Study of Nucleic Acids and Protein Structure and Function by Methods of Computational Chemistry

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The high fidelity of DNA replication has been maintained by at least three different discrimination steps. The first step occurs at the template-primer complex, and it is assumed to be governed by the free-energy difference between complementary and noncomplementary base pairs. The elucidation of structure and energetics of mutagenic mispairs has been the focus of this laboratory in the past two decades. A brief review of our achievements involving quantum mechanical, geometrical, conformational and molecular mechanical studies on the elucidation of molecular mechanism of point mutations will be presented. Recently our research has been expanded by utilizing the molecular dynamics (MD) simulation technique to study oligonucleotide duplex structures in solution. As a first step along this direction, the results on the analysis of normal Watson-Crick paired DNA oligonucleotide duplex structure by the MD simulation technique will be presented. The MD simulation was performed on the hexamer duplex, (dG)g.(dC)g, including counter ions and 292 water molecules for 60 ps. The resulting time averaged structures presented unusual hydrogen bonding patterns accompanied by large propeller twists. Similar structures were found in the crystal studies of oligo(dA).oligo(dT) stretch. The correspondence with available experimental data will be discussed further.

Another example of the application of modeling to the structure of biological molecules is our work on the structure of calmodulin and its interaction with various peptide antagonists. Calmodulin has been shown to play a role in the process of DNA synthesis and repair. Inhibition of calmodulin activity via calmodulin antagonists has been shown to block the initiation of DNA synthesis and prevent DNA repair. We report a structure for the complete calmodulin molecule that has been computed based on a 2.2 Å resolution set of C-alpha coordinates. A virtual bond analysis program, developed by Purisima and Scheraga, was used to determine the backbone conformation. The molecule was optimized using CHARMM. Calcium ions were treated explicitly. The computed model and a recently reported crystal structure of the complete structure are compared. Positional displacements as well as differences in backbone and side chain conformation are discussed.

Monte Carlo Studies of Solvation of Amino Acid Derivatives

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Solvation of proteins and ligands by water plays such an important part in folding and docking that efforts are continually needed to improve the quality of calculations aimed at simulating this solvation. We have chosen to investigate the solvation of amino acid residues. This has been done before by others, but we have made a number of essential improvements in our calculations.

In an earlier work (e.g., Reference 1), geometries were obtained from the crystallographic data bank, and charges were calculated by CNDO methods. We maintain that the crystallographic structures cannot be regarded as adequate representations of the structures in solution, and we have chosen instead to use MINDO/3 methods, which give both an optimized geometry and considerably improved values for the partial charges.

Another deficiency of earlier calculations is the inferior quality of the force fields used. The force fields available for such calculations have undergone a dramatic improvement in recent years. For example, Weiner, Kollman, *et al.* have proposed[2] a second-generation force field specifically for the molecular mechanical simulation of nucleic acids and proteins, which corrects for some apparent inconsistencies in earlier force fields and also argues successfully for the explicit use of hydrogen bond potentials. Together with partial charges taken from the MINDO/3 calculations referred to above, the new potential functions should represent the best force field available at present.

The previous calculations[1] have furthermore been carried out on amino acids in their zwitterion form. This is, of course, a valid model for the amino acids themselves in aqueous solution, provided that satisfactory values for the atomic charges are used. What is of much greater interest, however, is to study the behavior of amino acid residues as they occur in a peptide chain. Here, with the exception of the terminal residues, both the amino group and the carboxylate group are blocked by adjacent residues, and thus the electronic nature of these residues is very different from what it would be in the free amino acid or its corresponding zwitterion. The particular interest in studying amino acid residues as they occur in peptides is related to important questions such as how protein–protein interactions are formed and how proteins fold. The amino acid derivatives chosen for this work are the N-acetyl amides. MINDO/3 calculations show that, from the point of view of electronic charge distribution, these can be regarded as valid models of amino acid residues in a peptide chain. These can thus be used to simulate the solvation of an amino acid residue as it would appear in a peptide chain.

The method for doing this is the Monte Carlo method of Metropolis *et al.*[3] This is a method for evaluating equilibrium thermodynamic and structural properties of a system of molecules, based on the theory of Markov chains. The equilibrium state is simulated by generating molecular configurations belonging to the Boltzmann energy distribution. This requires many evaluations of the potential energy functions, and it is in this way that they are responsible for the quality of the resulting prop-