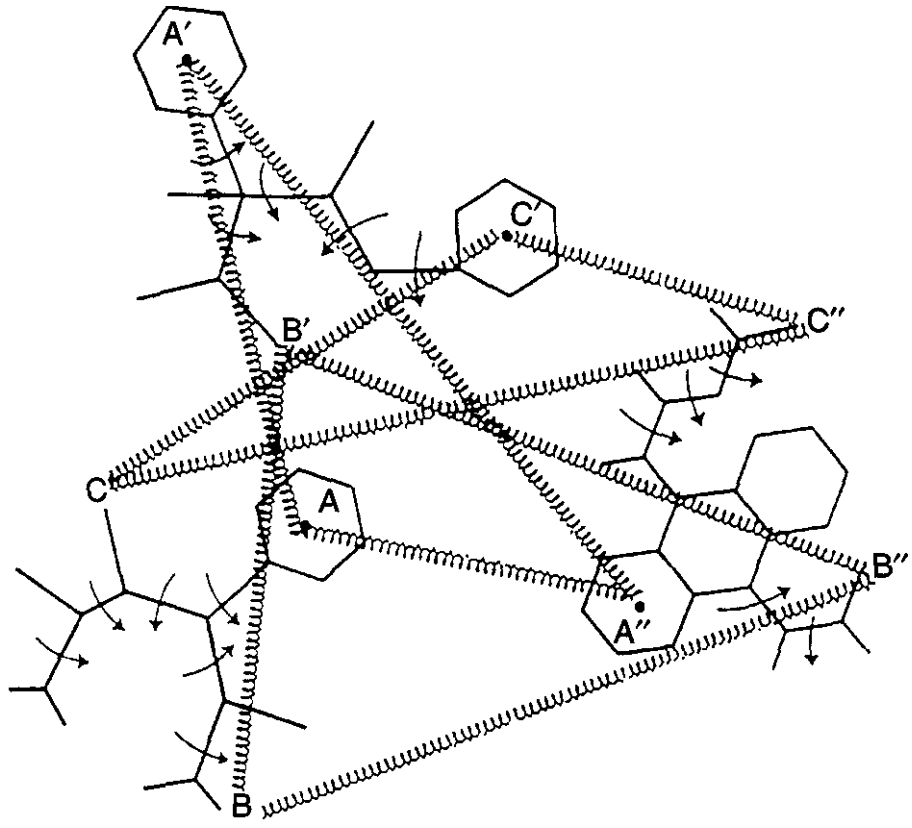


**Figure** 3.43. Simultaneous minimization of molecules to force overlap of pharmacophoric groups A, B, and C. Springs represent constraints between groups and only interatomic forces evaluated.

rigid and mobile domains. In general, the difficulties with most methods are similar to those seen with minimization procedures. If one is in the area of the global minimum, then one is likely to converge to that solution. Otherwise, one will be trapped in some local minimum. In contrast, systematic search methods are algorithmic, so that all sterically allowed conformations are generated at the selected torsional grid parameters. Systematic search methods, therefore, do not have problems in sampling and are path independent, but are combinatorial in complexity, which may limit the fineness of the sample grid and thus compromise the results. Only in small systems such as cycloalkane rings (121) and small peptides (90, 436) have the potential energy hypersurfaces been mapped.

**4.4.1 Constrained Minimization.** In cases where one has internal degrees of freedom, besides the six associated with position and orientation. the use of constrained minimization procedures becomes a useful technique. Often the standard molecule for comparison has a fixed conformation and the molecule to be fitted has internal degrees of freedom. Several groups have published methods for dealing with this problem. In case one has simultaneous degrees of freedom in both the molecule to be fitted and the target, a different approach with simultaneous minimization of all variables is recommended (Fig. 3.43).

The combination of molecular mechanics with flexible minimization routines allows penalty functions to be assigned to force geometrical correspondence of groups, whereas individual molecules have their internal energy evaluated, but are invisible to the other molecules under consideration. A program has been described (437) with this capability and its use illustrated on histamine antagonists by Naruto et al. (438). Template forcing allows one molecule to be set up as a template and another molecule to be constrained to overlap in a specified manner. The strain energy involved in forcing correspondence gives an upper-bound estimate of the distortion energy required, given that the results depend on the initial-problem definition.

An alternative approach uses the distance geometry paradigm, in which all the constraints are combined to form the distance matrix from which energetically feasible conformations of the set of molecules are sought mathematically. Sheridan et al. (439) demonstrated this approach on acetylcholine analogs that are muscarinic agonists. Both of these approaches ask the same question and suffer from the same limitations, and differ only in computational technique. Each suffers from the local minima problem, in that each uses a