minimization technique, and the results will be dependent on the starting geometries of the initial set of molecules. Both have the advantage that the unique constraints imposed by particular molecules enter consideration at an early stage and minimize comparison of conformations.

Another variant recently reported by Hodgkin et al. (440) uses a Monte Carlo search procedure to generate candidate pharmacophoric patterns. A reduced force-field parameter set is used initially to lower energy barriers between conformations to ensure greater configurational sampling. Candidate pharmacophores are then refined to produce low energy conformations of molecules overlaid in a common binding mode. Application to antagonists of the human platelet-activating factor led to a consistent binding model for a set of five diverse structures when active-site hydrogen-bonding groups were postulated. Barakat and Dean (441, 442) utilized simulated annealing to optimize structure matching by minimizing the difference matrix between the two molecules. A somewhat similar approach is that of Perkins and Dean (443), who used simulated annealing to search conformational space followed by cluster analysis for each molecule, with subsequent comparison of a small number of diverse conformers between different molecules.

4.4.2 Systematic Search and the Active Analog Approach. Once the existence of a common pattern has been determined, then the issue of uniqueness needs to be addressed. The Active Analog Approach (398) uses a systematic search to generate the set of sterically allowed conformations based on a grid search of the torsional variables at a given angular increment. For each sterically allowed conformation, a set of distances between the postulated pharmacophoric groups are measured. The set of distances, each of which represents a unique pharmacophoric pattern, constitutes an OMAP. Each point of the OMAP is simply a submatrix of the distance matrix and, as such, is invariant to global translation and rotation of the molecule. If the initial assumption is valid, that the same binding mode of interaction, or pharmacophoric pattern, is common to the set of molecules under consideration, then the OMAP for each active molecule must contain the pattern encrypted in the set of distances. By logically intersecting the set of OMAPs, one can determine which patterns are common to all molecules (444). In other words, all potential pharmacophoric patterns consistent with the activity of the set of molecules can be found by this simple manipulation of OMAPs, and the question of uniqueness addressed directly (Fig. 3.44).

A good example is the work of Nelson et al. (445) on the receptor-bound conformation of morphiceptin. Based on structure-activity data, the tyramine portion and phenyl ring of residue three of morphiceptin, Tyr-Pro-Phe-Pro-NH,, were postulated to be the pharmacophoric groups responsible for recognition and activation of the opioid preceptor. It was assumed further that the aromatic rings bound to the receptor in the different analogs were coincident and coplanar. A series of active analogs with a variety of conformationally constrained amino acid analogs in positions two and three were analyzed. A unique conformation was found for the two most constrained analogs that allowed overlap of the Phe and Tyr portions of the molecules (Fig. 3.45). In this case, a five-dimensional orientation map with distances between the nitrogen and normals to the two aromatic rings was used in the analysis.

The Active Analog Approach (Fig. 3.46) is appropriate for the unknown receptor problem, given that no objective criteria function, such as potential energy, can be used *a priori* in the absence of information regarding the receptor. Adequate sampling of the potential surface to ensure that the complete set of local minima is found is still problematic because of the phenomenon known as "grid tyranny." This relates to the fact that the combinatorial explosion that results by decreasing the increment of the torsion angles scanned limits one to a finite increment for a given problem, say, 10° for a seven-rotatable bond problem. Because the energetics of the system is very sensitive to interatomic distances, a conformation generated at the 10'' increment may be sterically disallowed, but very close to a minimum. Relaxation of the structure might find the relevant conformation, for example, by allowing a torsional angle to vary by 1°. Im-