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MODEL CALCULATIONAL APPROACH TO THE CONFORMATION OF ADSORBED POLYPEPTIDE FRAGMENTS

Timothy J. McKeon

Introduction

The focus of the paper is to examine possible conformational changes of peptides when placed in the presence of a poly-synthetic material. A major concern in the pharmaceutical industry is the loss of potency of polypeptide drug products during processing, packaging and storage. An example of this is polymer syringes being used in place of glass ones. The effect is that some protein-derived products experience structural changes due to contact with the polymer. This is otherwise known as surface denaturation. In order to understand the energetics of interfacial polypeptide systems, a calculational approach was used via the program Alchemy. The organization of this paper is as follows: first, is the manner in which the peptide bonds are arranged and the ways in which they were synthesized on the computer screen and shown in three dimensional space. Ideas incorporated into the "experiments" will follow. In conclusion, a comparison of the stable structures to those in the model interfacial systems will be given. If these experiments can be shown to give reasonable results this setup could potentially save time and money, and further be used in the development and understanding of potential laboratory experiments.

Background

In discussing this project and its concepts it is necessary to have a basic working knowledge of the peptide nomenclature. Polypeptide structures generally have four types of structures, primary, secondary, tertiary and quaternary. In this paper, the secondary structure is the most significant. The secondary structure or conformation has three specific subgroups within it, alpha-helical, beta-sheet and random coil structures. These structures become stable due to the internal hydrogen bonding. In setting up the model molecules bond angle information was needed. More specifically what was discovered is that the two main structures of interest alpha-helix and beta-sheet were described in terms of torsion angles. The peptide bond is often considered to be planar which infers that the HNCO atoms all lie within the same plain. Then, came the more difficult task of defining phi and psi, the torsion angles on either side of the peptide bond. These can be more fully explained by referring to Figures 1 and 2, in which phi is described as the rotation of the the HN bond about the NC bond with respect to CC' bond. Psi however resides on the other side of the peptide bond, and is rotation of the NC bond about the CC' bond with respect to the OC' bond. Where C refers to the alpha-carbon with the R group attached to it, and C' is the carbon double bond oxygen. These angles are said to be zero when the molecule was flat and the bonds on each end of the torsion angle are in a cis configuration.¹ In other papers x-ray data had been used to determine regions of stability and the phi and psi angles that corresponded to these low energy states. These stable regions can be seen in Figure 3.²

The modeling package being used to complete the calculations and minimum energy state determinations is Alchemy. Alchemy contains programs for some good "hands on structure building" and the minimizer program which were the two main features which brought it to be the package of choice. Alchemy takes into account all the energies in the molecules from bond energies to van der Waal effects. The equation used by Alchemy for the total energy is $E = E_{str} + E_{eng} + E_{str} + E_{vdw} + E_{cop}$ where the subscripts describe the energies considered as follows:

str - bond stretching
 ang - angle bending
 tor - torsion deformation
 vdw - van der Waal's interactions
 oop - out-of-plane bending

The bond stretching and angle bending are self-explanatory. The torsion deformation is the moving of a torsion angle away from the zero torsion angle. The van der Waal's interactions are the attractions and repulsions between two atoms in a molecule as determined by their atomic radius, the distance between them and any charge they might contain. This includes bonded and nonbonded atoms within the molecule. Out-of-plane bending is the term that takes into account the interactions of perimeter atoms attached to a central atom, this includes sp^2 and aromatic atoms in which a modification to the equation is used. In the case of sp^3 atoms, the plane refers to the trigonal base opposite the atom in question. For the latter cases the out-of-plane distance refers to the distance from the base line between the two adjacent atoms.³

Experimental Design

In experimental design the idea was to choose appropriate molecules such that the experiments could be easily visualized and manipulated, since some of the concepts were very complicated. Also, there was some need to attempt to keep the experiment relevant to a process environment. With this in mind, the two polymers chosen for study were polyethylene and polyvinylalcohol. Since, many of today's storage media are polymeric materials rather than glass these seemed to be good choices. They were simple structures and both hydrophilic and nonhydrophilic interactions could be studied. The peptide chosen was glycine, since it had the simplest R group side chain. At times the pictures become confusing and difficult to understand, so it was necessary to use one that was simple in the beginning.

