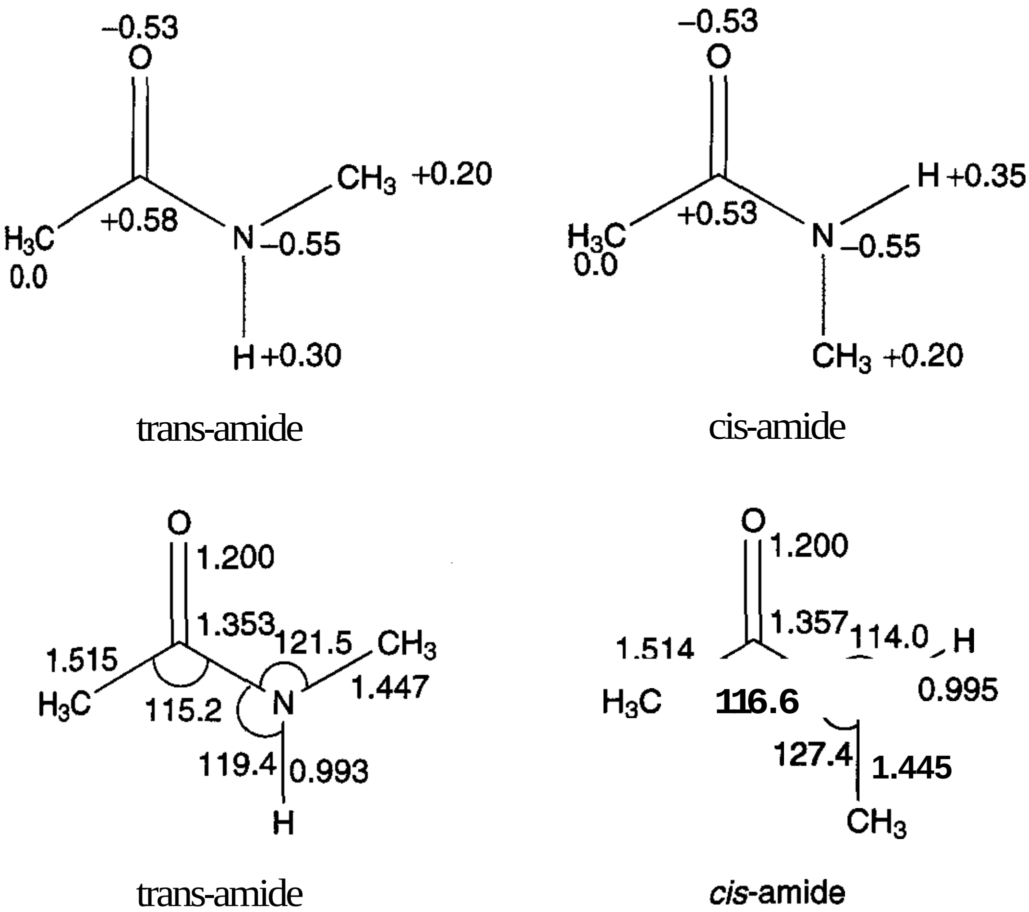

Figure 3.1. Differences in OPLS charge distribution (top) between cis- and trans-isomers of amide bond and geometries (bottom) as calculated by *ab* initio parameterization (26).

veloped a functional form that allows electronic d-orbitals of metals to be reasonably represented within molecular mechanics.

Because different force fields may use different mathematical representations of the forces between atoms and the details of their parameterization will in general differ also, it is unwise to use parameters derived for one force field to replace missing parameters in another. One often hears of a "balanced" parameter set that reproduces well the phenomena under consideration, but which is inadequate for other applications. A comparison by Burkert and Allinger (19) shows the different van der Waals (VDW) potentials used in several of the popular force fields, and the situation has not improved significantly in the intervening years. Because of other differences in parameters and functional forms of the equations used in the rest of the individual force fields, these quite different approaches to the VDW potential give excellent results when used in the correct combination. Indiscriminant combination of one part of a force field with another derived independently would lead to considerable divergence in the calculated results from those obtained by experimental observation.

The most extreme difference between force fields arises in the method by which the hydrogen bond is included. Because atoms involved in a hydrogen bond are often closer than the sum of their VDW radii, they must be handled in a special manner. Several force fields have special functional forms with angular dependency that not only have special VDW parameters, to ensure that the close approach of the atoms involved is calculated correctly, but that the angular distribution observed for hydrogen bonds is also reproduced. Hagler et al. (34) used an amide hydrogen with a zero VDW radius for hydrogen bonding and a slightly greater nitrogen radius to give a correct amide hydrogen bond distance. The charges on the atoms involved (including the amide hydrogen) are adjusted to give an appropriate balance of VDW repulsion and dipole attraction. Clearly, the method for handling the electrostatic interaction is an integral part of each force field and cannot be modified independently.

2.1.2 Electrostatics. The most difficult aspect of molecular mechanics is electrostatics (35–38). In most force fields, the electronic distribution surrounding each atom is treated as a monopole with a simple coulombic term for the interaction. The effect of the surrounding medium is generally treated with a continuum model by use of a dielectric constant. More