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De Santis P, Giglio E, Liquori A M & Ripamonti A. Stability of helical conformations of simple linear polymers. *J.Polym. Sci. Part* A—*Gen. Pap.* 1:1383-404, 1963. [Istituto Chimico, Universita di Napoli, Naples, Italy]

The use of van der Waals functions to describe the interactions among nonbonded atoms in simple polymers has allowed prediction, with surprising accuracy, of their most stable conformations. The most prominent features of the potential energy diagrams are discussed in connection with the possibility of predicting the regular conformations of macromolecules. Preliminary results obtained in the conformational analysis of polypeptides are mentioned. [The *SCI*® indicates that this paper has been cited in more than 195 publications.]

Conformational Energy Calculations of Macromolecules

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The first attempt to evaluate the conformational stability of linear polymers was tried during the preparation of my thesis in 1958-1959, at the Universita di Bari, Italy, supervised by A.M. Liquori.

He first realized the possibility of predicting the most stable conformations of a linear polymer in the solid state by locating the deepest minimum of the conformational energy as evaluated in terms of the internal parameters. The work hypothesis was that the van der Waals intramolecular interactions in macromolecules would play the major role in determining the structure.

Adopting the principle of the conformational equivalence of the monomer units, the conformational energy diagrams of the regular structures of some linear polymers were obtained in terms of the torsional angles of the monomer unit, summing up the van der Waals pairwise interactions among all the nonbonded atoms. We used semiempirical potential energy functions obtained by different authors from scattering experiments of molecular beams and second virial coefficient data. Such van der Waals functions were, at that time, used to reproduce the thermodynamic behavior of simple gases.

Different functions were explored, and a consistent set of van der Waals potential functions was selected for the most common atom pairs in polymers. As a matter of fact, the deepest minima of the conformational diagrams were found very near to the representative points of the experimental structures of polymers investigated, as obtained by X-ray fiber diffraction methods.

Publication of these results was delayed because the laboratory was mainly interested in other topics. Also, the lab was transferred to the University of Naples. They were published in *Il Nuovo Cimento* prior to the *Journal of Polymer Science,* but the principles were previously illustrated in a lecture by A.M. Liquori at the IV Corso Estivo di Chimica and published in the proceedings.[2]

The postscript to the story is that the theoretical calculations were extended to more complex macromolecules, such as the polypeptides (the first conformational diagrams of poly-L-alanine, polyglicine, and poly-L-proline *(trans and cis)* were published in *Nature*[3]), in good agreement with the experiments. They also were extended in the theoretical prediction of the molecular structure of natural peptides, such as Gramicidin S and Actinomycin.[4]

Methods based on the evaluation of the conformational energy (model building and molecular dynamics) are currently and successfully used in many laboratories in the structural investigation of complex macromolecules as proteins, where they are supplemented by X-ray or NMR data. I recently obtained striking results in the prediction of sequence-dependent superstructures of DNA.[5] While other contributions to the conformational energy are included in the calculations, the dominant role of the van der Waals interactions remains well established as the main determinant of the conformational stability of macromolecules.

Theoretical conformational analysis is, at present, a simple and heuristic approach to a wide variety of problems in many areas of chemistry and biochemistry.

1. **De Santis P, Giglio E, Liquori A M & Ripamonti A.** Conformational analysis of some linear polymers in the solid state. *Nuovo Cimento* 26:616-8, 1962. (Cited 35 times.)
2. **Liquori A M.** Chimica inorganica. IV Corso Estivo di Chimica. Varenna. Rome. Italy: Accademia Nazionale dei Lincei. 1959. p. 311.
3. ----------. Van der Waals interaction and stability of helical polypeptide chains. *Nature* 206:456-8, 1965. (Cited 160 times.)
4. **De Santis P, Rizzo R & Ughetto G**. Structure of Actinomycin based on conformational studies. *Nature* 237:94-6, 1972.
5. **De Santis P, Morosetti S, Palleschi A, Savino M & Scipioni A**. Structural information in deterministic fluctuations of base sequences in DNAs. Theoretical prediction of DNA superstructures. (Clementi E & Chin S, eds.) *Biological and artificial intelligence systems.* Leiden. The Netherlands: ESCOM, 1988. p. 143-61.

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