Long-Range Effects in Oligopeptides. A Theoretical Study of the β-Sheet Structure of Gly_n ($n = 2-10$)

Viktória Horváth,[†,‡] Zoltán Varga,[‡] and Attila Kovács*[,§]

Structural Chemistry Research Group of the Hungarian Academy of Sciences at Eötvös University, H-1518 Budapest, Pf. 32, Hungary, Institute of General and Analytical Chemistry, Budapest University of Technology and Economics, H-1111 Budapest, Szt. Gellért tér 4, Hungary, and Hungarian Academy of Sciences − Budapest University of Technology and Economics, Research Group of Technical Analytical Chemistry, H-1111 Budapest, Szt. Gellért tér 4, Hungary

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Long-range interactions in the β-sheet structure of oligoglycines Gly_n ($n = 2-10$) have been investigated by DFT computations using the B3LYP exchange-correlation functional in conjunction with a diffuse polarized valence triple-ζ basis set. The study focused on the evaluation of the title interactions in the Gly_n chain and on the quantitative determination of their consequences in both energy and geometry. It was found that the interactions contribute considerably to the stability of the β-sheet and have a substantial impact on the geometrical parameters. On the basis of the gradual build-up of energetic and geometrical effects, we determined the effective radius of long-range interactions to be around 10 Gly units in the β-sheet Gly_n. The energy gain from the long-range interactions of a Gly unit is around 2.5 kJ/mol, stemming to a large extent from the strengthening of the N−H···O═C hydrogen bonds. Among the geometrical parameters, the H···O hydrogen-bond length is the most sensitive to long-range effects, decreasing by several hundredths of an angstrom. Besides, there is a pronounced shortening of the C−N bonds (up to 0.009 Å), while the other bond distances vary within 0.002 Å and the bond angles within 0.5°. Our structure analysis revealed also a small (a few thousands of an angstrom) elongation versus contraction of the chain depending on the parallel versus antiparallel orientation of the NH_2 and COOH end-dipoles. The alterations of the bond distances upon long-range effects are associated with appreciable changes in the magnitude of the main hyperconjugation interactions.

1. Introduction

The three-dimensional structure of biological compounds, strongly related to their functions in living organisms, belongs to the most essential biochemical information.[1] Among the biocompounds, the structure of proteins is particularly complex. They consist of up to 20 different amino acids and form various (regular and nonregular) secondary structures. A way to understand their structural properties and the major forces determining them is through the study of homopolypeptide or block copolypeptide models. This field already has extensive literature:[2,3] for recent experimental studies, see, for example, refs 4−7; for theoretical studies, see refs 8−19. The increasing importance and advantages of theoretical studies are obvious. However, it should be noted that, due to the size of these systems, their investigation is still a serious challenge to computational chemistry. The energy differences between the various conformers are often a few kilocalories per mole only;[20,21] hence a relatively high precision is required, while cost considerations must also be kept in mind.

On the basis of the experimental and theoretical results of the past decades, we now have a fair description of the geometry and conformational properties of the most common secondary protein structures. They are formed by joint hydrogen bonding, dipole−dipole, and steric interactions.[22] From the above interactions, the first two can exhibit cooperative features and can extend for long distances. We note additionally the role of hyperconjugation interactions shown recently for the conformational properties of amino acid monomers,[23] although these interactions extend through a couple of bonds only.

Long-range effects in polypeptides were recently investigated by Improta et al.,[24,25] who modeled the infinite polypeptide chain of glycine (Gly), alanine, and α-aminoisobutyric acid using the periodic boundary condition (PBC) approach within the DFT framework. They observed characteristic changes in the geometrical parameters of the β-sheet structures, particularly in those related to the hydrogen bonds, as compared to the corresponding dipeptides. The data indicated strengthening of hydrogen bonding in the polypeptide chain, which was attributed to long-range effects. These stabilizing forces were explained in part by the arrangement of the residual dipoles and in part by cooperative effects between the hydrogen bonds. Cooperative effects are well known in complex hydrogen-bonded systems[26] and have been described thoroughly for β-diketones (resonance-assisted hydrogen bonding, π-cooperativity)[27,28] and carbohydrates (σ-cooperativity).[29,30] Hydrogen-bonding cooperativity in proteins is less known, although it has been suggested to be important for stabilizing the α-helix structure in the case of repeating motifs over several units.[31−33] Such an effect is possible by the delocalized N−C═O groups serving as link between two N−H···O═C hydrogen bonds.

