prerequisites for activity seen in others in the series. In a congeneric series, a significant portion of the molecular structure is common to the molecules under comparison. This common volume that is shared logically should not contribute to differences in activity. By subtraction of the volume shared by two molecules, one obtains a difference map in which the volume occupied by one molecule and not the other remains (398). Correlations between the shared volume and the biological activity of a congeneric series of inhibitors of DHFR have been shown by Hopfinger (425). Simon and his colleagues (426) emphasized the use of both overlapping volume and nonoverlapping volume in QSAR studies in a quantitative methodology, the minimal steric difference, or MTD method. This approach has been enhanced to allow comparison of low energy conformers of each molecule and use of those that are sterically most similar. An application to substrates of acetylcholinesterase illustrates this facility (427).

4.3.2 Field Effects. Once the frame of reference has been established, other properties of molecules, such as the electrostatic field, can be compared as well. Because the electrostatic properties can be sampled on a grid, differences between the values of two molecules can be calculated and a difference map contoured. Such difference maps (428) highlight more clearly the similarities and differences between molecules. Hopfinger (429) integrated the difference between potential fields and showed this parameter to be useful in QSAR studies.

An approach to statistically quantifying the similarity between two molecular electrostatic potential surfaces was developed by Dean and coworkers (430,431) and by Richards and coworkers (215). Here, the previously determined molecular electrostatic potential surfaces are projected outward onto surrounding spheres that provide a common surface of reference, and then statistical analyses are performed over the points on this common surface in an attempt to quantify the similarities or differences between the two molecules under consideration. Burt and Richards (432) introduced flexibility in the comparison of molecules based on their electrostatic potential fields.

4.3.3 Directionality. If one is comparing molecules that share interaction at a common site on a biological macromolecule, it is logical to assume that they may do so by interacting with similar sites in the receptor with optimal interaction shown by molecules with correctly oriented functional groups. If one does not have a three-dimensional model of the receptor from which to deduce potential interactive sites, then one can only attempt to deduce the potential interactive receptor-subsites by examination of the molecules that interact with them. Systematically, one can vary the conformation of a molecule and record the relative orientation of groups postulated, or shown experimentally, to play a dominant role in intermolecular interactions. In this way, one can map out the directionality of interactions of each functional group of the ligand in a common frame of reference. Comparison of these maps can often lead to hypotheses regarding pharmacophoric groups and their correspondence between molecules.

4.3.4 Locus Maps. One can generate a locus plot in coordinate space showing all the potential locations of one group relative to another by fixing one group in a particular orientation as a frame of reference and recording all possible coordinates of the other. An example would be the relative positions of the basic nitrogen to the aromatic ring in compounds such as dopamine interacting with biogenic amine receptors. One must choose the common fragment (in the example, the aromatic ring) of each molecule and its orientation to generate a similar frame of reference, so that the locus of positions of the atom (the basic nitrogen) leads to a meaningful comparison across a series of molecules (Fig. 3.40).

4.3.5 Vector Maps and Conformational Mimicry. Often, one is more interested in accessing the directionality of potential interaction rather than simply looking for overlap of atoms such as the basic nitrogen. In this case, for example, one is interested in determining both the locus of the lone pair of the nitrogen