usually employed to approximate the long-range shielding of electrostatic interactions by water (274). However, compounds with high formal charges still obtain unreasonably high scores as a result of overestimated ionic interactions. For this reason, a common practice in virtual screening is to separate databases of compounds into subgroups according to their total charges and rank these groups separately. When electrostatic interactions are complemented by a solvation term calculated by the Poisson-Boltzmann equation (32) or faster continuum solvation models (e.g., Ref. 275), effects of high formal charges are usually leveled out. In a validation study on three protein targets, Shoichet and coworkers observed significantly improved ranking of known inhibitors upon correction for ligand solvation (276). The current version of the docking program DOCK calculates solvation corrections based on the generalized Born (277) solvation model (278). The method has been tested in a study where several peptide libraries were docked into various serine protease active sites (279).

In the context of scoring, the van der Waals term of force fields is mainly responsible for penalizing docking solutions with respect to overlap between receptor and ligand atoms. It is often omitted when only the binding of experimentally determined complex structures is analyzed (280–282).

Very recently, a new contribution to the list of force-field-based scoring methods has been developed by Charifson and Pearlman. This so-called OWFEG (one window free energy grid) method (283) is an approximation to the expensive first-principles method of free energy perturbation (FEP). For the purpose of scoring, an MD simulation is carried out with the ligand-free, solvated receptor site. During the simulation, the energetic effects of probe atoms on a regular grid are collected and averaged. Three simulations are run with three different probes: a neutral methyl-type atom, a negatively charged atom, and a positively charged atom. The resulting three grids contain information on the score contributions of neutral, positively, and negatively charged probe atoms located in various positions of the receptor site. They are used for scoring a ligand position by linear interpolation based on the partial charges of the ligand atoms. This approach seems to be successful for K_i prediction as well as virtual screening applications (284). Its conceptual advantage is the implicit consideration of entropic and solvent effects and some protein flexibility.

The calculation of ligand strain energy traditionally also lies in the realm of molecular mechanics force fields. Although effects of strain energy have rarely been determined experimentally (3), it is generally accepted that high-affinity ligands bind in low-energy conformations (285, 286). If a compound must adopt a strained conformation to fit into a receptor pocket, this should lead to a less negative binding free energy. Strain energy can be estimated by calculating the difference between the global energy minimum of the unbound ligand and the current conformation of the ligand in the complex. However, force field estimates of energy differences between individual conformations are not reliable for all systems. In practice, better correlation with experimental binding data is observed when strain energy is used as a filter to weed out unlikely binding geometries rather than including it in the final score. Estimation of ligand strain energy based on force fields can be time-consuming and therefore alternatives are often employed, such as empirical rules derived from small-molecule crystal data (140). Conformations generated by such programs are, however, often not strain-free because only one torsional angle is regarded at a time. Some strained conformations can be excluded when two consecutive dihedral angles are taken into account simultaneously (287).

4.1.2 Empirical Scoring Functions. The underlying idea of empirical scoring functions is that the binding free energy of a noncovalent receptor-ligand complex can be factorized into a sum of localized, chemically intuitive interactions. Such decompositions can be a useful tool to gain some insight into binding phenomena, even without analyzing 3D structures of receptor-ligand complexes. Andrews and colleagues derived average functional group contributions to the binding free energy by analyzing a set of 200 compounds for which the affinity to a receptor had been experimentally determined (266). Such average functional