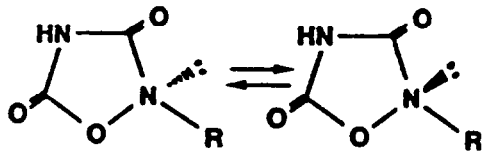

Scheme 1

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).

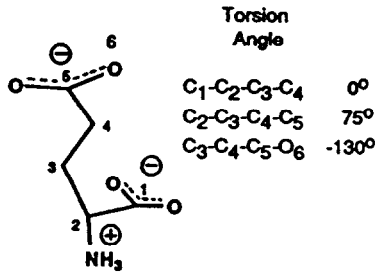

Figure 1

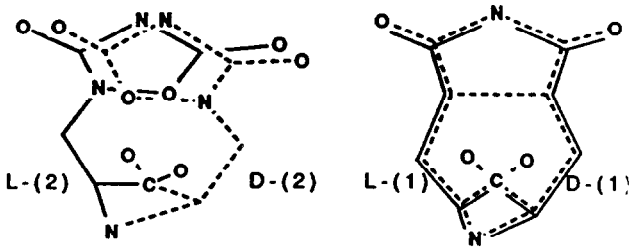

Figure 2

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

D. Higgins
Department of Chemistry, Purdie Building, University of St. Andrews, St. Andrews, Fife, KY16 9ST, UK

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

Peter V. Maye and Carol A. Venanzi
Chemistry Division, New Jersey Institute of Technology, Newark, NJ 07102, USA

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