* Corresponding author. E-mail: akovacs@mail.bme.hu.
† Eötvös University.
‡ Institute of General and Analytical Chemistry, Budapest University of Technology and Economics.
§ Hungarian Academy of Sciences − Budapest University of Technology and Economics.

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Although the studies of Improta et al.[24,25] pointed unambiguously to the importance of long-range effects in peptides, some questions remained unanswered. The fact that the PBC approach was used for the calculation of the polypeptide, whereas the parameters of the dipeptide were obtained by exact DFT calculations, hindered a quantitative assessment of the long-range interactions. Moreover, investigating only two species, the dimer Gly_2 and the model for the infinite Gly_∞, severely limited the evaluation of these interactions in the peptide backbone. What are the exact consequences both in energy and in geometry of the long-range interactions, and how far do they extend? These are the main questions addressed in our present study, in which we evaluated the changes in the β-sheet oligoglycine structures upon a gradual increase of the chain size.

We performed full geometry optimizations on Gly_n ($n = 2-10$) oligopeptides using density functional theory in conjunction with a diffuse polarized valence triple-ζ basis set. We focused on molecular properties, such as the stabilization energy, geometrical parameters, and hyperconjugation effects, as a function of the peptide chain size. The data of Gly_n ($n = 3-10$) were compared to those of the smallest oligopeptide Gly_2, except for the relative stabilization for which the energy difference between Gly_3 and Gly_2 was used as reference. Among the geometrical parameters and hyperconjugation interactions, both terminal and in-chain parameters were assessed.

2. Computational Details

The molecular geometries of Gly_n ($n = 2-10$) were preoptimized at the HF/6-31G(d) level followed by optimizations with the B3LYP[34,35] DFT method using "Tight" optimization criteria. In the DFT calculations, 6-311+G(d) and 6-311G(p) basis sets were used for the heavy atoms and hydrogen, respectively. For a more accurate description of the hydrogen-bonding energetics, the basis of the NH hydrogens was extended with a single set of diffuse functions. This basis set is denoted in the following as 6-311+(+)G(d,p).

Natural bond orbital analyses[36] were performed on the DFT geometries using the B3LYP electron densities. The threshold for the second-order perturbation energies was 0.1 kcal/mol. All of the calculations were performed using the Gaussian 98[37] program.

3. Results and Discussion

3.1. Stabilization Energy. The most important consequence of long-range interactions may be the stabilization of oligo- and polypeptide chains. To separate that from the obvious decrease of the absolute energy by increasing chain size, we defined the stabilization energy (ΔE_s) as the energy gain obtained upon the addition of the nth Gly unit to Gly_{n-1} with respect to the energy gain of the formation of Gly_3 from Gly_2 (eq 1, where E_n is the absolute energy of Gly_n). The reference energy difference ($E_3 - E_2$) represents the change of the absolute energy at the formation of Gly_3, being free from long-range effects.

$$\Delta E_s = (E_n - E_{n-1}) - (E_3 - E_2) \qquad (1)$$

Figure 1 shows the gradual variation of the ΔE_s stabilization energy from Gly_4 to Gly_{10}. The stabilization upon the long-range effects of a Gly unit starts with 1.16 kJ/mol in Gly_4 and increases gradually to 2.42 kJ/mol in Gly_{10}. The change in ΔE_s between Gly_9 and Gly_{10} is only 0.05 kJ/mol; hence a saturation value of about 2.5 kJ/mol can be expected for $n > 10$. This sets the effective radius of long-range interactions in the β-sheet structure of polyglycine to around 10 Gly units.

