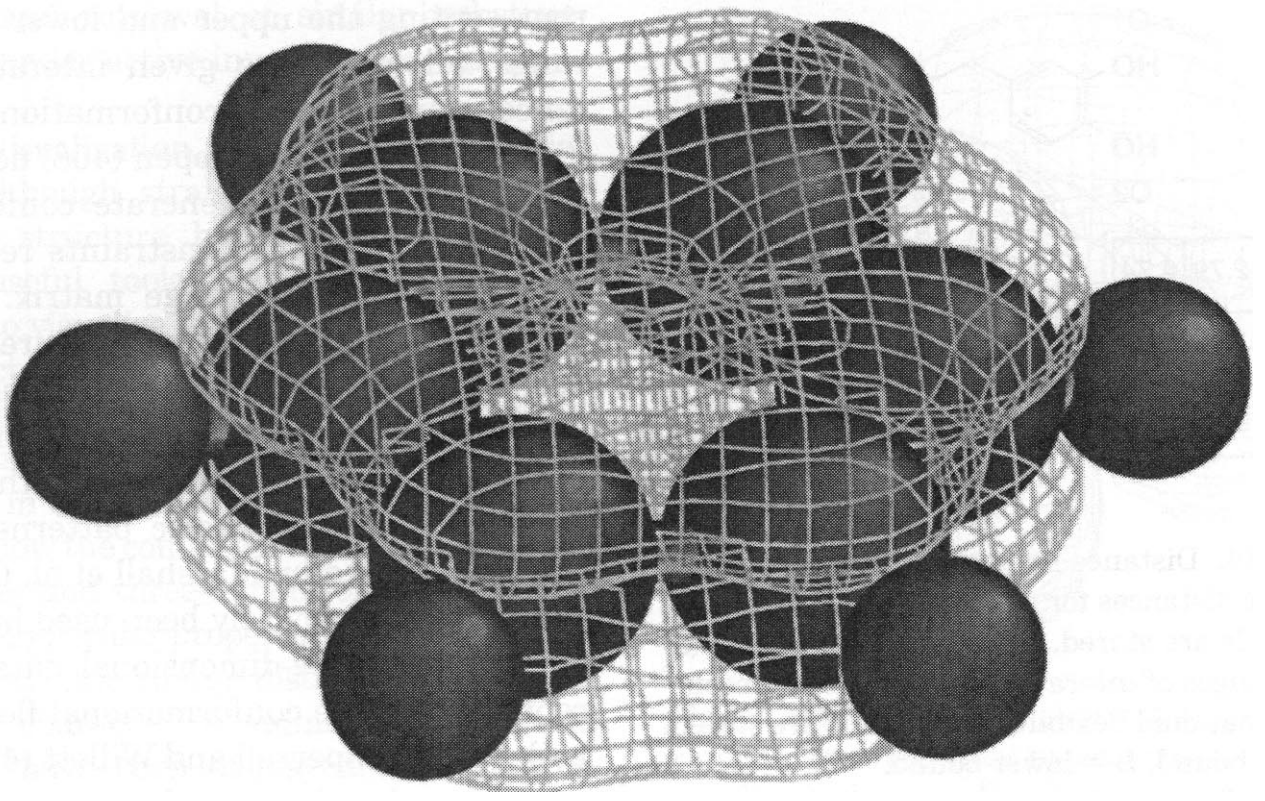

Figure **3.33.** Torus of electron density representing benzene ring. Atom-to-atom correspondences of ring atoms used in normal fitting routines lead to overconstrained fits.

tures implies more information regarding the conformational requirements of the system. **A** congeneric series requires that the basic chemical framework of the molecule remains constant and that groups on the periphery are either modified (e.g., aromatic substitution) or substituted (e.g., tetrazole for carboxyl functional group). Implicit in this concept is the notion that the compounds bind to the receptor in a similar fashion and, therefore, the changes are localized and comparable for each position of modification. Introduction of degrees of freedom in the substituents as well as consideration of differences in properties that are conformationally dependent, such as the electric field, require conformational analysis in an effort to determine the relevant conformation for comparison.

The problem can be divided into two: what are the aspects of the molecules that are in common and that may provide the basis for molecular recognition, and which conformation for each molecule is appropriate to consider. For the first problem, studies on a congeneric series can often yield valuable insight. For determination of the three-dimensional arrangement of the crucial recognition elements, diversity in the chemical scaffolds imloses different constraints on possible three-dimensional patterns and generates an opportunity for determining a unique solution.

4.2 Searching for Similarity

4.2.1 Simple Comparisons. To gain insight into molecular recognition, subtle differences in molecules must be perceived. Comparisons can be divided into two categories: those that are independent of the orientation and position of the molecule and those that depend on a known frame of reference. Simple comparisons deal with properties independent of a reference frame. For example, the magnitude of the dipole moment is frame independent, but the dipole itself is a vectorial quantity dependent on the orientation and conformation of the molecule, Similarly, the bond lengths, valence angles and torsion angles, and interatomic distances are independent of orientation. The distance matrix, composed of the set of interatomic distances (Fig. 3.34), is a convenient representation of molecular structure that is invariant to rotation and translation of the molecule, but which *reflects* changes in internal degrees of freedom. The distance range matrix is an extension (Fig. 3.34) that has two values for each interatomic distance