Biomolecular Springs: Low-Frequency Collective Helical Vibrations of Ace-Gly$_n$-NHMe (n = 3−8). A DFT Study Employing the PW91$_{XC}$ Functional

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The collective helical vibrations of the Ace-Gly$_n$-NHMe (n = 3, 4, 5, 6, 7, 8) series of molecules were studied. The computational vibration analysis at the DFT PW91$_{XC}$/6-31+G* level of theory confirmed the kinds of vibrations that were previously described for helical polysulfanes. The vibrations resembling the motion of (a) a transverse wave, (b) a longitudinal wave, and (c) a transformation of the cylindrical shape to a breathing pulse, to an ellipsoidal−hyperboloidal, or to a cone were also located in helical oligopeptides of glycine. The precursors of both the transverse and the longitudinal wave are C−C and C−N torsional vibrations while the origin of the cylindrical transformation is attributed to bond angle bending vibrations. The helical stretch 1r was located in all molecules but helical stretches 2r and 3r were not located in any molecule. Also, it was observed that helical twist is present, and mixed with helical bend. These collective motions are known to be interesting for their biological functions. They can also play an important role in the new field of nanomechanics as properties of molecular springs. Two additional computational experiments were carried out: (a) A 50-peptide α-helix consisting of consecutive dipeptides of gly-ala, was also studied employing molecular mechanics (AMBER force field). The motion of the helix is better observed in this helical peptide because of its length. (b) 3_{10} helical Ace-Ala$_4$-NHMe employing the PW91$_{XC}$/6-31+G* was also studied to assess the use of glycine as a model. The sensitivity of the frequencies, intensities, and modes to grid quality was also assessed.

1. Introduction

The emergence of the low-frequency vibrations of biopolymers in the scientific literature engaged a respectable number of scientists in their study.

Mainly, two scientific groups, leaded by Peticolas and Shimanouchi, respectively, collected data concerning low-frequency vibrations in biomacromolecules and pioneered analysis related either to theoretical or to experimental treatment with a clear view to their potential functionality.[1−16]

To date, low-frequency vibrations are widely investigated, theoretically or experimentally, and new techniques are either developed or tested in a variety of systems with special interest in biologically important molecules.[17−33]

Helix is a very common secondary structure that can be found either in inorganic polymers[34] or in crystal structures of organic polymers.[35] The helical structure possesses a key role in molecules of life such as DNA, proteins, polypeptide chains and polysaccharides.

Molecular helical materials and especially helical nanosprings have recently attracted much attention in the scientific community.[36] Substances are characterized as molecular springs if they possess fundamental features of a typical cylindrical helix (e.g. its elastic ability to return to its usual shape). The elastic properties of individual nanosprings have been reported.[36g] Due to their high structural flexibility and strength, molecular helical springs should be suitable for applications in various nanodevices.[37] Spring mechanics of an α-helical polypeptide has also been reported.[38] Molecular springs are studied in organic synthesis,[39] in catalysis,[40] in solvent-driven helix equilibria,[41] or in medicine (e.g. the giant protein titin).[42]

In the majority of the works dedicated to low-frequency vibrations of helical biopolymers, special attention has been paid to global deformations of the helix such as bending, stretching, and twisting. Helical bending and stretching have also been located and classified in helical polysulfanes through high-level theoretical treatment.[27] This study revealed another kind of collective helical motion, which is the helical cylindrical transformation. Overall, the oscillation of the helical axis could be described as a transverse wave, a longitudinal wave, or a transformation of the cylindrical shape to a breathing pulse, to an ellipsoidal-hyperboloidal, or to a cone. Vibrations that produce such transformations are also found in mechanical springs.[43] The origin of a helical transverse wave in helical polysulfanes is SSSS torsional vibrations, while a longitudinal wave originates from SSS bending vibrations; aggregated SS stretching is the generative force of the transformations of the cylindrical helical shape (breathing, conical, ellipsoidal, hyperboloidal).

The progress in qualitative analysis brought forth new techniques such as Fourier self-deconvolution and second-derivative resolution enhancement,[44,45] accompanied by advances in Raman instrumentation such as Raman microscopy and 2D imaging. The outcome of all these achievements enriched the amount of data obtained from spectral observation. Nonetheless, profound elucidation of experimental spectroscopic information is still weak without accurate normal-mode analysis.[46−49] Thereupon, the normal mode calculation of low-

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frequency vibrations of helical biopolymers with high-level theory is a requisite procedure for the better understanding of these motions since, in many cases, the assignment of such modes are still a matter of debate.[30]

Mechanical properties of DNA have received much attention the last two decades due to its pivotal role in functions of life. Its collective modes have been studied theoretically and have been categorized in terms of helicoidal and backbone parameter variations with emphasis to global bending, twisting, and stretching.[18,19,24,25] To our knowledge, to date, there is no high-level theoretical normal-mode analysis of DNA due to the large-scale computations that this calculation demands.

Remarkable work has been published on proteins and polypeptides concerning analysis of normal modes of low-frequency vibrations.

Corbin, Smith, and Lavery employing the P-Curves algorithm[50] simulated α-helix vibrations via molecular dynamics and determined a set of parameters describing the helix of polyalanine and myoglobin.[17] Global bending, stretching, and twisting were present at 11, 20, and 40 cm^{-1}. Krimm and Lee developed a general formalism for the vibrational dynamics of a helical macromolecule and applied the concepts of their theory to α-helical poly(L-alanine).[20] They also refined an empirical force field that reproduces well-observed frequencies above 200 cm^{-1} and is based on ab initio force fields of small molecules.[21]

Sinusoidal standing waves of electronic polarization with either even or odd symmetry with respect to inversion through the chain center approximated well the electronic normal modes of a finite translational polymeric helix as studied by Applequist.[51] His results were applied to fully extended poly-[(*R*)-*β*-aminobutyric acid] chains.

Karplus and Vlijmen performed calculations for a series of conformations and different crystal structures of bovine pancreatic trypsin inhibitor (BPTI) and hen egg white lysozyme (HEWL) to determine the effect on the normal modes of the multiminimum surface of the protein native state.[52]

To our knowledge, a study of the helical low-frequency vibrations of a polypeptide or a helical protein employing correlated ab initio theory or DFT has not emerged yet in the scientific literature.