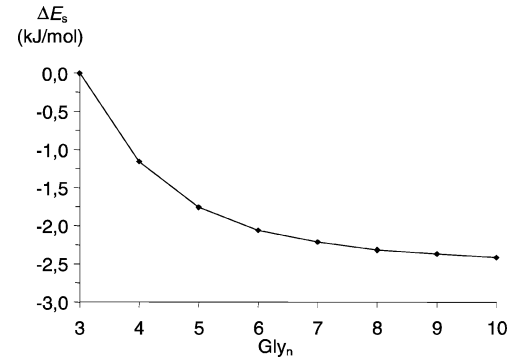

Figure 1. Stabilization energy (ΔE_s, see eq 1) of a Gly unit from long-range interactions in the β-sheet Gly_n chain.

A stabilization of 2.5 kJ/mol is quite substantial, although it is still much smaller than the energy gain observed in the delocalized π-systems of allenes (ca. 12.5 kJ/mol in butadiene[38]). Whereas the latter is due to extensive molecular orbital interactions in the conjugated π-system, the delocalized amide groups in peptides are separated by sp^3 $C_\alpha HR$ groups. The long-range interactions in peptides can operate only through the hydrogen-bonded network (connecting the amide moieties) and through dipole−dipole interactions,[24,25] both being less effective. Yet, the brutto stabilization in longer peptide chains can already be considerable: summing up the individual ΔE_s values from Gly_4 to Gly_{10} presented in Figure 1, we obtain a total stabilization of 14 kJ/mol for Gly_{10}.

3.2. Long-Range Effects on the Geometrical Parameters of the Terminal Glycine Units. The molecular geometry was shown to be sensitive to long-range interactions.[25] However, the weak effects can cause only small geometrical changes, which are hardly detectable by experimental methods. Quantum chemical calculations, on the other hand, can predict such small relative changes in a series of homologue compounds (unlike the absolute values) quite reliably.[39] As mentioned in the Introduction, the geometrical effects of long-range interactions were investigated by Improta et al.[25] Because of the PBC approach, however, their theoretical study was limited to the parameters within the chain. In-chain units are affected by long-range interactions from two directions, while the terminal amino acids are affected from one direction only. Therefore, the terminal geometrical parameters are more suitable for determining the effective radius of long-range interactions.

In Figure 2, the β-sheet structure of Gly_{10} is depicted introducing the notations used in the figures and discussions. In the following, we show (and discuss) the most significant changes in the geometry and hyperconjugation effects attributed to long-range interactions. Figures describing the gradual change of the less significant geometrical parameters and hyperconjugation interactions are available as Supporting Information.

Figure 3 shows the changes in selected bonds in the two (N- and C-) terminal Gly units with respect to the corresponding bond lengths in the dipeptide. The most remarkable effect appears in the length of the hydrogen bond, which is larger by 1 order of magnitude than those in the rest of the bond lengths. The sensitivity of the hydrogen bond to long-range interactions is not surprising, as hydrogen-bonding cooperativity is one of the main interactions in these structures. In agreement with the increased stability of the longer chains, the observed decrease of the H···O distances is consistent with the strengthening of the terminal hydrogen bonds. The second reason for the considerable effects is the weakness of the hydrogen bonds: the average H···O distance is 2.26 Å in the C-terminal unit,

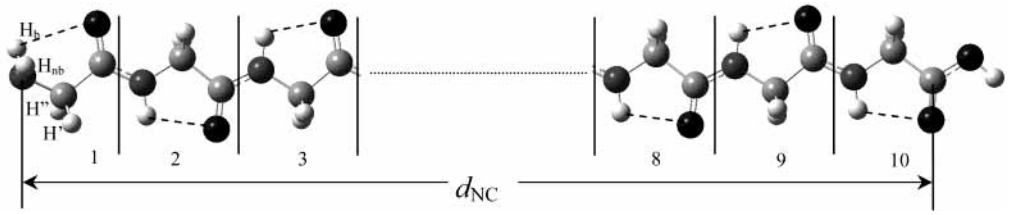

Figure 2. The β-sheet structure of Gly_{10}, and the numbering and notations used throughout the paper.

