tions of parameters and essential for charge approximations, a detailed analysis indicates that *in vacuo* calculations neglect many-body effects and can be misleading. A major effort by Hehre (personal communication) to derive parameters for water from extensive *ab initio* calculations with large basis sets failed even to give a parameter set that reproduced the radial distribution for bulk water. Parameters derived from relevant experimental data in condensed phase (especiallyif available in the solvent of theoretical interest) are generally more capable of accurately predicting results because the many-body effects are implicitly included in the parameterization. The basic assumption is that these "effective" two-body potentials implicitly incorporate many-body interaction energies.

Jorgensen has parameterized by fitting properties of bulk liquids to Monte Carlo simulations to give the AMBER/OPLS force field (26, 157, 158). Conceptually, one is attracted by the use of liquids and their observable properties as constraints during the derivation of a force field that is destined to study the properties of solvated molecules.

2.2.3 Modeling Chemical Reactions and Design of Transition-State Inhibitors. In cases, such as enzyme reactions, where chemical transformations occur, quantum chemical methods must be used to deal with electronic changes in hybridization and bond cleavage (159, 160). Hybrid applications (161–163) in which the reaction core is modeled quantum mechanically and the rest by molecular mechanics would appear a viable option. Alternatively, the geometry of the transition state has been modeled by molecular mechanics, with force constants derived from *ab initio* calculations that predict with amazing accuracy the relative selectivity of reactions. Andrews and coworkers (164) pioneered modeling of transition states (165) of enzymatic reactions to design transition-state inhibitors.

3 KNOWN RECEPTORS

A significant challenge is the design of novel ligands for therapeutic targets in which the three-dimensional structure has been determined by either X-ray crystallography or NMR (12, 13, 166). The availability of the coordinates of all the atoms of the target suggests use of modeling of the site and interaction with prospective ligands. Qualitative information can be discerned by simple examination of complexes by the use of molecular graphics and improvement of known ligands made by searching for accessory binding interactions through ligand modification. This approach was pioneered by groups at Wellcome Research Laboratories (167–169) in designing analogs of 2,3-diphosphorylglycerate (Fig. 3.13), to modulate oxygen binding to hemoglobin, and at Burroughs-Wellcome (170), to enhance affinity of dihydrofolate reductase (DHFR) antagonists. When used in an iterative fashion, novel compounds with improved affinity result (166, 171, 172). Quantification of interactions and design of novel ligands require application of molecular and statistical mechanics to quantify the enthalpy and entropy of binding. In other words, experimental measurements reflect free energies of binding and both enthalpic and entropic contributions must be estimated for prediction of affinities as part of the design process. When combined with combinatorial chemistry and high throughput screening, rapid identification of therapeutic candidates is feasible, as witnessed in the case of factor Xa antagonists (173) or TAR RNA inhibitors as possible HIV drugs (174).

3.1 Definition of Site

The availability of three-dimensional structural information on a potential therapeutic target does not guarantee identification of the site of action of the substrate, or inhibitor, unless the structure of a relevant complex has been determined. In fact, conformational changes often occur during binding of ligands to enzymes that are not reflected in the three-dimensional structure of the enzyme alone. Illustrative examples are the major conformational changes seen (175, 176) in HIV protease on binding the inhibitor MVT-101 (Fig. 3.14) and the changes in domain orientation observed (177) in the complex of an anti-HIV peptide antibody with the peptide. Until the two β-strand flaps have been folded in, to complete the active site of HIV protease, many of