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

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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

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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

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Our laboratory is using molecular mechanics programs (DISCOVER and INSIGHT) developed by Biosym Technologies, Inc. to simulate the interactions of proteins with polymer surfaces. Biosym's software is installed on the Silicon Graphics 4D/70GT workstation. In the first part of the simulation, crambin (642 atoms) was used to evaluate the performance of DISCOVER and the SGI computer. Hydrogen atoms were included in the molecular models to maximize the effectiveness of the simulation. Consistent valence force field (CVFF) and AMBER force field parameters were compared in the minimization of the crambin model. Several minimizations *in vacuo* were performed with CVFF, and the results were consistent with earlier reports of simulations performed with AMBER force field and united atom models.[1]

Efforts are under way to perform molecular dynamics with crambin in the periodic boundary conditions with water molecules. An important part of the analysis is the examination of the interaction of water molecules with the surface atoms of crambin. Structure and number of water molecules were determined for hydrophobic and hydrophilic surfaces. Solvent-accessible areas were calculated and correlated with experimental results. In the second part of the simulation, individual molecules of alkanes of various lengths were placed in the periodic boundary conditions. It was shown that primary coordination numbers for alkanes were in close agreement with results obtained previously with united atom models.[2] Other published results showed that a water molecule separated two noble gas atoms, and a methane molecule from the hydrophobic surface. Our goal is to demonstrate the hydrophobic effect more definitely with larger nonpolar molecules, such as octadecane. These results will be compared with those obtained for polyethylene oxide, a water-soluble polymer. In the future, we plan to study the solvated protein-polymer system. Although various questions concerning simulation conditions still need to be answered, growing efficiency in computer programming and hardware will make simulation of a complex molecular system practical.

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DNA As a Target for Drug Action

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DNA is a structurally well-characterized molecule, but its large size and seemingly repetitive nature make it an elusive target for selective drug action. However, some of the more clinically important antineoplastic agents (e.g., cisplatin, adriamycin and cyclophosphamide) are thought to exert their toxic effects by reacting with DNA in the tumor cells.

Proteins such as repressors and endonucleases have evolved to attain a remarkable selectivity of binding to predetermined sequences. Likewise, several low-molecular-weight ligands are known to bind to certain regions in DNA in preference to others. But the question remains in this case whether and how the binding is linked to an effective pharmacological (drugs) or toxicological (carcinogens) response.

Interaction of drugs and a target site in DNA can result in chemical cleavage, steric blockage of enzymes, prevention of the conformational changes required for protein binding and/or other long-range effects.

Computer graphics and theoretical calculations are helpful in our understanding of the molecular basis for sequence-specific recognition of DNA by drugs[1,2] and also to explore the ability of DNA to adopt different types of unusual conformations[3] in special circumstances.[4]

Molecular mechanics calculations provide binding enthalpies rather than free energies, and they often ignore solvation effects.[1,2] The problem can sometimes be formulated in terms of differences in free energy of binding, which can be checked against available experimental data[5] (e.g., netropsin binding to poly[d(GC)]·poly[d(GC)] and poly[d(IC)]·poly[d(IC)]). One can slowly mutate the inosine bases into guanine bases in the complex poly[d(IC)]·poly[d(IC)]-netropsin with the solvent molecules explicity considered. By comparing the changes in energy associated with this perturbation with those from the perturbation of the free oligonucleotide in solution, it is possible to derive the difference in free energy of binding to both sequences.

A chemically modified DNA is a potential substrate for DNA repair processes, the best studied of which are those responsible for removal of photoproducts caused by UV light.[6] Questions relating to DNA damage recognition and how to avoid repair will probably become increasingly significant in drug design.

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