Vibrational frequencies produced by correlated ab initio theory and DFT are available for amides and amide dimers though.[46,53,54]

The present work aims at the analysis, description, assignment, and categorization of the normal modes of a helical oligopeptide that produce collective motion such as global bending, stretching, and cylindrical deformation, implementing density functional theory. It also aims at the consolidation of helical cylindrical transformation as a universal phenomenon along with global stretching, bending, and twisting of a helix. The choice to focus on global bending, stretching, and cylindrical deformation was made because, in addition to their biological functions, these motions are of great nanomechanical interest.

Polyglycine was chosen as a model of study. The justification of this choice is thoroughly discussed in the Results and Discussion section.

PW91$_{XC}$ functional was also recently assessed for interaction energies of a wide variety of systems (e.g. formamide dimer) connected with either strong or weak dispersion forces in the presence of hydrogen bonding. It performed very well in comparison with experiment in contrast with B3LYP.[55]

In a recent work,[56] we assessed PW91$_{XC}$ vibrational calculations for a variety of molecules containing amide and hydrogen bonds. The produced unscaled vibrational frequencies for amidic modes I, II, and III were in very good agreement with experiment and, along with EDF1,[57] PW91$_{XC}$ are the best functionals for the calculation of the characteristic amide frequencies. The PW91$_{XC}$ functional showed also the better performance for all calculated normal modes, compared with experimental data available.

In the present work, we study the low-frequency helical vibrations of polyglycine oligopeptides employing the PW91$_{XC}$ functional; we compare the findings with our previous work on molecular sulfur springs[27] and with previous referred work of other scientists. We also propose possible nanomechanichal functions of such collective vibrations based on the recent literature in the new field of nanomechanics.

2. Computational Methods

The collective helical vibrations of the Ace-Gly$_n$-NHMe series of molecules were studied with $n = 3, 4, 5, 6, 7, 8$. Scheme 1S in the Supporting Information brings out the systematic search for the location of the minimum of the 3_{10} helix conformation and the calculation of frequencies of the Ace-Gly$_n$-NHMe series.

The initial geometries of the molecules were built in HYPERCHEM 6.0.[58] There was an effort to avoid constrained optimization. The model of chemistry that is proposed here is capable of locating the minimum structure of the 3_{10} helix with no constraints starting with the ideal 3_{10} geometrical ϕ, ψ angles (-74, -4, respectively). They were then fully minimized (no constraints) employing the Amber96[59] parameter set. (The minimization algorithm and the termination condition of the gradient were Steepest Descent and 1×10^{-5}, respectively. The electrostatic and the van der Waals scaling factors were 0.833 and 0.5. The dielectric epsilon was distance dependent with a scaling factor of 1.)

After proper transformation of the AMBER minimized HYPERCHEM files to Gaussian *Z*-matrix files, done by BABEL,[60] these were used as input for the fully unconstrained PM3MM[61] minimization in the G98 A7[62] program under very tight optimization criteria. These calculations ended in successful frequency calculations of the 3_{10} helical structures. The minimized geometry of the PM3MM model was then minimized employing PW91$_{XC}$ functionals with a 6-31+G* basis set. All calculations in the DFT level were carried out on internal coordinates and met full unconstrained minimization employing very tight optimization criteria. Successful frequency calculations followed the same functional, employing the same basis set. This basis was chosen because (a) it is the basis set used for the assessment of the PW91$_{XC}$ and EDF1 functionals and has given very good results in frequency calculations of peptides when compared with experimental values and (b) it is a relatively small basis set that permits its use for large molecules such oligopeptides, which are the subject of our study.

All calculations are made under the default grid, which is a pruned (75 302) grid, having 75 radial shells and 302 angular points per shell, resulting in about 7000 points per atom.

For the corroboration of the potential results of this work, three additional computational experiments took place: (1) A mixed (heteropolymeric) α-helical peptide of 50 residues of alanine and glycine, alternated sequentially (...gly-ala-gly-ala...), was minimized employing the AMBER force field and frequency calculations followed. This experiment was chosen because the length of the helix permits a better view of the motions of interest. (2) The 3_{10} helical Ace-Ala$_4$-NHMe was minimized by employing very tight optimization criteria and the PW91$_{XC}$/6-31+G(*) level of theory under the default grid. The initial geometry was built in HYPERCHEM 6.0 with the

characteristic angles (φ and ψ) adopting the values of $-74°$ and $-4°$, respectively. The result of this calculation, compared with that of Ace-Gly_4-NHMe, can play the role of an evaluator for the choice of glycine as a model. (3) The covalent dipeptides of glycine and alanine (Ace-Gly-NHMe and Ace-Ala-NHMe), both in C_7^{eq} conformation, were also minimized employing very tight optimization criteria and the $PW91_{XC}$/6-31+G(*) level of theory. Both experiments were calculated twice: The first time the grid had its default value reported above, while the second time a pruned (99 590) grid was requested. The initial geometries were taken from ref 55. These results were used for the assessment of the sensitivity of the frequencies, intensities, and modes to the quality of grid.

For the three computational experiments reported above, G98 A7 was used again.

For the visualization of vibrations HYPERCHEM and MOLDEN v3.6[63] software was used while all calculations took place on a 16 Origin 2000 processors machine.

3. Results and Discussion

3.1. The Choice of Helical Glycine Based Oligopeptides as a Model of Study. Before proceeding further, we should first substantiate the use of glycine as a model of study. A reasonable objection could be raised for the usage of glycine: The first part of the objection is that, since it is the only amino acid without a Cα substitute, polyglycine is probably not the best model for a peptide helix, as it will be more flexible than a typical helix. The second part of the objection is that, experimentally, polyglycine does not adopt a helical conformation in the gas phase or solution. It should be mentioned that glycine is known to be one of the least helix-stabilizing amino acid; only proline performs worse than it.