The alpha-helix that was used is a right hand structure and if it had chiral centers would be an L-amino acid, as these are more common. From figure as described above stable angles of phi and psi equal to 120 degrees. This structure was built as well as the structures for the polymers and each was minimized individually. Then, each of the polymers was placed in the presence of the alpha-helix and these were each minimized.

Results

alpha-helix	E(kcal/mol)	E_{str}	E_{ang}	E_{tor}	$E_{oop}E_{vdw}$
alone	23.48	3.09	9.40	48.11	.3287-37.45
ethylene	12.44	4.05	9.97	48.46	.4135-50.46
alcohol	26.83	7.03	20.0	56.17	.2544-56.61

The overall energy of the alpha-helix and polyvinylalcohol system is slightly higher than the alpha-helix alone, and the alpha-helix and polyethylene system is by far the lowest. The alpha-helix and polyvinylalcohol system has the largest potential for intermolecular interactions as reflected by the large E_{ang} of 20 kcal/mol as opposed to 9-10 kcal/mol for the other 2 systems.

Conclusions and Future Work

From the data obtained it can be seen that there is a significant difference in the overall energy of the molecules in the different systems. It can be seen also from Figures 3, 4, and 5 that there is a difference in the structure from the initial alpha-helix consisting of bond angles of 120 degrees for phi and psi. The angles varied in some instances by as much as 20 degrees. The low value for E in the polyethylene system shows that adsorption would be probable. Since the

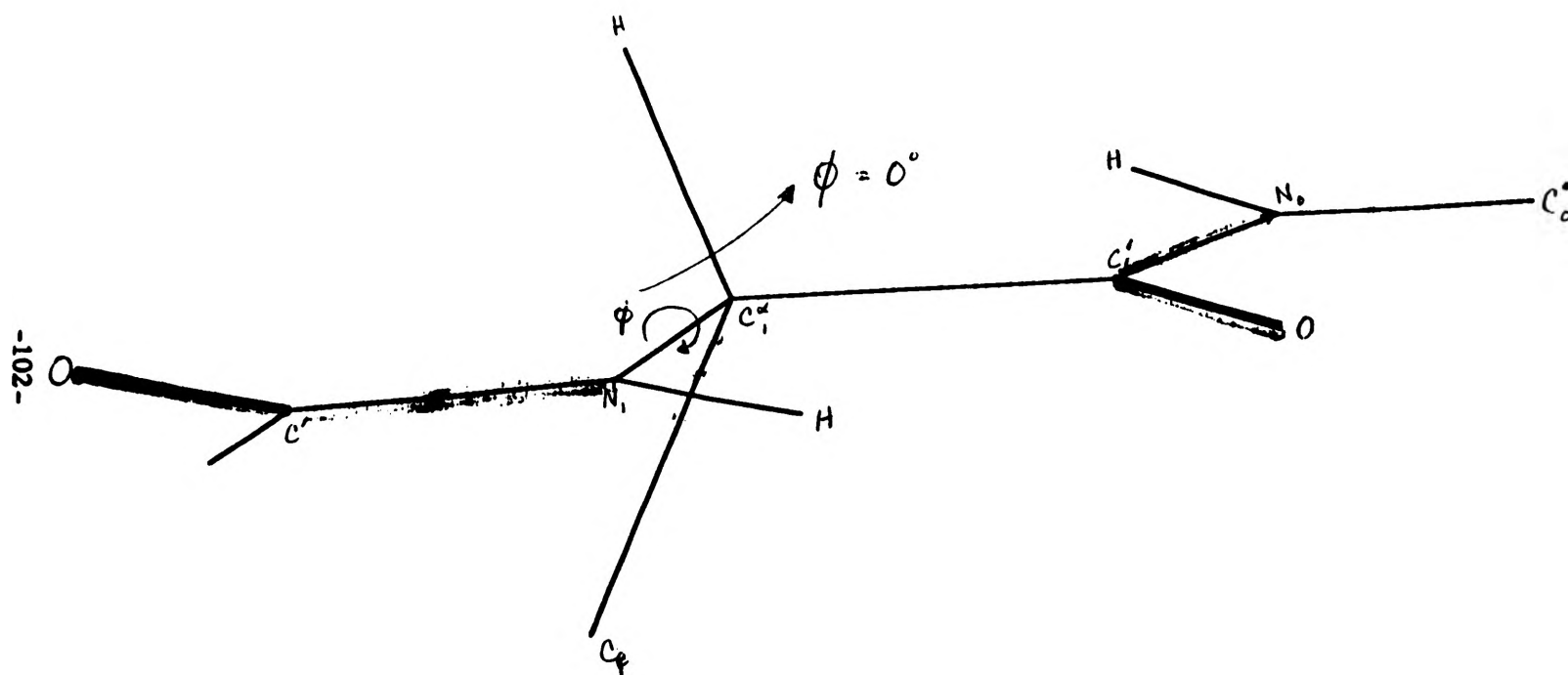
major influencing factor is the large value with respect to E_{vdw} , while the other values are essentially the same as those in the single molecule system. The slight difference in overall energies of polyvinylalcohol/alpha-helix systems shows that there would be none, or maybe slight adsorption.

