overlap (even if the electronegativities of the two atoms are quite dissimilar). The sum is the gross atomic population, and the net atomic charge is simply this plus the nuclear charge. The result is very sensitive to the basis set (the number of atomic orbitals) used. Despite poor fit of the molecular electrostatic potential derived with point charges to the *ab initio* electrostatic potential, or that derived from a distributed multipole analysis (150), widespread use continues because they do reflect chemical trends and are reportedly compatible with known electronegativities. In addition, this option is commonly available in software packages. Unfortunately, poor representation of the electric field surrounding the molecule results from use of atom-centered monopole models (42), even when more careful methods are used to distribute the charge.

2.2.1.2 Methods to Reproduce the Molecular Electrostatic Potential (MEP). The electrostatic potential surrounding the molecule that is created by the nuclear and electronic charge distribution of the molecule is a dominant feature in molecular recognition. Williams reviews (42) methods to calculate charge models to accurately represent the MEP as calculated by *ab initio* methods by use of large basis sets. The choice between models (monopole, dipole, quadrapole, bond dipole, etc., Fig. 3.12) depends on the accuracy with which one desires to reproduce the MEP. This desire has to be balanced by the increased complexity of the model and its resulting computational costs when implemented in molecular mechanics.

The first problem is to select points where the MEP is to be evaluated and eventually fitted, the position of the shell outside the VDW radii of the atoms in the molecule, and the spacing of grid points on that shell. Sampling too close to the nuclei gives rise to anomalies because the potential around nuclei is always positive. Singh and Kollman (151) report the use of four surfaces at 1.4, 1.6, 1.8, and 2.0 times the VDW radii, with a density of one to five points per Å^2. This paradigm was reported to give an adequate sampling to which the fitted charges were fairly insensitive, at least at the higher values. An improved procedure, the restrained electrostatic potential fit (RESP), was developed by Bayly et al. (41) to enhance transferability of the resulting point charges. Williams (42) derived a procedure to derive the best fit to a given MEP with a defined set of monopoles, dipoles, and so forth.

Typically, fragments of molecules of interest are analyzed by *ab initio* techniques to generate their MEPs that are the reference for parameterization of charge. Besler et al. (152) reported fitting of atomic charges to the electrostatic potentials calculated by the semiempirical methods AM1 and MINDO. The MINDO charges derived by fitting the MEP can be linearly scaled to agree with results derived from *ab initio* calculations. Among the motivations for semiempirical methods are the facts that semiempirical methods using high quality basis sets often yield better results than *ab initio* techniques employing minimal basis sets, and the significant reduction in computational time in moving from *ab initio* to semiempirical calculations. Rauhut and Clark (153) used the AM1 wave function to develop a multicenter point-charge model in which each hybrid natural atomic orbital is represented by two charges located at the centroid of each lobe. Thus, up to nine charges (4 orbitals and 1 core charge) are used to represent heavy atoms. Results using this approach affirm the observations that distributed charges are more successful than atom-centered charges in reproducing intermolecular interactions (154, 155).

2.2.2 Parameter Derivation for Force Fields. Because molecular mechanics is empirical, parameters are derived by iterative evaluation of computational results, such as molecular geometry (bond lengths, bond angles, dihedrals) and heats of formation, compared with experimental values (20). Lifson has coined the expression "consistent" for force fields in which structures, energies of formation, and vibrational spectra have all been used in parameterization by least-squares optimization. In the case of bond lengths, bond angles, and VDW parameters, crystallography has provided most of the essential experimental database. Major efforts (156) to derive general sets of parameters from quantum mechanical calculation have been made, especially for systems for which adequate experimental data are unavailable. Although quantum mechanics is certainly adequate for initial approxima-