The answer to this objection is the strong advantages for the use of polyglycine, given below:

(I) Glycine is an important biological compound and it together with its oligopeptides they have been used as models for a peptide helix for the evaluation of many theoretical treatments involving amide bonds.[53,64,65] Improta, Barone, Kudin, and Scuseria, for example, "...report results of a thorough PBC analysis of the conformational behavior of glycine infinite homopolypeptides (GIH), which should provide a first unbiased evaluation of the applicability of this method for the treatment of biological systems."[65] Herz, Gedeck, and Clark "...report semiempirical (AM1) configuration interaction (CI) calculations designed to elucidate the mechanism of the long-range electron transfer in model polyglycine α-helices."[66] Wu and Zhao studied theoretically the origin of cooperatively in the formation of 3_{10} and α-helices based on polyglycine.[67] Zhang et al. chose polyglycines Gly_n ($n = 1-6$) as a model to study gas-phase basicities of peptides considering the lack of side chains as an advantage.[68] Sagnella, Laasonen, and Klein used the density functional theory based ab initio molecular dynamics Car−Parrinello method to investigate the structure and dynamics of proton diffusion through a polyglycine analogue of the gramicidin A (gA) ion channel.[69] Besides, radio astronomers wish to compare its spectrum at the gas phase with their collected data, to identify interstellar amino acids.[70]

(II) The absence of a β-carbon atom is a potential advantage for the present study: It can reveal phenomena connected to the appearance of new collective vibrations or the disappearance of the collective helical vibrations reported in the present work in helical oligopeptides where their amino acids do contain side chains. The results of this work, as presented below, compared with those in sulfur helices[27] indicate that the simplicity of the model plays a key role for the observation of such critical phenomena. The replacement of the one atom building block (sulfur atom in sulfur helices) with the glycine amino acid, which implies hydrogen bonding in the helix, entailed loss of some helical vibrations.

To further corroborate this point of view (importance of the simplicity of the model), we adduce the experimental study that demonstrated the conformational dependence of the low-frequency spectra of proteins.[30] For this reason "...three systems of increasing structural complexity were investigated: di-L-alanine, α-helical poly-L-alanine, and α-helical protein lysozyme."[30] In this study the increasing structural complexity revealed the conformational dependence of the low-frequency spectra of proteins.

(III) Additionally, the kinds of collective helical vibrations that are studied and presented below are all exclusively generated by backbone orchestrated motions. The backbone of every peptide helix is the same and does not depend on the kind of amino acid. Reasonably, polyglycine oligopeptides can be used as model compounds for this study. Connecting this argument with the previous one, the need for a study of the configurational dependence of low-frequency spectra can be supported: If these motions are conformationally dependent, then this fact may spur someone to study the influence on the low frequencies of the substitution of glycine with a different amino acid in the homopolypeptidic helix. Glycine, the simplest amino acid, should be an ideal starting reference since it can reveal the tendency of the helix for low-frequency vibrations without side chain effects and can be the comparable reference for the exclusive effects of the side chain substitution for every other amino acid in a systematic study.

The answer to the second part of the objection is that glycine has indeed one of the lowest helix propensities either in aqueous solution or in vacuo[71] (see also references therein). In the same study[71] though, it is mentioned that "...both entropy and energy appear to contribute to the low helix propensity. If the temperature is lowered, however, the $T\Delta S$ term will become smaller and ultimately the free energy should favor the helical conformation for the Ace-Gly_n-$LysH^+$ peptides." The dependency of the helix propensity of glycine oligopeptides on temperature and the fact that every oligopeptide of the present study is optimized under very tight optimization criteria for the location of a well-defined minimum of the 3_{10} helical conformation may allow us to use 3_{10} helical oligopeptides of glycine as a model of study.

The 3_{10} helix was chosen because it is one of the two more stable structures of long glycine homopeptides.[65] The most stable structure is α-helix. However, it is less stable than 3_{10} helix for short alanine oligopeptides.[64,65,72,73] Although only 10% of the helical protein structures exhibit the 3_{10} secondary motif,[74] its importance in helical folding and enzymatic activity has been repeatedly stressed in previous works.[75] Another main reason for the choice of 3_{10} helix is that it is longer and gives more spiral growth than an α-helix. The last element is very important for our study: Given the fact that even with a small basis set, the computations in DFT are heavy for the Ace-Gly_n-NHMe with $n = 7, 8$ (concerning our present computational resources), it is vital to have a helix with the largest spiral number per number of residues. This is the theoretical plan. Recently, it was experimentally shown that the kind of helical structure of an oligopeptide can be decided in advance. More thoroughly, a heptapeptide has been shown to behave as a solvent driven molecular spring: An α-helical heptapeptide expanded to a 3_{10} helix when the polarity of the solvent changed, proving the

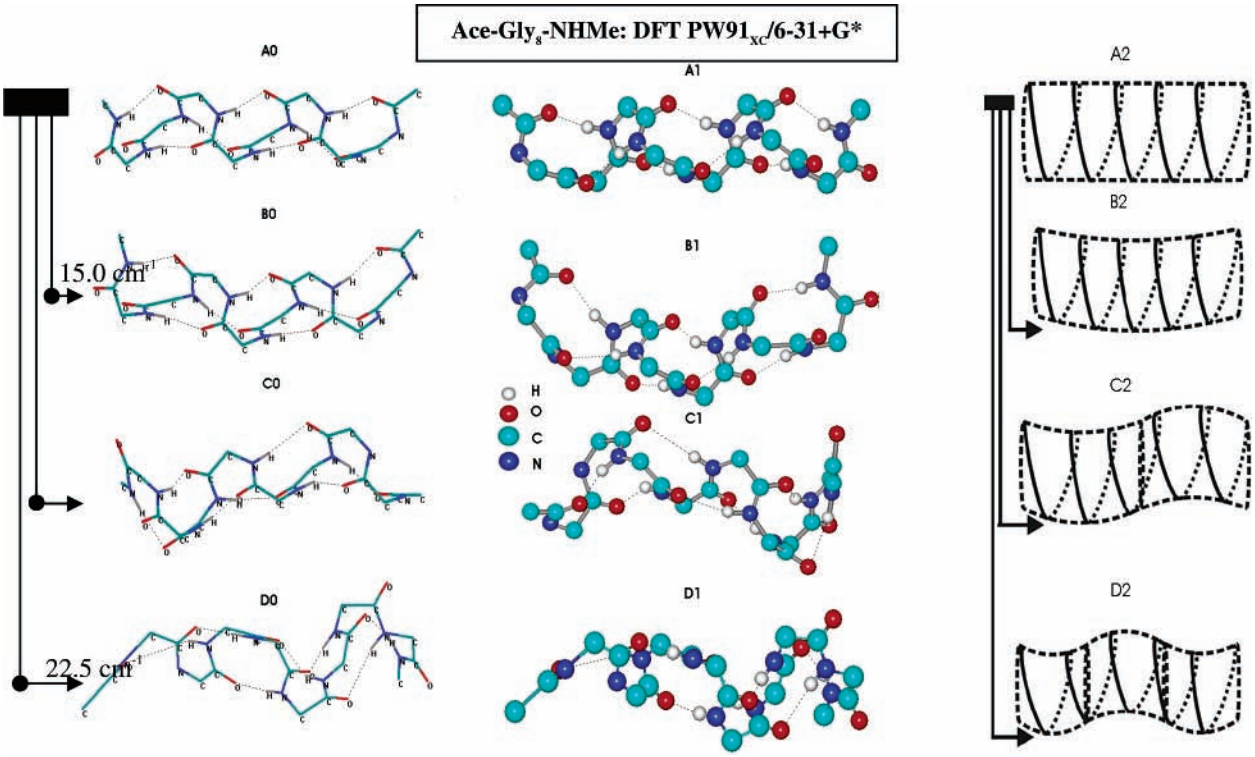

Figure 1. The helical bending in the stick, the ball and stick, and the mechanical analogue representation. From top to bottom: (A) the helix in its equilibrium position; (B) the helical bend 1c appears at 15 cm^{-1}; (C) the helical bend 2c appears at 22.5 cm^{-1}; and (D) the helical bend 3c appears faintly at 38 cm^{-1}.