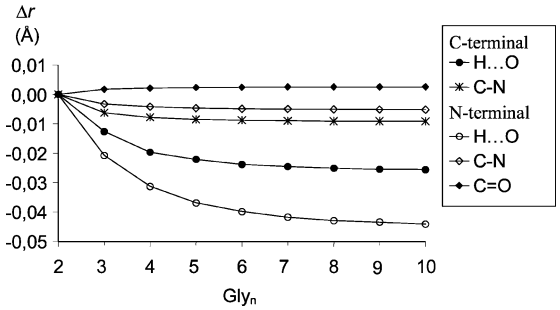

Figure 3. Long-range effects on selected bond distances (Δr) in the terminal Gly units.

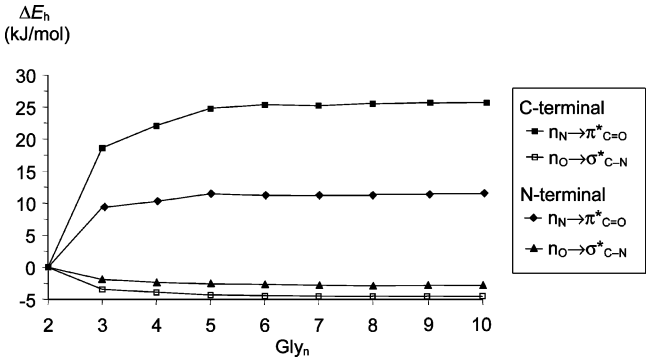

Figure 4. Long-range effects on the characteristic hyperconjugation interactions (represented by the second-order perturbation energies, E_h) in the terminal Gly units.

whereas it is 2.58 Å in the N-terminal unit. The latter corresponds to the sum of van der Waals radii of the O and H atoms[40] and is more strongly impacted by weak forces than by a stronger hydrogen bonding.

The magnitude of hydrogen-bond shortening differs considerably in the two terminals. The hydrogen-bond length in the N-terminal Gly decreases by 0.04 Å, while the one in the C-terminal unit decreases by 0.025 Å in Gly_{10} as compared to Gly_2. As seen above from the hydrogen-bond lengths, the bond in the C-terminal Gly unit is somewhat stronger and hence has smaller changes. The effect converges in the C-terminal unit at around Gly_6, whereas in the N-terminal unit it converges at around Gly_{10}. The falloff of the changes agrees well with the effective radius of long-range interactions deduced from the variation of the stabilization energy (vide supra).

Among the backbone parameters, the amide C−N bond length is most remarkably sensitive to long-range interactions. It decreases by 0.005 Å in the N-terminal unit and by 0.009 Å in the C-terminal unit with respect to Gly_2 (cf. Figure 3). This means a pronounced redistribution of the electron density within the amide group resulting in a strengthening of the C−N bond. Another consequence of this redistribution is the slight elongation and weakening of the C═O bond.

The rest of the bonds change within 0.002 Å upon long-range effects. Similar very weak effects were found for the bond angles (within 0.5°) and for the angles of torsion (within 2°, except for the decrease of the N−C_α−C═O angle by 4°), the strongest ones appearing in the hydrogen-bonded amide moiety. We note also a small tilt of the NH_2 group toward the side of H′ with respect to the plane of the β-sheet (cf. Figure 2), facilitating some attractive interactions between the nitrogen lone pair and the C_α−H″ hydrogen. We observed a slight increase of the tilt with increasing chain length.