In the future these ideas will hopefully be carried on and the systems under consideration will become more realistic. There is another system to be considered called Sybil which is more accurate and could possibly handle larger systems. Another consideration is certainly the dynamics of such a system, how long does it take for this change to occur. In the future this could hopefully provide insight without the loss of costly chemicals and/or time.

References

1. "A Proposal of Standard Conventions and Nomenclature for the Description of Polypeptide Conformations"; *Biopolymers*; Vol. 4, 1966; pp. 121-130
2. Walton, A. G. and Blackwell, J.; *Biopolymers*; Academic Press, 1973; New York; pp. 34-37
3. *Alchemy Handbook*

TOP OF PAGE
UPPER RIGHT
 ϕ , phi
2/2/11
L configuration



-102-

Figure 1: Torsion Angle, ϕ , when equal to zero degrees

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ψ , psi

2/26/91

L configuration.

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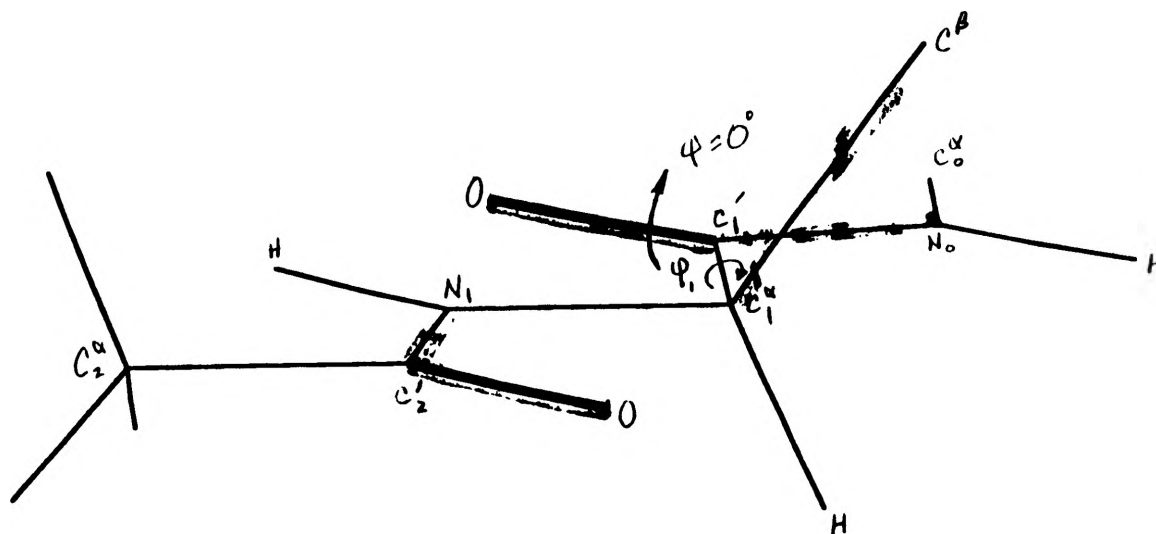