existence of the unique property that the type of helical conformation adopted is dependent on the polarity of the solvent.[41]

3.2. Geometrical Aspects of the Optimized Structures of Oligopeptides. The characteristic structural data of glycine should be expected to be slightly different from the averages of other amino acids since glycine is the only amino acid that does not possess a Cα substitute.

The structural characteristics of the Ace-Gly$_n$-NHMe peptides for $n = 3-8$ at the PW91$_{XC}$/6-31+G* level of theory are described as follows: In general, extreme values are observed in the terminal groups. The N−C′ bond length values, in all cases, vary close to 1.36 Å with the exception of the extreme groups. The C′−O bond length values are very close to 1.24 Å while the N−Cα−C′ bond angle fluctuates slightly around 115°. The ϕ value swings between −69° and −60° and ψ between −20° and −17°, always excluding the terminal parts. Comparing our data with PBE PBC results for the 3_{10} helix of the GIH (glycine infinite homopolypeptide)[65] it is easy to conclude that these values are very close to each other. The PBE PBC results produce the values 1.358 Å, 1.247 Å, 114.5 Å, −58.2°, −18.0° for N−C′, C′−O, N−Cα−C′, ϕ, and ψ, respectively. For a tabulated report of the structural results at this level, see Table 1S in the Supporting Information.

PM3MM results differ from those of the PW91$_{XC}$ model as expected. The N−C′ bond length rises to an average of 1.41 Å while the C′−O bond drops to close to 1.23 Å. The N−Cα−C′ bond angle remains invariable as the theoretical level changes. The ϕ angle drops into the interval of [−57, −48] and the ψ value rises to [−31, −20].

We will further not comment on the structures of the molecules for space reasons. It is significant to report though that the 3_{10} helical motif is successfully located and we can thus proceed to the characterization of the collective helical vibrations of the oligopeptides. Full geometries of the minimized molecules in DFT (PW91$_{XC}$), semiempirical (PM3MM), and molecular mechanics (AMBER) levels are available in the Supporting Information (Tables 2S−18S). Energies are given for DFT results.

3.3. Vibrational Analysis. The vibrational analysis of the collective vibrations of the 3_{10} helix of polyglycine confirmed the analysis of our previous work on polysulfanes: In summary the molecular helices oscillate resembling a standing transverse longitudinal wave, or a cylindrical transformation to a cone or an ellipsoidal. The origin of these vibrations for the helix of polyglycine, though, differs surprisingly when we compare it with the origins of the same kind of collective vibrations of polysulfanes. This is a piece of evidence that is discussed below and confirms our comments in the previous paper,[27] which predicted differences in these vibrations due to structural effects in other molecules.

The description of each vibration will comprise a report and a general discussion of each characteristic vibration, the molecular representation, with Ace-Gly$_8$-NHMe in its extreme position, and the calculated frequencies that provide the characteristic motion in the DFT PW91$_{XC}$/6-31+G* level of theory.

As mentioned above, the study and analysis of the collective motions are confined to helical bend, helical stretch, and helical cylindrical shape transformation. We also have observed other collective vibrations, which may prove to be interesting as well, but their existence, analysis, and discussion is a subject of another research work.

3.3.1. Helical Bend 1c, 2c, and 3c. Figure 1B(0,1,2) depicts the 1c bend of the helical oligopeptide of glycine (helical bend 1c: 1 curve formed; helical bend 2c: 2 curves formed, etc....). The characteristics of this motion are identical with those observed in polysulfanes:

The helical axis is bending and a sinusoidal curve is forming in the interval of [0, π]. The molecular axis now resembles a

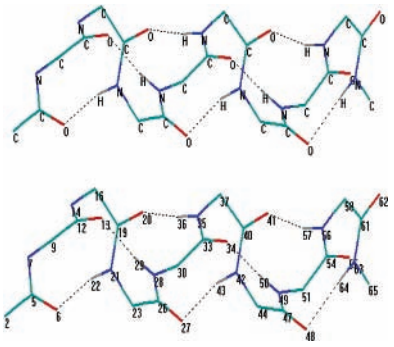

Figure 2. Labeling of the 3_{10} helix of the minimized nonapeptide of glycine in the $PW91_{XC}$/6-31+G* level of theory. The atom types and their respective numbers are shown. Hydrogens that are not part of a hydrogen bond are not shown.

standing transverse wave. Figure 1C describes the 2c bending vibration of the same oligopeptide of glycine of which its molecular axis is bending and a sinusoidal curve is forming in the interval of $[0, 2\pi]$. The molecular axis has two asymmetric curves during this oscillation, while in the 3c $[0, 3\pi]$ vibration it has three (Figure 1D).

The 1c bending vibration is always produced by the first and second normal mode in long polypeptides. In the tetrapeptide, only the first normal mode produces this motion. The only difference between the first and second normal mode is the direction of the oscillation: the first is perpendicular to the second. The 2c bending vibration follows which starts to appear in the hexapeptide and is generated by one normal mode. In the heptapeptide, two normal modes produce this motion, while in the octapeptipe and nonapeptide, it is produced by one more normal mode. The helical bend 3c is observed only in the nonapeptide and is produced by one normal mode.

For the helical bending, the generative force is the torsional vibration of C−C and C−N bonds. The exact combination became available after an exhaustive graphic study of the motion of each atom for every peptide under study for all levels of theory used. Because of the large amount of data we only present the results in the nonapeptide in the DFT level. The 1c bending vibration of the nonapeptide (normal modes 1 and 2) is generated from many C−C and one C−N torsion. The 2c (normal modes 3, 4, and 5) and 3c (normal mode 6) bending vibrations emanate from different combinations of C−C and C−N torsions. The numbering of atoms is shown in Figure 2. Hydrogens are excluded in the figure but are included in the numbering. This is mentioned so that no confusion appears because of the numbered hydrogens that are not present in the figure.

