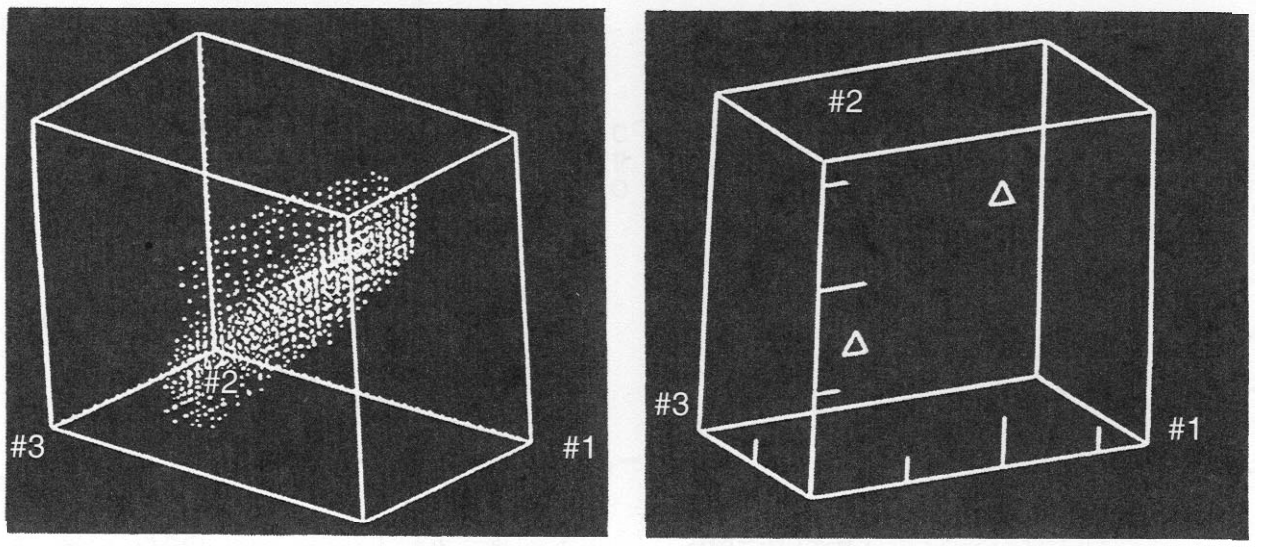

Figure 3.32. Change in ***OMAP*** (projection of three of the five dimensions) as new compounds were introduced to analysis of ACE inhibitors (397). Left is original ***OMAP*** of compound ***1*** (Fig. 3.30). Right is ***OMAP*** after completion of analysis.

available for analysis determine the methodology to be used. If there is a limited data set, then the pharmacophoric approach should be assessed first because of its fewer degrees of freedom. If no pharmacophoric patterns are consistent with the set of analogs, then introduction of logical molecular extensions to enable the active-site approach is warranted. Operationally, one first determines the set of potential pharmacophoric patterns consistent with the set of active analogs [leading to its name of Active Analog Approach (398)]. If there are sufficient data, then a unique pharmacophore, or active-site model, may be identifiable. The basic assumption behind efforts to infer properties of the receptor from a study of structure-activity relations of drugs that bind is the idea of ***complementarity.*** It follows that the stronger the binding affinity, the more likely that the drug fits the receptor cavity and aligns those functional groups that have specific interactions in a way complementary to those of the receptor itself. Certainly, our understanding of intermolecular interactions from studies of known complexes does not dissuade us of this notion, but may make us somewhat skeptical of the naive models that often result from such efforts. Andrews et al. (403) reviewed efforts of this type with regard to CNS drugs.

Clearly, the key to insight relies on chemical modification to determine the relative importance of functional groups for molecular recognition. Often more subtle effects than the simple presence or absence of a group are important and then comparison of molecular properties becomes of interest. A major impediment to analysis is the definition of a common frame of reference by which to align molecules for comparison. This is equivalent to solving the three-dimensional pharmacophoric pattern, and implies that one has distinguished those properties of the molecules under consideration in a manner similar to the receptor. Initial efforts to rationalize structure-activity relationships (SARs) among noncongeneric systems was hampered by an "RMS mentality." That is, a point of view that required atomic centers to align rather than overlap of steric and electronically similar grouping of atoms. An example would be requiring the six atoms of aromatic benzene rings to overlap at each of the six atoms of the ring vertices rather than simple requirements for coincidence and coplanarity that would recognize the torus of electron density that the rings share in common (Fig. 3.33). In congeneric series, the difficulty in assignment of correspondence is less (nonexistent by definition). This allows a variety of approaches, including those based on molecular graph theory (404–407), to detect similarities between molecules that can form the basis of a correlation analysis. Extrapolation outside of the group of congenerically related compounds on which the analysis was based would appear difficult, if not impossible.

Although it is simpler to start an analysis with a congeneric series to identify the recognition elements, diversity in chemical struc-