Figure 2: Torsion Angle, ψ , when equal to zero degrees

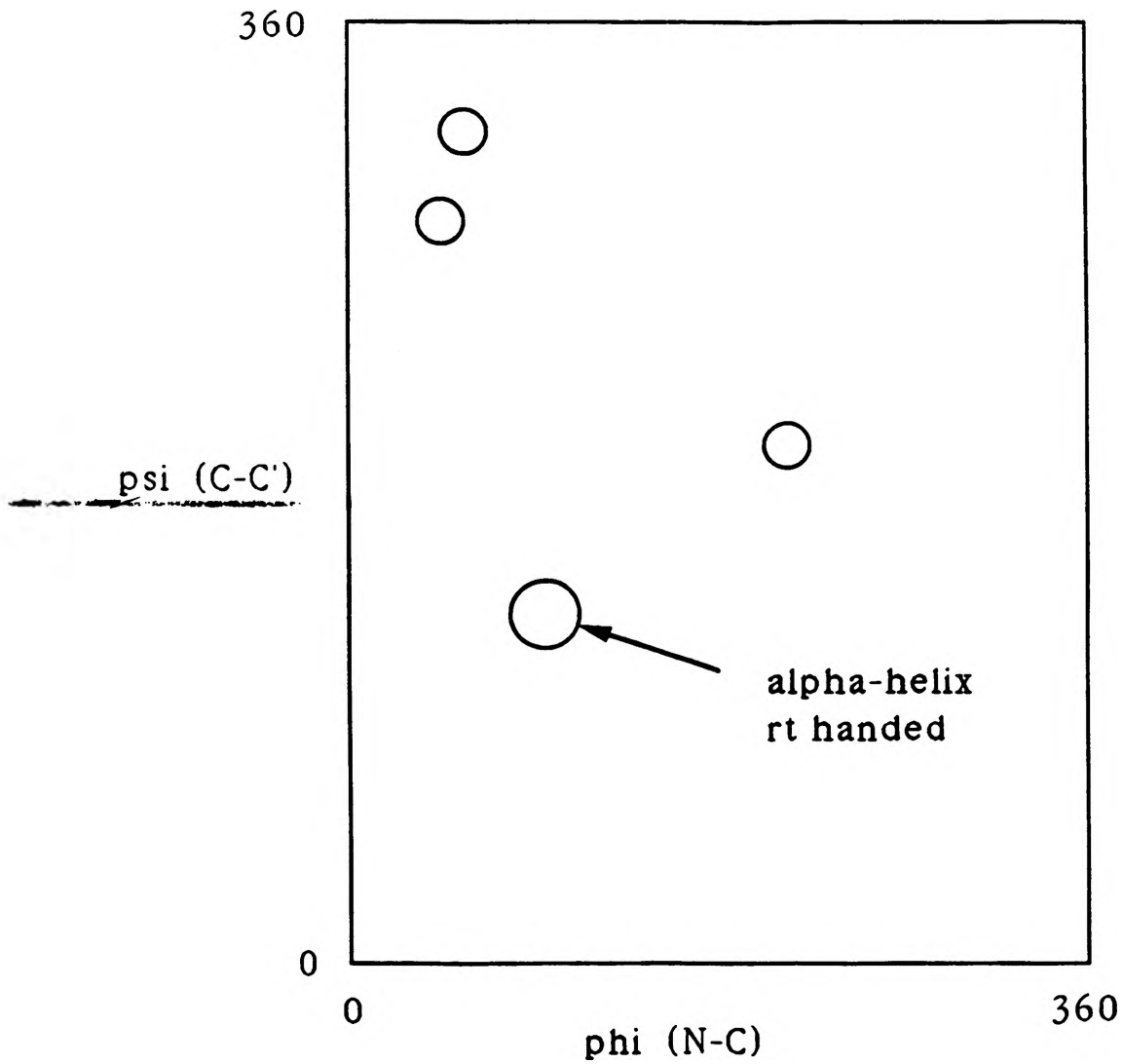


Figure 3: Stable regions for ϕ and ψ angles