Normal mode 1: torsions of C12−N14, C16−C19, C23−C26, C30−C33, C44−C47, C51−C54. Normal mode 2: torsions of C16−C19, C23−C26, C37−C40, C51−C54, N56−C58. Normal mode 3: torsions of C16−C19, C30−C33, C37−C40, C51−C54, N56−C58, C58−C61. Normal mode 4: torsions of C23−C26, C30−C33, N35−C37, C44−C47, N56−C58, C58−C61. Normal mode 5: torsions of C12−N14, C16−C18, C23−C26, C30−C33, C37−C40, C44−C47, N49−N51, C51−C54, C58−C61. Normal mode 6: torsions of C5−N7, C9−C12, C16−C19, C23−C26, C30−C33, C37−C40, N42−C44, C51−C54, N56−C58, C58−C61.

It should be mentioned that in the same frequency both C−C and C−N torsions are observed. It seems that backbone vibrations and proper combination of them build the proper conditions for the production of bending collective helical vibrations.

An important observation that was not reported in our previous paper is that helical bending 2c and 3c are also twisting vibrations of the helix. This is a common phenomenon in biopolymer helices: These low-frequency helical vibrations are of mixed behavior and this is observed in DNA and in other helical peptidic chains.[17,18,24] The twisting vibration of a helical chain is characterized by the rotation of a part of the helix around its molecular helical axes.

In Table 1 there is a summary of the frequency and intensity values for all oligopeptides of glycine studied in this work, which produce helical bending. As the number of monomers increases the frequency for every characteristic helical bend falls.

The height of the wave that is formed during the helical bend 1c motion shows a calculated value of about 0.3 Å. The calculation is based on maximum Cartesian displacement during the oscillation.

3.3.2. Helical Stretch 1r. An impressive element of this work is that the helical stretching is limited in oligopeptides. The only stretching vibration that is clearly observed is the helical stretch 1r (Figure 3, helical stretch 1r, 1 rarefaction observed). The helix is elongated symmetrically and one region of rarefaction is formed, which contracts during the coming two-quarters of oscillation.

Helical stretches 2r and 3r disappear. Helical stretching 1r coexists in the same frequency with helical twisting. It is also impressive that the precursor of this helical oscillation is not angle bending but C−C and C−N torsions. For helical stretch 1r, the motion is molecularly global: Nearly all backbone torsional angles seem to contribute to this motion. For the nonapeptide this motion is generated from normal mode 7. Furthermore, this collective motion is described analytically below:

Normal mode 7: torsions of C5−N7, C16−C19, C19−C21, C26−N28, C33−N35, N35−C37, C40−N42, C47−N49, C49−N51, C51−C54, C54−N56.

Questions are arising from the observations above: Why do the other vibrations disappear? Why is the helical stretch generated from torsional and not bond angle vibrations as is done in polysulfanes?

The answer to the first question may probably be the primary structure of the oligopeptides. One difference is that the backbone of the polymeric sulfur is homogeneous (the sulfur atom) while the backbone of the peptides consists of two heterogeneous atoms C and N. In addition, every C atom is differently characterized because its chemical environment is not equivalent since different units are associated to C_a atoms in contrast to non-C_a atoms. This fact makes the backbone of a helical oligopeptide lose the symmetry of the motions of torsional angles, which polysulfanes may possess.

Another important element is the hydrogen bonding. Hydrogen bonding makes every coil of the helix more rigid and reduces the degree of freedom of the coil freedom. As a result, the asymmetric vibrations of helical stretching may not be expressed.

These two explanations are based on the optical characterization of the vibrations. The rigidity of substantiation of the answers above demands the design of a new study.

Vibrations that can be locally characterized as helical stretching are observed but they were not characterized as such since the symmetry and the collective helical motion did not give a clear collective stretching.

Figure 3 pictures the helical stretch 1r and a part of Table 1 presents the values of the characteristic frequencies. The reader can observe that as the number of oligomers rises the frequency moves to lower values.

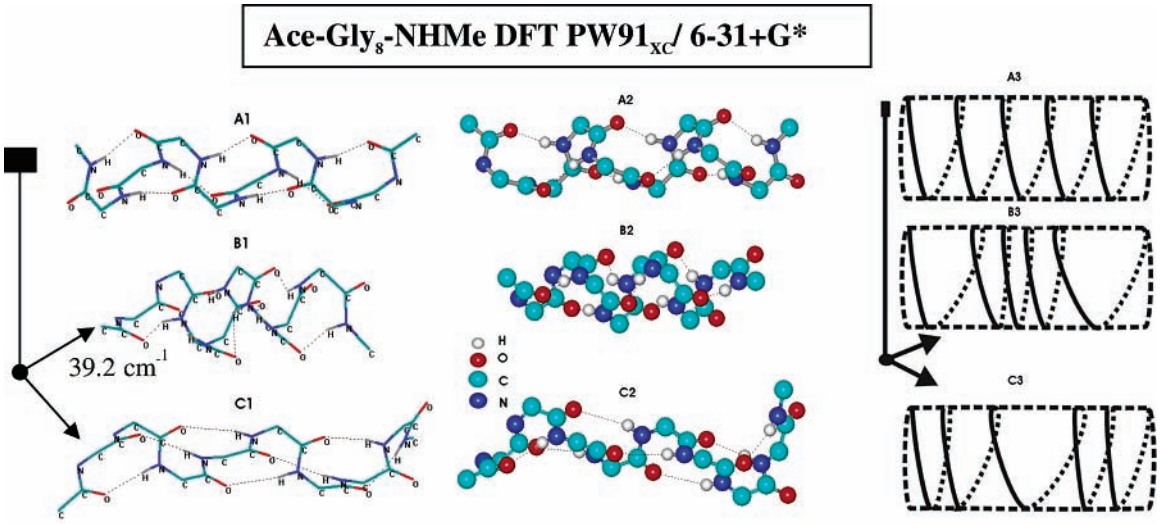

Figure 3. The helical stretching in the stick, the ball and stick, and the mechanical analogue representation. From top to bottom: (A) the helix in its equilibrium position; (B) the helical contraction is presented during the motion of helical stretch 1r, which appears at 39.2 cm^{-1}; and (C) the helical rarefaction during the helical stretch 1r is presented. Helical stretches 2r and 3r are absent in all molecules under study.

