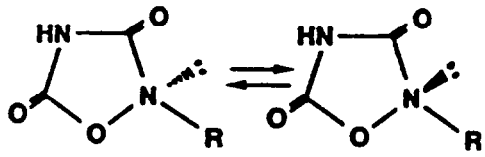

Scheme 1

gies, and can therefore occur freely at room temperature. A comparative study of the conformational space available to our active glutamate analogues using intramolecular functional group distance geometry criterion (COSMIC/ASTRAL) has identified a unique conformation of glutamate as it binds to the quisqualate-sensitive receptor (Figure 1). This conformational model accounts for the observed activity of all active and inactive compounds that we evaluated. In particular, it describes the activity of D-quisqualate (equipotent with L-glutamate) through both the ability to invert the geometry at the ring nitrogen and to form an extended anion involving both ring carbonyls. Such a spatial relationship between functional groups is unavailable to D-glutamate (inactive) (Figure 2).

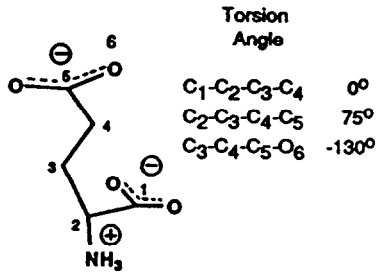

Figure 1

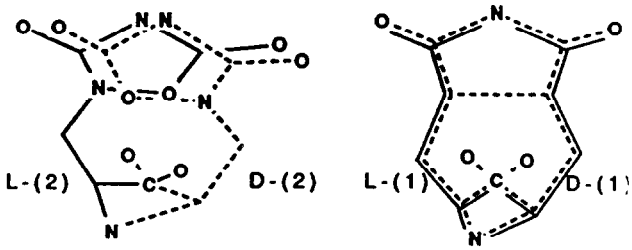

Figure 2

The observation of pyramidal amide nitrogens in biologically active molecules is not restricted to quisqualic acid, and we believe such systems may have significant potential in the design of novel receptor ligands and transition-state analogue enzyme inhibitors.

Applications of Molecular Graphics and Molecular Electrostatic Potentials to the Inhibitors of the Enzyme ADPRT

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In the study of complex chemical systems, such as those of biological importance, there is often a need to use theoretical methods as an aid to the interpretation of available experimental data. One property that can be easily calculated, and that can be used to obtain a reliable indication of molecular interaction, is the Molecular Electrostatic Potential (MEP). The use of the MEP as an aid in the correlation of biological activity with electrostatic features has been widely reported, and the extents and limitations have been explored.

A major drawback to the use of the MEP in biological applications is that its calculation can be time consuming and restricted to relatively small systems, when *ab initio* methods are used. One approach that enables the MEP to be calculated for large molecules is to introduce various levels of approximation into the calculation. The simplest approximation, and the one that we will describe here, is the point charge model, where the MEP is approximated by replacing the molecular charge distribution with a set of point charges. The accuracy of such a model ultimately depends upon the source and location of the point charges, and although this may seem to oversimplify the calculation of the MEP, it is applicable to any size of system as long as the point charges can be calculated or estimated. It should also be noted that the usefulness of such approximate methods should not be judged on the crudeness of the approximations employed, but upon their ability to predict experimental trends and by their general applicability.

Poly (ADP-ribose) transferase (ADPRT) is a chromatin bound enzyme, located in the nucleus of eukaryotic cells, which catalyzes the polymerization of ADP-ribose to poly(adp-ribose). This enzyme has an absolute affinity for DNA and is required for the efficient repair of DNA after certain kinds of damage have occurred. Inhibitors of the enzyme have been found that increase the cytotoxicity of various DNA damaging agents. The use of such compounds could be important in the field of cancer chemotherapy, and therefore the ability to predict compounds that are more potent inhibitors of ADPRT would be extremely useful.