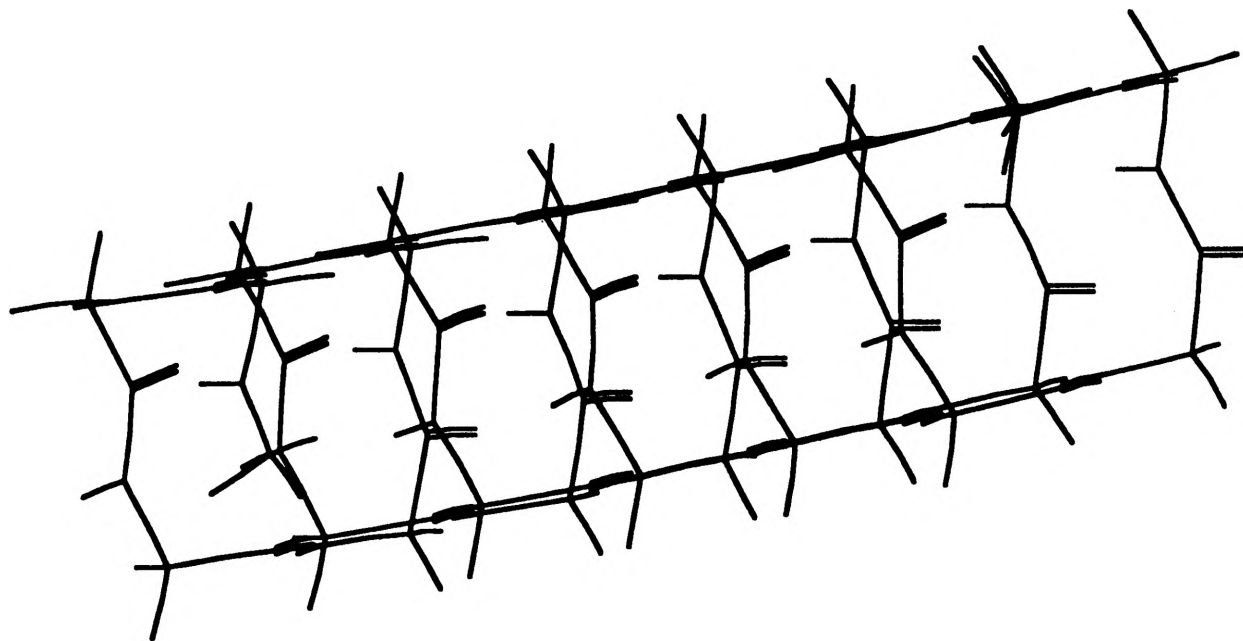


Figure 4: α -helix molecule, right handed $\phi = \psi = 120^\circ$