TABLE 1: Computed Frequencies and IR Intensities for the Characteristic Collective Helical Vibrations

	freq (cm^{-1})/intensity (km/mol) for Ace-Gly$_n$-NHMe DFT PW91$_{XC}$ /6-31+G*					
	$n = 3$	$n = 4$	$n = 5$	$n = 6$	$n = 7$	$n = 8$
helical bend 1c	27.3/0.8	22.7/0.8 28.0/0.1	20.5/0.2 24.6/0.5	18.4/0.3 23.5/0.5	18.1/0.4 19.8/0.1	15.0/0.2 15.6/0.1
helical bend 2c			29.9/0.1	27.2/0.2 33.4/0.3	26.7/0.2 31.0/0.3 34.6/0.4	22.5/0.1 28.3/0.5 32.5/0.7
helical bend 3c						38.0/0.7
helical stretch 1r	54.6/3.6	53.0/0.6	47.3/0.4	45.7/0.2	42.9/0.2	39.2/0.3
helical breath	274.4/7.4	275.5/7.3	275.4/9.2	274.3/13.3	274.9/15.4	274.5/16.3
helical cone		284.2/14.1	283.5/6.1	280.9/2.1	280.0/3.8	278.7/8.2
helical hyperboloidal−ellipsoidal					287.4/1.7	284.1/1.3

The amplitude of the oscillation for the nonapeptide is again calculated close to the value of 0.3 Å.

Such motions of the molecular helices may play a crucial role in the nanomechanical functionality. Molecular pistons may be based on these oscillations in principle (e.g. helical bend 1c and helical stretch 1r) in order to function while helical twist may be the principle of a possible molecular drill.

3.3.3. Helical Cylindrical Transformation: *Helical Breathing, Helical Cone, Helical Hyperboloidal−Ellipsoidal*. The vibrations concerning helicoidal cylindrical transformation due to radial changes are graphically represented in Figure 4. All transformations described in polysulfanes are present in polyglycine as well:

Helical breathing is described as a motion that forces the radius of the helix to fluctuate periodically between a minimum (contracted) and a maximum (elongated) value. The equilibrium value lies in the middle of this interval. The helix now resembles a breathing pulse. This motion is present in all molecules.

Helical cone is described as an asymmetric periodical fluctuation of the length of the radius of the cylinder: when it reaches the highest value at one end, it reaches the lowest value at the other. Consequently, a cone is forming during this oscillation. This motion is absent for the $n = 3$ (tetrapeptide).

Helical hyperboloidal−ellipsoidal is an asymmetric oscillation of the radius of the helix between the two ends of the helix and its part in the middle: when the radius reaches its highest value in the two terminal parts it reaches the lowest value in the middle. A hyperboloidal is forming that transforms to ellipsoidal after half of the period of the oscillation. As we have notice, helical hyperboloidal demands a minimum number of monomers in order to appear.

The difference that is observed in helical stretching between polysulfanes and peptides is also present here: the generative force and the precursor of the motion are not the same. Actually, bond stretching (polysulfanes) ceases to be the precursor of the motion. Now this role belongs to bond angle bending. Why is this happening?

Suppose that we have three atoms A, B, and C bonded sequentially with a bond angle of about 109°. If atoms A, B, and C are equivalent (example 1: S−S−S) then, when a bond stretch takes place the result of the forces acting on the atom in the middle (B) drives it to oscillate almost perpendicular to the line that joins the other atoms (A, C). If atoms A, B, and C are not equivalent (example 2: N−C−C) then when a bond stretch occurs for the A−B part it does not occur for the B−C part. Consequently, if these atoms are part of a helix, then in the first case that resembles sulfur helices, bond stretching is the generative force of radial changes, while in the second case, radial oscillation of the helix will not occur.

Bond angle bending frequencies of C−N−C and N−C−C are close and coincide. This fact causes a carbon atom (if proper timing of motions is present) to be under the influence of a resultant force that resembles the motion of the first case (oscillation almost perpendicular to the line that joins the neighbor atoms of B: A and C). Therefore, the ability of bond stretching to produce helical breathing, cone, and ellipsoidal is transferred to bond angle bending.

