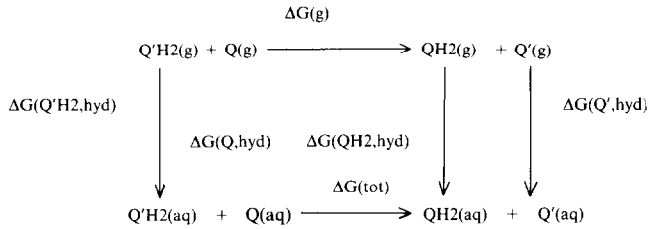
The ability to calculate electrode potentials would be advantageous in many areas of molecular design because many molecules are activated by enzymatic oxidation or reduction. Previous theoretical approaches to this problem have usually neglected the solvent and have often neglected the reduced molecules, 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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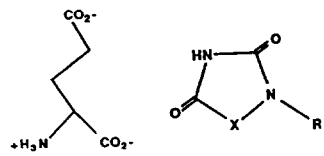
L-Glutamate **(1)** is now regarded as an important excitatory neurotransmitter in a number of vertebrate and invertebrate systems in which three principal receptor types have been identified: quisqualate (Q, N-methyl-D-aspartate (NMDA) and kainate (K). As part of our ongoing structure/activity program 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-