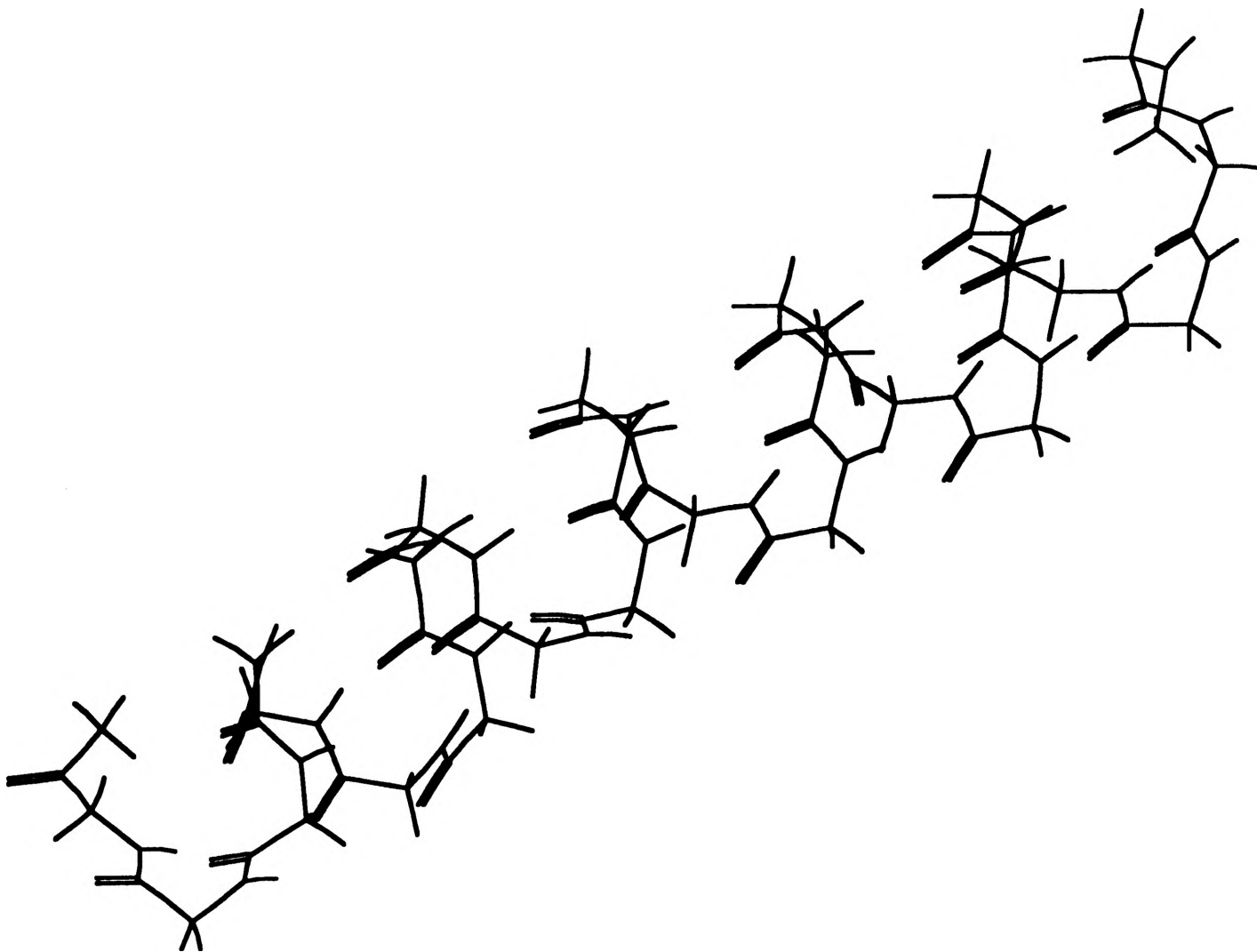


Figure 5: α -helix, right handed, after minimization in presence of polyvinyl alcohol.