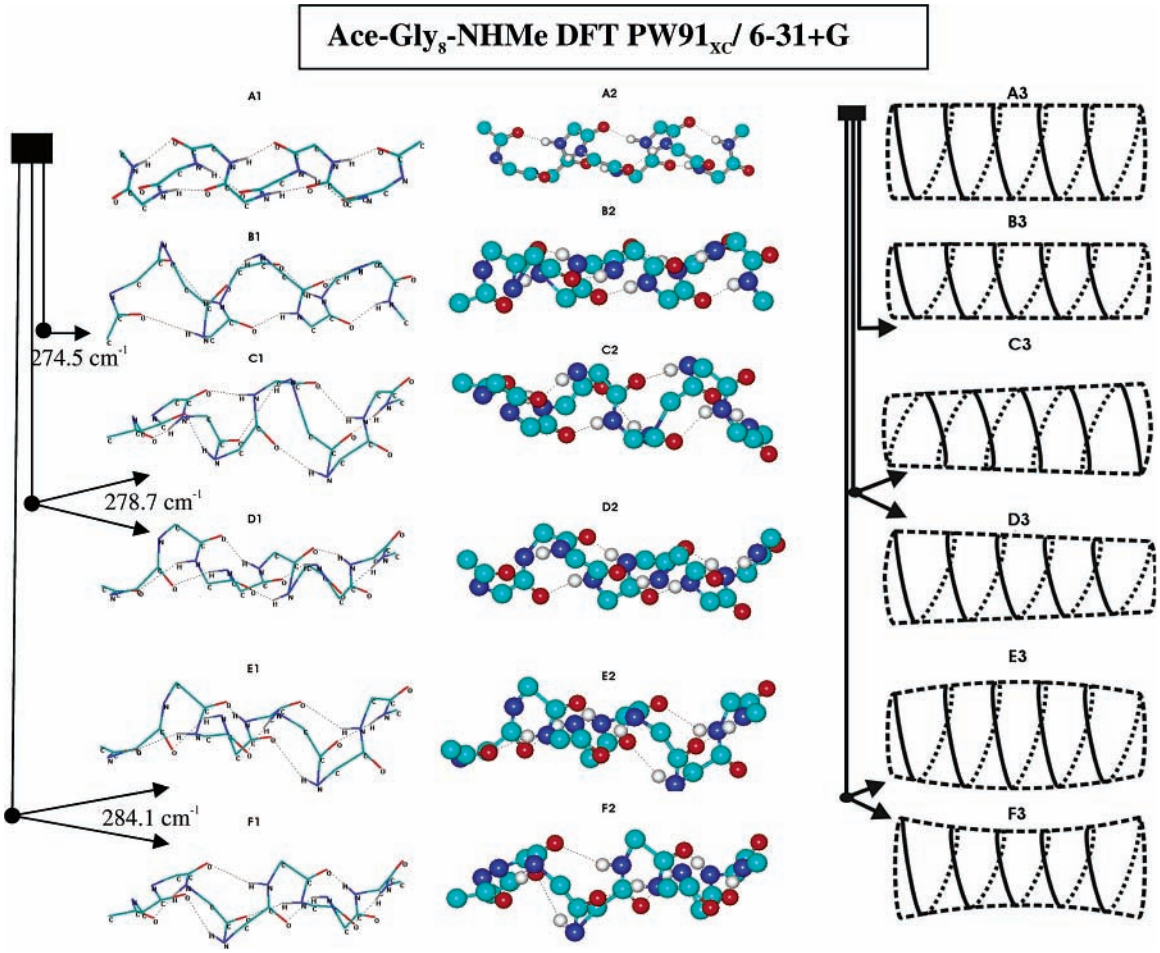

Figure 4. The helical cylindrical transformation in the stick, the ball and stick, and the mechanical analogue representation. From top to bottom: (A) the helix in its equilibrium position; (B) the helical breathing appears at 274.5 cm^{-1}; (C and D) the helical cone in its two extreme positions during the oscillation (this motion appears at 278.7 cm^{-1}); and (E and F) the helical hyperboloidal and ellipsoidal, respectively. The two extreme positions of the same oscillation appear at 284.1 cm^{-1}.

Usually, the terminal parts of the helical chain do not participate in the motion of helical breathing. This exception is probably due to the limitations of the dipeptide approximation, which neglects the dynamics of interaction of the subunits.[76]

The results of the calculations of the frequency values for each characteristic oscillation for every oligopeptide are presented in Table 1 as well. The values of helical breathing as *n* rises are almost invariable while helical cone and helical hyperboloidal−ellipsoidal values seem to fall as *n* rises.

3.3.4. Intensities. The values of IR intensities show that helical bend and stretch are IR inactive (the intensities interval for every helical bend and stretch for every molecule is between 0.1 and 0.8 km/mol). Helical breathing, cone, and hyperboloidal−ellipsoidal values should show a weak peak in the IR spectrum (maximum intensity: 16.3 km/mol helical breathing for $n = 8$). Raman active vibrations were not calculated. However, we report all the characteristic collective helical motions that we observe even if they are IR inactive for two reasons: (a) in order to fully describe the spring-like behavior of helical molecules and (b) because such motions are currently observed by employing special experimental techniques. Current experimental efforts for the observation and interpretation of low-frequency motions are described in a recent work (see ref 30 and references therein). One of these techniques is the time-resolved optical Kerr-effect spectroscopy that is applied to di-L-alanine, poly-L-alanine, and lysozyme in solution for the study of the low-frequency dynamics.[30] The assignment of low-frequency modes, some of which have been observed in the spectrum either in solution or in the solid phase, is still a matter of debate. The interpretation involves normal mode calculations, neutron scattering experiments, and analytical model calculations.

3.3.5 The Heteropolymeric α-Peptidic Helix. The results of the mixed (heteropolymeric) α-helical peptide of glycine-alanine produced a better pictorial representation of our findings, based on the longer helical chain. A piece of these results is presented graphically in Figure 5. All the expected motions appeared and, furthermore, the length of the helix gave us the ability to observe the expected vibrations of helical bend 3c, 4c that are not expressed in shorter lengths of molecular helices such as nonapeptides. The importance of these results is further fortified by the fact that this level of theory is applicable to longer molecules. Nonetheless, frequency calculations concerning peptides in this level of theory should always be escorted either by high-level theory on small molecules or by well-documented material.

3.3.6. Ace-Ala4-NHMe. The computed frequencies of 3_{10}-helical pentapeptide of alanine reproduced the motions that were described for the 3_{10} helical pentapeptide of glycine. Helical bend 1c was produced by the first two modes. Their frequencies and intensities are 21.5 cm^{-1}/0.2 km/mol and 23.8 cm^{-1}/0.3 km/mol, respectively. Helical stretch 1r is present at 44.4 cm^{-1}. Its intensity is 1.1 km/mol. Helical breathing and helical cone were found at 262.2 and 285.3 cm^{-1}, respectively. The intensity of helical breathing is 19 km/mol while for helical cone it is 4 km/mol. The precursors of these motions are the same with those described for glycine oligopeptide.

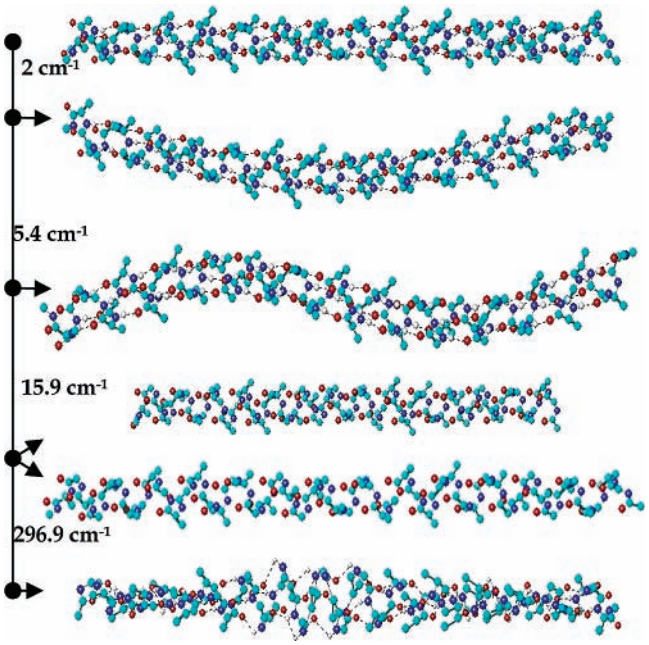

Figure 5. Helical vibrations of the 50-peptide of glycine-alanine in sequential alternation. Minimization was done employing the AMBER force field. From top to bottom: (1) the helical bend 1c is excited at 2 cm^{-1}; (2) the helical bend 2c is found at 5.4 cm^{-1}; (3) the helical stretching 1r is found at 15.9 cm^{-1}; and (4) the helical breathing is found at 296.9 cm^{-1}.

