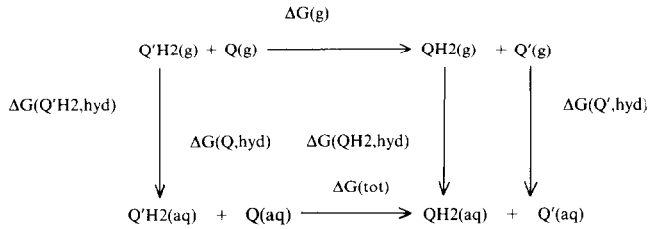
The ability to calculate electrode potentials would be advantageous in many areas of molecular design because many molecules are activated by enzymatic oxidation or reduction. Previous theoretical approaches to this problem have usually neglected the solvent and have often neglected the reduced molecules, too, using the LUMO energy as a guide to the electrode potential. However, the free-energy perturbation method has recently been used to calculate free energies of hydration with astonishing accuracy, and combined with high-level quantum mechanical calculations, it is possible to treat the problem accurately using the following thermodynamic cycle to evaluate differences in free energy in aqueous solution.



$$\Delta G(tot) = \Delta G(QH2,hyd) - \Delta G(Q,hyd) + \Delta G(Q',hyd) - \Delta G(Q'H2,hyd) + \Delta G(g)$$

Here, Q and Q′ are, for example, two quinone molecules. The gas phase reactions have been treated with a variety of basis sets of 6-31g* (or superior) quality, at both the RHF and MP2 levels. Zero-point, enthalpy and entropy corrections to the *ab initio* energies have been made using semiempirical MO theory. The hydration free-energy components have been calculated using the free-energy perturbation method during computer simulations in which QH2 is mutated to Q during about 40–50 ps of molecular dynamics.

The results for the difference in electrode potentials between parabenzoquinone and ortho-benzoquinone are accurate to 20 mV, and this level of accuracy has been reproduced for a growing range of compounds. However, the work is significant beyond its potential use in the design of bioreductive compounds because it shows that free energies can now be calculated for reactions in solution, as well as for reactions in the gas phase.

REFERENCE

1 Reynolds, C.A., King, P.M. and Richards, W.G. Computed redox potentials and the design of bioreductive agents. *Nature* 1988, **334**, 80–82

The Use of Molecular Modeling in Anticancer Drug Design

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DNA is generally regarded as the most sensitive and appropriate molecular target for the action of cytotoxic drugs, and the majority of current antitumor agents indeed interact with DNA.

The full description of structural features of intercalation (the binding mechanism utilized by clinically important agents such as adriamycin and actinomycin) has not yet been obtained from X-ray crystallographic analyses. We have used computer modeling to extend crystallographic data so as to produce a model for an intercalation site in the middle of an oligonucleotide sequence. This has subsequently been used for modeling a number of intercalating molecules and derivatives in order to derive structure-activity relationships. Several examples of this approach will be given in the presentation, and its scope and limitations will be discussed.

Identification of a Bioactive Conformer of Glutamate at a Quisqualate-Sensitive Glutaminergic Receptor

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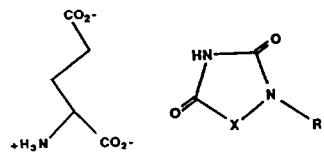
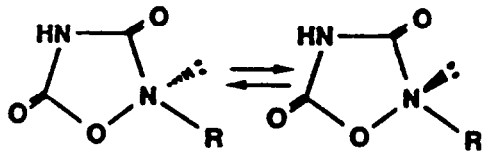
L-Glutamate **(1)** is now regarded as an important excitatory neurotransmitter in a number of vertebrate and invertebrate systems in which three principal receptor types have been identified: quisqualate (Q, N-methyl-D-aspartate (NMDA) and kainate (K). As part of our ongoing structure/activity program on glutamate agonists and antagonists, several glutamate analogues have been synthesized and evaluated in the well-defined, quisqualate-sensitive, glutaminergic synapse of the locust leg nerve-muscle preparation. In order to provide a molecular rationale for our experimental observations, a combination of X-ray crystallographic analyses, semiempirical MO calculations and molecular mechanics studies have been used to identify a bioactive conformer of glutamate at this Q receptor.



	R	X
(2)	$-CH_2CH(NH_2)CO_2H$	O
(3)	$-CH_2CH(NH_2)CO_2H$	CH_2
(4)	-Me	O
(5)	-Me	CH_2
(6)	-Me	NH

(1)

Semiempirical MNDO calculations on model systems (4–6), together with X-ray crystallographic data on quisqualic acid **(2)** and its carbon analogue **(3)**, have shown that the amide nitrogen attached to the alkyl side chain in systems **(2)**, **(4)** and **(6)** is in fact pyramidal. Those in the hydantoin type systems **(3)** and **(5)** are, as expected, planar. Data from the MNDO calculations along with observed crystal lattice structures suggest that the barriers to inversion in the pyramidal nitrogens (Scheme 1) are low, comparable to bond rotation ener-



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).

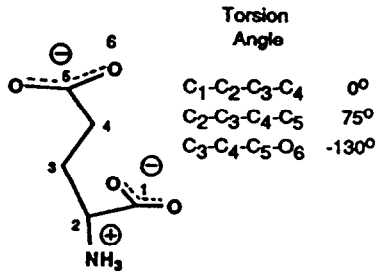


Figure 1

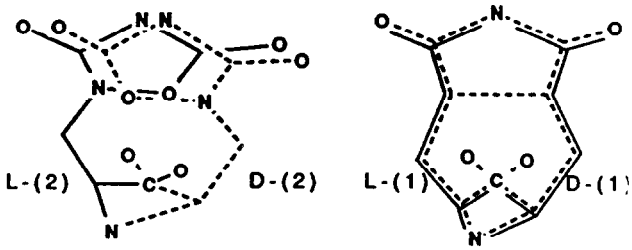


Figure 2

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-