Arg	174.8	178.1	174.5	177.8	177.2	175.5	170.8	177.9	**153.8**	84.22	**55.32**	**55.80**	**58.07**	**64.43**	**98.66**	107.6	88.91	147.8	69.5	64.73	60.69	67.87	81.08	20.4	−403.21
Asn	175.1	178.2	179.6	177.1	179.0	177.6	178.8	177.8	**154.1**	84.76	**99.46**	83.75	84.72	85.46	84.50	112.0	89.85	148.6	68.8	52.81	71.00	59.66	66.05	67.5	−466.91
Asp	176.5	177.6	173.8	178.4	175.1	175.8	171.2	177.6	83.95	84.25	**55.63**	**58.31**	**57.94**	**65.12**	**96.96**	105.4	165.7	68.18	65.5	65.35	67.72	65.51	85.81	11.3	−518.10
Cys	177.2	178.1	177.3	180.0	176.7	178.1	178.8	177.9	83.88	84.16	83.25	**119.0**	85.47	84.34	84.61	111.9	165.5	68.15	65.9	71.27	29.84	66.98	65.10	67.9	−425.69
Gln	176.8	177.2	177.0	176.8	169.1	177.4	178.3	178.1	84.01	84.05	**60.29**	**75.00**	**100.0**	84.88	84.83	112.4	165.6	67.96	62.7	41.99	23.01	73.4	64.84	67.4	−479.54
Glu	177.1	177.9	179.2	175.2	173.9	175.5	170.3	177.4	84.08	83.70	**56.53**	**58.12**	**58.18**	**66.22**	**97.54**	104.0	165.5	67.71	65.0	70.01	70.15	62.91	0.18	7.58	−531.69
Gly	174.5	178.3	178.0	174.0	170.5	174.1	169.6	177.5	**154.2**	83.96	83.61	**61.13**	**60.26**	**67.81**	**96.05**	103.9	88.85	147.7	70.2	66.20	84.81	60.08	5.81	0.94	−420.86
His	177.1	177.0	179.7	178.3	172.0	178.7	167.0	176.9	84.00	84.74	**98.03**	84.38	**57.95**	**68.82**	**98.38**	104.5	166.0	68.08	64.3	53.56	67.73	53.98	8.69	4.30	−378.92
Ile	177.3	177.6	179.8	178.4	177.3	177.9	178.6	178.0	84.03	84.56	**100.0**	84.19	84.71	84.51	84.71	112.3	165.7	67.98	65.6	54.44	69.35	65.40	65.52	67.3	−449.57
Leu	177.2	177.7	174.8	178.7	179.2	178.3	178.7	177.9	84.07	84.84	**73.44**	89.12	85.65	84.32	84.69	111.9	165.5	67.53	62.4	88.36	34.34	67.84	64.78	67.8	−448.27
Lys	176.7	177.7	174.2	176.1	176.3	175.6	170.8	177.7	83.94	84.17	**57.01**	**56.82**	**57.58**	**65.09**	**97.90**	105.3	165.6	68.08	65.8	69.29	60.00	67.25	84.49	14.2	−446.97
Met	176.7	177.6	174.4	176.8	176.3	175.7	170.7	177.7	83.95	84.07	**56.51**	**56.68**	**57.83**	**64.76**	**98.75**	106.4	165.5	68.09	66.1	67.62	62.09	66.55	83.64	17.0	−435.34
Phe	176.7	177.7	173.8	174.2	176.6	174.7	170.7	178.2	83.91	84.21	**58.12**	**56.64**	**57.45**	**64.02**	**95.29**	107.6	165.6	68.23	65.9	73.96	54.30	72.69	76.86	21.7	−376.77
Pro	177.4	178.0	179.4	168.7	169.8	174.1	169.6	177.5	83.96	84.08	**99.91**	**66.16**	**60.18**	**67.49**	**95.92**	103.9	165.7	67.77	67.2	108.1	85.07	60.00	5.26	1.25	−422.17
Ser	177.5	178.7	178.5	173.4	177.3	178.7	178.7	177.8	83.78	84.09	83.62	**111.9**	83.23	83.94	84.58	111.7	165.7	68.51	65.4	68.22	171.0	68.88	65.28	67.9	−479.75
Thr	176.9	177.7	175.8	177.8	178.2	176.6	170.7	177.4	83.91	83.86	**54.73**	**51.83**	**56.78**	**65.66**	**98.00**	104.5	165.7	68.22	66.8	60.79	60.16	62.32	88.36	9.70	−483.37
Trp	177.6	178.5	177.4	178.3	177.3	178.1	178.7	178.1	83.47	83.63	84.19	**110.0**	84.66	84.27	84.63	113.0	165.6	69.17	68.1	69.71	36.44	66.02	65.73	68.3	−365.49
Tyr	176.7	177.7	173.7	173.9	176.5	174.9	170.6	177.9	83.87	84.17	**58.16**	**56.49**	57.22	**64.70**	**95.38**	106.2	165.4	68.24	65.9	74.36	52.91	72.22	79.89	17.5	−446.32
Val	174.7	179.1	179.5	175.8	172.9	172.7	178.8	177.9	154.2	83.97	81.88	81.90	81.69	86.60	84.58	111.4	89.23	147.2	70.5	70.77	45.30	64.97	63.94	68.1	−434.30