With analysis of the hyperconjugation effects, we wanted to elucidate the role of these interactions (that is, that of their changes upon long-range effects) on the structural properties. The relative second-order perturbation energies of the most characteristic hyperconjugation interactions are depicted in Figure 4. The most pronounced effects appear in the $n_N \rightarrow \pi_{C=O}^*$ interactions that increase already in Gly_3 by from 9 (N-terminal) to 18 (C-terminal) kJ/mol, whereas in Gly_5 they increase by 11−25 kJ/mol with respect to Gly_2. Noteworthy is also the decrease of the $n_O \rightarrow \sigma_{C-N}^*$ interactions by ca. 4 kJ/mol. These changes are in qualitative agreement with the shown elongation of the C═O and shortening of the C−N bonds upon long-range effects.

3.3. Long-Range Effects in the Intrachain Units. In this section, we analyze the geometrical and hyperconjugation characteristics of the in-chain Gly units. The variations of the most important geometrical parameters (H···O, C═O, and C−N bond distances, N−C_α−C angle) from Gly_2 to Gly_∞ have been noted by Improta et al. Their predicted trends are unambiguous, and they agree with our results, vide infra. The magnitudes of the changes, however, include the (unknown) errors of the PBC approach. In the present study, we provide a good approximation of the quantitative effects of long-range interactions inside the polyglycine chain. Although our largest model peptide, Gly_{10}, is smaller than the expected effective radius of long-range interactions for an in-chain Gly unit (ca. 10 units from both directions), our data (given in detail as Supporting Information) showed already a satisfactory convergence in the middle of Gly_{10}.

Analyzing the geometrical parameters of Gly_{10}, we found the following most characteristic (maximum) changes within the chain with respect to the values of the second Gly unit: a decrease of the hydrogen-bond length by 0.03 Å, a shortening of the C−N bond by 0.002 Å, lengthening of the C_α−N, C_α−C, and N−H bonds by 0.002 Å, and decrease of the C_α−N−H and N−C_α−C angles by 0.3° and 0.5°, respectively. All of these data support again the hypothesis that long-range interactions operate through the N−H···O═C−N path, consecutively through the amide and hydrogen bonds.[25]

In addition to the above geometrical characteristics, we observed a slight oscillation of the chain length expressed by the $d_{NC}(n) - d_{NC}(n-1)$ parameter (Figure 5, for definition of d_{NC} see Figure 2), meaning a slight contraction and elongation of the Gly_n chains with even and odd values of n, respectively. Note that this slight oscillation appears also in the interglycine nonbonded angles C_α−C_α−C_α, N−N−N, and C−C−C (for details, see the Supporting Information). The phenomenon can be ascribed to the different relative orientations of the NH_2 and

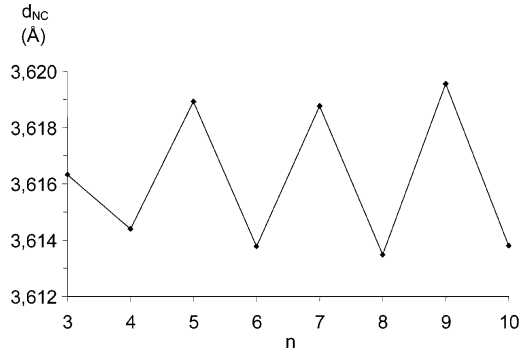

Figure 5. Variation of the $d_{NC}(n) - d_{NC}(n-1)$ parameter in the Gly_n ($n = 3-10$) series. For the definition of d_{NC}, see Figure 2.

COOH end-groups in Gly_n with even and odd n. The parallel and antiparallel relative orientations of the end-groups may result in slightly different dipole−dipole interactions impacting the nonbonding angles. The slightly increasing magnitude with the chain length points to the role of cooperativity in the phenomenon.

