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

Robert Rein, Masayuki Shibata, Joseph McDonald, Mary McCourt and Theresa Zielinski
Roswell Park Memorial Institute, Department of Biophysics, Buffalo, NY 14263, USA

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

Robert Bywater and Mark Wojcik
Pharmacia AB, Uppsala and Department of Inorganic Chemistry, Uppsala University, Sweden

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-

erties. Such simulations can also indicate the effects of including different kinds of intermolecular forces, and so can help to model the real system with greater fidelity.

The present work will demonstrate, using molecular graphics, and discuss hydration structures around amino acid residues as they would appear in a peptide chain. Future work will address the importance of cooperative effects (i.e., explicit polarization forces) on the hydration structures and energetics.

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Modeling and Measuring DNA Deformation

Richard Lavery
Institut de Biologie Physico-Chimique, 13 rue Pierre et Marie Curie, Paris 75005, France

Experimental evidence on the biological role of fine structure within DNA is rapidly accumulating. In principle, theoretical modeling should be able to help in deciphering this new "code"; however, the size and complexity of the molecular systems involved has hindered progress in this area.

Recent developments in our laboratory have led to two new methodologies that should improve the situation. First, we have developed an energy minimization procedure, specifically oriented to the treatment of nucleic acids, which directly uses helicoidal parameters as variables. We are thus able to describe DNA oligomers with 10 times fewer variables than are necessary in classical molecular mechanics. At the same time, we are able to study much more easily the energy dependence of structural deformations. Second, we have formulated an algorithm for rigorously describing the conformation of irregular nucleic aicd oligomers and, in particular, their curvature. We will present applications of these techniques to studying the influence of base sequence on the fine structure, the flexibility and the conformational transitions of DNA.

Modeling Organometallic Reactivity Using Quantum Chemistry and Molecular Graphics Techniques

Jacques Weber, Pierre-Yves Morgantini and Peter Fluekiger
Laboratory of Computational Chemistry, University of Geneva, 30 quai Ernest Ansermet, 1211 Geneva 4, Switzerland

A new formalism has been developed in order to evaluate the intermolecular interaction energy between an organometallic or inorganic substrate S and an incoming reactant R in the framework of the extended Hückel (EH) method. Approximate procedures are used to estimate electrostatic (E_{es}), charge transfer (E_{ct}) and exchange repulsion (E_{ex}) components, which leads to short response times that make it possible to use the model as a routine tool on an interactive molecular graphics facility. Test calculations performed for ferrocene and iron pentacarbonyl have indeed shown that a model based on the electrostatic component alone is not adequate for describing electrophilic or nucleophilic attack. Therefore, in addition to the electrostatic potential of S, evaluated using EH wavefunctions and the NDDO or the Mulliken approximations for the one-electron integrals, we have derived a model based on the S–R orbital interactions at the EH level to estimate the E_{ct} component. Finally, the short range E_{ex} exchange repulsion energy is approximated using the hard spheres model for S–R interaction on the molecular surface of S. The total S–R interaction energy is then used as a reactivity index and evaluated at selected points belonging to the molecular envelope of S, a proton with an empty 1s orbital being chosen as the model electrophile, and an H^- hydride ion with two 1s electrons as the model nucleophile.

Color-coded three-dimensional Connolly dot surfaces are used for the graphics representation of the reactivity index of the substrates, together with special procedures we have recently developed on the PS-390 in order to generate solid models clipped so as to allow the simultaneous visualization of the structural skeleton. On the basis of the results obtained for a large series of organometallic reactions, this model is shown to describe adequately the initial stage of electrophilic and nucleophilic addition or substitution mechanisms. In particular, ferrocene and iron pentacarbonyl are correctly predicted to undergo an electrophilic attack on metal, whereas for arene-$M(CO)_3$ species and their derivatives, the nucleophilic attack takes place as expected on the exo-face of the ligand ring. Finally, it will be shown that regioselectivity may even be properly predicted in the case of competing sites on the same ligand, as exemplified by the nucleophilic attack to the meta position of the substituted ring in anisole-$Cr(CO)_3$ and to the internal carbon of diene in butadiene-$Fe(CO)_3$. When applied to the modeling of organometallic reaction mechanisms, the combination of simple quantum chemistry methods and molecular graphics techniques seems therefore able to bring an interesting contribution toward a better understanding of the processes of specific interactions between chemical species.

Molecular Modeling of Protein-Polymer Interactions

Kap Lim, Russell J. Athay, Joseph D. Andrade and James N. Herron
Center for Biopolymers at Interfaces and Department of Bioengineering, University of Utah, Salt Lake City, UT, USA