Main Lectures

ML–05.01 STRUCTURE BASED DRUG DESIGN. By L. N. Johnson, Laboratory of Molecular Biophysics and Oxford Centre for Molecular Sciences, University of Oxford, Oxford, OX1 3QU, UK.

The earliest known drugs were those derived from natural products whose effects were detected from observation. Such compounds include aspirin, acetylsalicylate, present in the bark of willow (*salix*) and in the plant meadow sweet (*Spiraea ulmaria*) from which the name comes and whose organic synthesis was achieved nearly 100 years ago; another example is the antimalarial drug, artemisinin from the chinese herb qing hao (*Artemisia annua*) whose medicinal use was documented over 2000 years ago. A later phase of drug design developed from an intimate coupling of clinical experience and pharmacological modelling as exemplified in the design cimetidine for treatment of duodenal ulcers. A feature of this work was that, although much was known of the active agent, histamine, and its physiological effects, nothing was known of the structure of the target molecule, the histamine H2 receptor. The most recent phase in drug design has utilised knowledge of the structures of target proteins or of related macromolecules. Knowledge of the structures of carboxypeptidase and thermolysin was used in the design of the clinically useful compounds captopril and cilazapril, two potent inhibitors of angiotensin converting enzyme, the enzyme involved in the regulation of blood pressure. Knowledge of protein structures forms a basis for understanding how existing agents function as in work with acetyl cholinesterase for agents that block neurotransmission, with bacterial DNA gyrase for the action of the coumarin antibiotics, or with HIV reverse transcriptase for the mechanism of AZT. Structural data have led to clues for improvement in properties and explanations of drug resistance as in the crystallographic studies on the binding of anti-viral compounds to the human rhino virus, the causative agent of the common cold. Knowledge of enzyme mechanism and specificity has led to good mimics of the transition state to provide powerful inhibitors as in work with the HIV protease. Structures of thymidylate synthase, dihydrofolate reductase and nucleoside phosphorylase have been exploited in the design of agents against cancer. Understanding protein structure has led to new proteins produced by recombinant DNA technology such as a fast acting insulin for treatment of diabetes, or "humanised" antibodies for the treatment of leukemia and rheumatoid arthritis. Finally new results on the human histocompatibility complex and associated bound peptides and of cytokines and the cytokine receptor complex, or the human growth hormone and its complex with its receptor have provided new insights into basic recognition events in the immune response, the inflammatory response and hormone response, respectively.

The talk will review these achievements of structural biology and describe work from myself and colleagues in Oxford and Athens on the design of new compounds that may be relevant for the treatment of type II diabetes, the non-insulin dependent form of the disease, for which there is a continued need for improved drugs. Modern genetic analysis has focussed attention on defects in the enzyme glukokinase in the regulation of insulin release in response to glucose and in defects in glycogen synthase in the synthesis of glycogen. In Type II diabetes, as a result of diminuished insulin release or insulin resistance, there is a decrease in the rate of muscle glycogen synthesis and failure to suppress the output of glucose from the liver resulting in elevated blood glucose levels. Glycogen synthesis and glycogen breakdown are regulated by mechanisms that involve the reversible phosphorylation of glycogen synthase and glycogen phosphorylase. Regulation of phosphorylase is also achieved through the inhibitor glucose. Through knowledge of the detailed structure of glycogen phosphorylase we have designed inhibitors that should perturb glycogen metabolism in favour of glycogen synthesis. Our programme has involved the design, organic synthesis, crystallographic and kinetic analysis of over 50 compounds and has led to compounds with only small modifications from the parent glucose that are nearly 100 fold better inhibitors of glycogen phosphorylase. Knowledge of the structures of the target proteins together with advanced computational analysis techniques allows inhibitors to be designed on sound stereochemical principles. But it is still a long road to the treatment of patients.

ML–06.01 SYSTEMATICS OF CRYSTAL PACKING IN MOLECULAR SOLIDS. Carolyn Pratt Brock, Department of Chemistry, University of Kentucky, Lexington, KY 40506-0055, USA.

The ability to predict structures of molecular crystals, and thus the ability to design molecular crystals, has long been a goal, but the enormous variety of possible structures, as well as the sensitivity of crystal packing to minor molecular modifications, have made the problem appear intractable. The rationalizations of structure type possible for simple inorganic salts seemed out of reach.

The availability of large structural databases has changed that situation. Analyses of subsets of structures have begun to reveal principles of molecular aggregation for specific molecular symmetries (*e.g.*, point group 3) and certain intermolecular interactions (*e.g.*, H bonding). Even probabilistic rules are of great value to those seeking to synthesize specific types of molecular solids such as non-linear optical materials (polar direction required), or to resolve racemic products by crystallization (chiral space group required).

Phase diagrams are important guides to the synthesis of stoichiometric molecular compounds (co-crystals, host-guest complexes, *etc.*). Such diagrams also illuminate the energy relationships among polymorphs, between pairs of chiral and racemic crystals, and between solvated and unsolvated materials. By combining results from semi-empirical atom-atom potential-energy calculations, melting-point determinations, and thermal-motion analyses, free-energy *vs.* T curves can be estimated and schematic phase diagrams drawn.

A major unresolved question is the degree of kinetic control over crystallization. Nucleation is often a very slow process, and surface effects are very important for crystal nuclei.

ML–07.01 RECOGNITION IN SUPRAMOLECULAR STRUCTURES. W. Saenger, Institut für Kristallographie, Freie Universität Berlin, Takustr. 6, 1000 Berlin 33, Germany.

Highly specific recognition between two different molecules is one of the most salient characteristics of many biological processes. In this recognition, the receptor molecule forms a complex with a certain ligand for which it is specific or, in other terms, it is able to discriminate one molecule against all the others that are present in the biological cell. Two principal conditions apply: (1) purely geometrical fit between receptor and ligand, and (2) electronic complementarity which involves van der Waals and hydrogen bonding interactions.

In inorganic and organic chemistry, molecular recognition is also observed. Small molecules can crystallize in lattices with cavities in which ligands of suitable size are accommodated as in ice, urea, hydroquinone and deoxycholic acid clathrates, or in Hofmann-, Werner-type intercalation compounds, and in zeolites. In contrast to these unspecific complexes which are bound to the solid state, a number of larger natural or synthetic supramolecular organic compounds are known that bind more specifically to suitable ligands even in solution. They can be crystallized and studied at atomic detail so that the mutual recognition interactions between receptors and ligands are well understood. In this contribution, cyclodextrins, crown ethers, cryptates, ionophores, calixarenes and other macrocyclic receptors and their complexes with ligands will be described. An excursion will be made made to biologically relevant systems where even more sophisticated recognition with extreme specificity is observed.

Ref.: J.L. Atwood, J.E.D. Davies, D.D. MacNicol
Inclusion Compounds Vols. 1-3, Academic Press London, 1984