This presentation will discuss the use of the theoretical methods mentioned above, along with molecular graphics in the study of a range of inhibitors of ADPRT. All the MEPs presented were calculated using AM1 geometries and point charges. Comparison of the approximate MEPs with *ab initio* MEPs will be made where possible. A program will also be described which enables MEPs to be calculated and displayed on a Microvax II/GPX workstation.

Cationic Complexes of a Cyclic Urea-Anisole Spherand: an Analysis of Molecular Structure and Energetics

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Cram and coworkers[1] have shown that the cyclic urea-anisole spherand of interest in this work selectively com-

plexes cationic ligands. This spherand also constitutes the substrate binding site of a series of enzyme mimics[2,3] whose molecular recognition features have been analyzed in this laboratory.[4] The rationale behind Cram's design of the spherand was to provide a binding site that was optimally "preorganized" for substrate binding (i.e., one in which very little energy would be spent in conformational reorganization to accommodate the substrate). We probe this design concept at the molecular level by using (1) molecular mechanics analysis to study the energetics of the complexation process, and (2) molecular dynamics simulation to investigate the degree of structural rigidity of the spherand.

Our molecular mechanics results show that the energy change of the spherand during complexation is generally quite small, especially when compared to the binding energy of the cation. In addition, we have found that the spherand undergoes very little structural change upon complexation of the cation. In agreement with the experimental results, some ligands are found to "perch" above the cyclic urea oxygens of the spherand, whereas others "nest" inside. It is the latter situation that exhibits the largest conformational change in the macrocycle.

Superposition of "snapshots" of the spherand from the molecular dynamics simulation also illustrates the structural rigidity of the macrocycle. This, together with the molecular mechanics results, illustrates the structural "preorganization" of the spherand for the cation ligands.

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Simulations of Receptor Activation Mechanisms As a Guide for Drug Design

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Dramatic new developments in the fields of molecular and structural biology offer new leads and exciting prospects for the design of therapeutic agents and other molecules with predetermined biological activities. Most important in this respect is the insight that the new findings have provided on details of structure function relationships for many key proteins, including soluble enzymes and even some membrane-bound systems. However, practical methods for the design of drugs and other biologically active molecules are hampered by the nearly complete lack of structural information, at the detailed atomic level, for molecules of membrane-bound receptors and effectors. This lack of information makes the design effort dependent on inferences from the molecular pharmacology of drug-receptor interactions. Insofar as part of this interaction depends on the process of recognition of a small molecule by a protein, these design efforts can further be aided by models based on the biochemistry of enzyme-substrate interactions.

In its ability to combine disparate insights in a rigorous frame at the molecular level, theoretical chemistry is irreplaceable in the quest for understanding the chemical basis for the action of various ligands in biological systems. Such understanding is essential for the success of any method of molecular design, for it relates the molecular properties of the ligands to specific chemical reactivities that determine their interactions in biological systems. The set of chemical reactivities that determine the selectivity of the ligands for specific receptors constitutes the molecular determinants for recognition of the ligand. Another, possibly different, set of reactivities could be most important for triggering the consequence of the binding that leads to the response.

A strategy for the design of biologically active ligands with selective affinity can begin with a search for molecular determinants for recognition of a series of ligands with known affinities for a receptor. Chemical intuition and theoretical insight can be used to infer on the chemical nature of the species that are most likely to match these reactivities and to form stable, discriminant interactions with the ligands. Such species are candidates for the receptor sites that recognize and bind the ligands, and proteins containing such putative recognition sites can be identified in the Protein Data Bank. When the formation of complexes with ligands is simulated computationally with the methods of theoretical chemistry, important insight can be gained concerning the likely consequences of the complexation. Such consequences could constitute a triggering mechanism for receptor activation. The inferences are a basis for design of receptor activating agents (i.e., agonists), as opposed to receptor blocking agents (i.e., antagonists). Our ongoing work on the molecular pharmacology of receptors for the neurotransmitter serotonin (5-hydroxytryptamine; 5-HT) illustrates such a complex strategy for heuristic design, based on the molecular details of drug–receptor interactions and including the consideration of whole protein environments in simulations of receptor-triggering mechanisms.