

03.X-3 AN APPROACH TO MODELLING SPECIFICITY DETERMINANTS IN RECEPTOR LIGAND COMPLEXES, Michael N. Liebman, Department of Physiology and Biophysics, Mount Sinai School of Medicine of the City University of New York, New York 10029.

The fundamental requirement for understanding the molecular mechanisms of action in biological systems is the quantitative description of the relation of molecular structure and resulting physicochemical properties to biological activity.

Although the isolation, purification and structural analysis of several biological systems have been achieved, primarily as proteins or enzymes complexed with cofactors, inhibitors, substrates or transition-state analogs, we are commonly hampered by the lack of information detailing these interactions at the molecular level. To circumvent this limitation we have been developing heuristic approaches to permit the identification and evaluation of the physicochemical properties responsible for intermolecular recognition and reactivity. One such approach involves the examination of the crystalline environment and its use in classifying properties, both physicochemical and toxicological in nature. We will describe the application of these methods to the pesticides related to DDT, and to the colchicine analogs that are mitotic spindle poisons.

The modeling tools which we are utilizing for this research have been integrated within an expert system as part of our ongoing research in the uses of artificial intelligence as integrated with molecular modeling. The development of this system and its relationship with existing modeling approaches will be described.

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03.X-4 EXPERIMENTAL CHARGE DISTRIBUTIONS AND ELECTROSTATIC POTENTIALS IN CHEMICAL DESIGN[†]. By E. D. Stevens, Department of Chemistry, University of New Orleans, New Orleans, LA 70148, U.S.A.

The distribution of atomic charges is one of the factors which determine not only the structure and conformation of a molecule, but also the interactions between molecules. Until recently, distributions of atomic charges have been obtained almost exclusively from molecular orbital calculations.

However, full three-dimensional mapping of the electron density distribution is now possible using careful high-resolution x-ray diffraction measurements. On small molecules, measured electron density distributions are comparable to near Hartree-Fock limit *ab initio* calculations. Unlike theoretical calculations, difficulties in experimental measurements increase only moderately with the size of the molecule. Thus detailed information on electronic structure may now be obtained on moderately large molecules of biological interest from x-ray experiments.

From the electron distribution, other one-electron properties of the system such as dipole moments, electric field gradients, and electrostatic potentials may be calculated. Defined properties such as the net atomic charges may also be obtained, but will depend on the partitioning method. We have collected high-resolution x-ray data on a variety of compounds of biological interest on the premise that the experimental electron distribution (and electrostatic potential) will yield information which may be used to predict sites of chemical attack, possible reaction mechanisms, and drug-receptor interactions.

A survey of recent experimental and theoretical results will be presented including electron densities and electrostatic potentials of opiate and antipsychotic drugs, chemical carcinogens, and nucleotides.

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03.X-5 MOLECULAR MECHANICS AS AN ACCOMPANIMENT TO X-RAY CRYSTALLOGRAPHY IN THE STUDY OF DRUG ACTION. By Penelope W. Coddington, Departments of Chemistry and of Pharmacology and Therapeutics, University of Calgary, Calgary, Alberta, Canada.

Since the activity of most drugs is contingent on the recognition of the drug at a macromolecular receptor site, the three dimensional structure of a drug molecule is a key determinant of drug action. X-ray crystallography is the primary source of structural information for most drug molecules. These data, however, depict the solid state conformation of the molecule and must be examined to ascertain whether the conformational properties of the drug molecule in the biological system differ from those in the solid. The actual environment of a drug-receptor recognition event may often be the interface between the intercellular fluid and the "rigid" cell membrane, a region of unknown fluidity and pH. Without more specific information regarding this environment, it is difficult to experimentally determine the relevant conformation for a drug molecule. To provide some data regarding the conformations that are possible, molecular mechanics calculations can be used to probe the potential energy surface of molecule and to identify all conformations of the molecule that are energetically feasible.

Several examples of the use of molecular mechanics to extend the information available from the crystallographic experiment will be presented. These include evaluation of alternative conformations to those found in the crystal lattice, substantiation of the solid state structure as the relevant low energy conformer, evaluation of the effect of a substituent on the torsional freedom of an important side chain and complete characterization of the potential energy surface of a flexible molecule to identify the conformer that matches a more rigid analogue of similar activity. In addition, some of the difficulties arising from the approximate nature of the molecular mechanics force field will also be presented. On balance, a cautious use of these calculations can enhance a study of drug action.