The results of alanine oligopeptide validate the use of glycine as a model. All the predicted motions in glycine oligopeptide are present in alanine oligopeptides as well. Small differences in intensities and frequencies are observed. Side chain effects are present though. At the frequency of 215 cm^{-1}, a mode that is generated mainly from side chain motion and resembles helical breathing was observed. Also, helical stretch is observed in parts of the helix. These results indicate the importance of the study of glycine: The side chain effects on the backbone motion of a polypeptide are located more easily when they are compared with the backbone that is not affected by side chain interactions. We are currently working on side-chain effects on such motions and the results will be presented in a future paper. The minimized structure of the alanine oligopeptide in Cartesian coordinates is given in the Supporting Information (Table 19S).

3.3.7. Sensitivity of the Results to Grid Quality. The quality of grid in DFT calculations is an important parameter for successful results. It influences both the minimization procedure and the normal mode calculations in the low-frequency region. In G98 v. A7, there are four choices available for the quality of grid: (a) a 35 110 grid, (b) a pruned version of (50 194) grid, (c) the default grid, which is a pruned (75 302) grid, and (d) a pruned (99 590) grid. The first two choices are not recommended for production calculations.[77] The frequencies and intensities of covalent dipeptides of glycine and alanine in C_7^{eq} conformation, minimized with the pruned (75 302) grid and the pruned (99 590) grid, are given in the Supporting Information (Table 20S). In general, the results are very similar for glycine dipeptide while for alanine dipeptide an important difference is observed for the first mode: The frequency produced by the 99 590 grid is 21.7 cm^{-1} lower than the other. The first two modes in both alanine and glycine differ. With the exception of the first mode of alanine, the difference is not higher than 8 cm^{-1} though. The visualized motion of both molecules shows the oscillation is the same for both grids. Considering that the covalent dipeptides are short, we can conclude that the quality of grid may have a bigger effect in longer peptides. As a conclusion, we suggest that for small molecules the highest quality of grid should be used while for longer molecules, where the computational demands are higher, it should not certainly fall below 75 302.

If the highest accuracy is demanded in the low-frequency region, anharmonic treatment is required since scaling factors show many discrepancies in the whole range of frequency calculations especially in cases where hydrogen bonds are present.[78,79]

The present work proves that peptidic helices are able to behave like mechanical springs. Because of their dimension, we suggest that they can be characterized as nanoscale building blocks. As S. C. Glotzer et al. suggest "...The functionalization of these nanoscale "building blocks" (NBBs) opens exciting new avenues for creating designer materials and devices by directed assembly."[80] Molecular motors[81] and pistons[82] are some of the applications in which molecular springs could play a key role.

4. Conclusions

A synopsis of the main attainments of this work is presented below:

To our knowledge it is the first time that DFT (PW91$_{XC}$) is employed for the calculation of the frequencies of the 3_{10} helical oligomers of glycine (Ace-Gly$_n$-NHMe with $n = 3-8$). A study of the helical low-frequency vibrations of a polypeptide of such length or a helical protein employing correlated ab initio theory or DFT had not emerged in the scientific literature before.

The oligomers of glycine share the same backbone with every polypeptide, but they are free of side chain effects, something that appoints them as a first-rate prototype for high-level polypeptidic calculations.

We confirmed findings of our previous theoretical work in polysulfanes by their presence in oligomers of glycine:

We found that helical bend *k*c [$k = 1, 2, 3$] (where 1, 2, 3 declares the number of curves, respectively), is present, and the helical axis resembles a transverse wave of the form of a sinuous curve(0, $k\pi$) [$k = 1,2,3$]. These motions originate from C−C and C−N torsions. Global helical stretch *k*r is also present for $k = 1$ forming one region of rarefaction and stemming from C−C and C−N torsions as well. We did not observed global helical stretch with 2 and 3 regions of rarefaction as in polysulfanes although some motions partially resemble such oscillations. One possible explanation for the disappearance of these motions could be the hydrogen bonding and the heterogeneity of the backbone atoms.

We also confirmed the existence of two collective motions that came up for the first time in the scientific literature for polysulfanes: helical vibrations yielding the helical cone and the helical hyperboloidal−ellipsoidal:

Bond angle bending of the backbone atoms C, N, and C produces (i) global helical breathing where the radii of the turns uniformly oscillate, (ii) transformation of a cylindrical to conical helix, and (iii) transformation of a cylindrical helix to the hyperboloidal−ellipsoidal helix. To our knowledge, it is now the first time that these motions are presented for helical polypeptides. On the basis of both works, we suggest that such helical motions must be universal.

The origin of the helical stretching and cylindrical transformation is qualitatively different: In polysulfanes the precursor was bond angle bending and bond stretching, respectively. On the contrary, torsions are responsible for the former motion and bond angle bending for the latter.

As the number of residues rises, more helical bending and cylindrical transformation appear. Helical bending with $k > 3$ is expected in longer helices while more local barrel like shapes

(ellipsoidal or hyperboloidal) are expected to form on the cylinder of the helix.

The frequencies of longitudinal and transverse transformations exhibit a decrease as the number of residues increases, while breathing, conical, and hyperboloidal vibrations are almost invariant.

The importance of the existence of such orchestrated motions in biological molecules is truistic. Such motions have been connected in the past with critical functions of the molecules of life.[16]

The study of collective helical motion was also extended to a heteropolymeric α-helix of 50 residues, based on molecular mechanics, with identical results. These results imply that molecular mechanics is qualitatively consistent with high-level theoretical results. Furthermore, it permits the study of biomolecules, the size of which sets them computationally interdicted.

Other biologically important molecules are polysaccharides and polynucleotides. Their backbone is substantially different; consequently, vibrational calculations of their helical structures at this level would be desirable.

On the basis of the fact that these motions are environmentally sensitive,[16] we suggest that such studies could also be extended to helices in solution.

The sprouting, as suggested recently in the literature, ability to handle molecular motion based on radiation (e.g. light-control molecular shuttles[83] phototriggered molecular springs[40]) boosts our efforts for possible nanomechanical applications.

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Supporting Information Available: Scheme of the efforts for the location of 3_{10} helical structures, selected structural data of the molecules studied, and Cartesian coordinates of the structures of glycine oligopeptides in every theoretical level studied and their energies in the DFT level. This material is available free of charge via the Internet at http://pubs.acs.org.

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