Similarly to the observations in the terminal units, we found several qualitative correlations between the changes of the in-chain geometrical parameters and main hyperconjugation energy contributions. Thus, the vicinal hyperconjugation from the lone pair of the carbonyl oxygen to the C−N antibonding orbital ($n_O \rightarrow \sigma_{C-N}^*$) decreases inside the chain (by 1 kJ/mol) in agreement with the in-chain strengthening of the C−N bond (vide supra). The hyperconjugation through the hydrogen bond, that is, from the lone pair of the carbonyl oxygen to the N−H antibonding orbital ($n_O \rightarrow \sigma_{N-H}^*$), as well as the $n_O \rightarrow \sigma_{C\alpha-C}^*$ interaction show a maximum in the middle of the chain (1 kJ/mol) in accordance with the lengthening N−H and C_α−C bonds (vide supra). On the other hand, we found an increased $n_N \rightarrow \pi_{C=O}^*$ interaction at the middle of the chain (by 6 kJ/mol), which, however, does not correlate with the nearly constant C═O bond distance in these in-chain units. This indicates that other interactions (e.g., Pauli repulsion in the hydrogen bond) are superior over hyperconjugation in determining the trend in the C═O bond distance.

4. Conclusions

The periodic structure of homopolypeptides is well suited for the study of long-range interactions operating through the hydrogen-bonded network and the antiparallel C═O/N−H dipole system. Both hydrogen bonding and dipole−dipole interactions can be strengthened through cooperativity effects leading also to an increased stability of a secondary structure.[24,25] Our present theoretical results support the above notion and provide quantitative information on the energetic and geometrical consequences of long-range interactions.

In the present study, we performed a systematic analysis of β-sheet Gly_n ($n = 2-10$) oligoglycines using B3LYP/6-311+-(+)G(d,p) computations. It was found that the interactions contribute considerably to the stability of the β-sheet and have appreciable effects on the molecular geometry. By a gradual build-up of the Gly_n chain, we determined the contribution of a Gly unit to the stabilization energy and its impact on the geometrical parameters. The effects were found to decline at around 10 Gly units, indicating also the effective radius of long-range interactions. The stabilization energy of a Gly unit in the β-sheet coming from the interaction with the units within the effective radius is about 2.5 kJ/mol. This means there is a considerable stabilization of the β-sheet by long-range interactions, as the total interactions in, for example, Gly_{10} reach the value of 14 kJ/mol.

The changes in the terminal geometrical parameters evolve gradually in the Gly_2-Gly_{10} series and, depending on the sensitivity of the parameter, reach a saturation value between Gly_5 and Gly_{10}. This supports the notion of effective radius of long-range interactions determined from the energy analysis. From the geometrical parameters, the hydrogen bond length is the most sensitive to the long-range effects; it shortens by 0.02−0.04 Å. These data provide primary quantitative evidence for the cooperativity of the C═O···H−N hydrogen bonds, being an important source of long-range interactions. Appreciable is also the shortening of the C−N bond upon the long-range interactions (0.003−0.009 Å), while the change of the other bond distances is below 0.002 Å, and that of the bond angles is below 0.5°. We believe that the present data constitute an improvement for previous studies[25] in which twice as large changes were reported using the PBC model.

Our structure analysis revealed a small but intriguing phenomenon within the Gly_n chain, that of the few thousands-of-angstrom elongation versus contraction of the chain depending on the parallel/antiparallel orientations of the NH_2 and COOH end-dipoles. It looks as if there would be some interaction between the end-dipoles (as if they sensed each other's orientation!) which operates through the dipole network. The effect appears directly in the nonbonded $C_\alpha-C_\alpha-C_\alpha$, N−N−N, and C−C−C interresidual angles and is strengthened by the cooperativity of the in-chain dipole−dipole interactions. Because of the small magnitude, studies on longer Gly_n analogues are necessary to explore the nature of this phenomenon.

The long-range effects appear also in the change of the hyperconjugation interactions associated with the characteristic changes in the bond distances. Most sensitive are the $n_N \rightarrow \pi_{C=O}^*$ and $n_O \rightarrow \sigma_{C-N}^*$ hyperconjugations with changes up to 25 and 5 kJ/mol, respectively.

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Supporting Information Available: Cartesian coordinates of the optimized structures and figures describing the gradual change of the geometrical parameters and hyperconjugation interactions (both terminal and in-chain) upon long-range effects. This material is available free of charge via the Internet at http://pubs.acs.org.

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