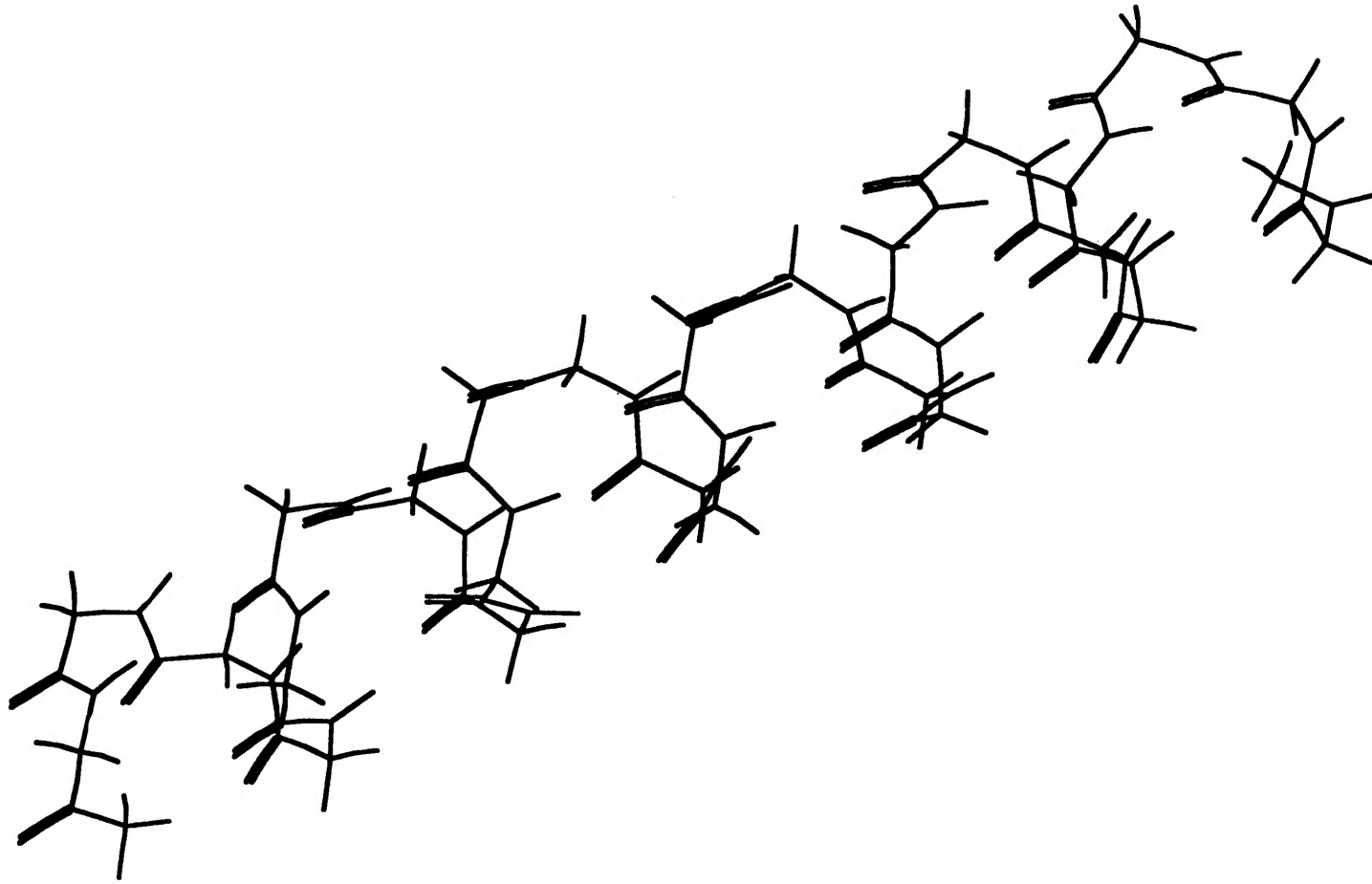


Figure 6 : α - helix, right handed , after minimization in presence of polyethylene