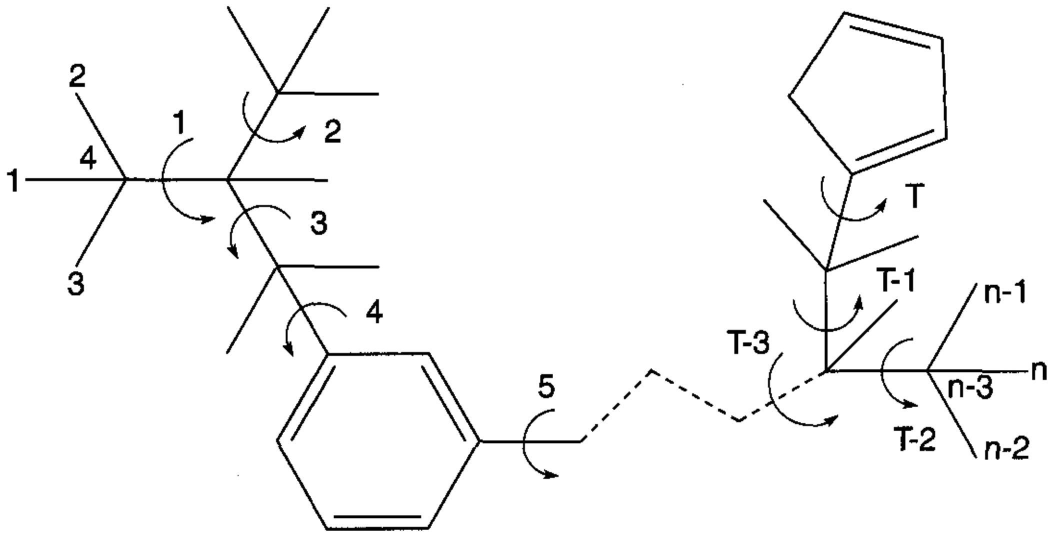

Figure 3.3. Schematic diagram of molecule with N atoms and T rotatable bonds.

oms and atoms bonded to the same atom from the check, which is necessary) and checked against the allowed sum of VDW radii for the two atoms involved. The number of VDW comparisons V is given by

$$V = (360/A)^T \times N(N - 1)/2$$

It should be clear that the VDW comparisons are the rate-limiting step by their sheer number, and any algorithmic improvement that reduces the number of such checks or enhances the efficiency of performing such checks is of value.

2.1.4.3 Pruning the Combinatorial Tree. From this simplified analysis, a systematic search of other than the smallest molecules at a coarse increment would appear daunting. A hybrid approach with a coarse grid search followed by minimization has been successfully used to locate minima. There are a number of algorithmic improvements over the "brute force" approach that enhances the applicability of the systematic search itself. To understand these improvements, some concepts need to be defined. First is the concept (110) of aggregate, a set of atoms whose relative positions are invariant to rotation of the T rotational degrees of freedom. n-Butane is divided into aggregates as an illustration (Fig. 3.4).

In this simple example, the atoms in an aggregate are all either directly bonded or have a 1–3 relationship (i.e., are related by a bond angle). Because of the rigid geometry approximation, their relative positions are fixed. Atoms contained within the same aggregate do not, therefore, have to be included in the set of those that undergo VDW checks for each conformation. For linear molecules, there are $n - 1$ bonds and the number of 1–3 interactions depends on the valence of the atom. This simplification leads to a reduction of the number of VDW checks by the factor $N(N - 1)/2$, which is multiplied by the number of conformations.

How can one reduce the number of conformations that have to be checked? Here the concept of construction becomes useful. One constructs the conformations in a stepwise fashion, starting with an initial aggregate and adding a second aggregate at a given torsional increment for the torsional variable T that is applied to the rotatable bond connecting the two. If any pair of atoms overlaps for that increment, then one can terminate the construction because no addition operation will relieve that steric overlap. In effect, one has truncated the combinatorial possibilities that would have included that subconformation; that is, one has pruned the combinatorial tree.

2.1.4.4 Rigid Body Rotations. If one constructs the molecule stepwise by the addition of aggregates, then one has two sets of atoms to consider. First are those in the partial mol-

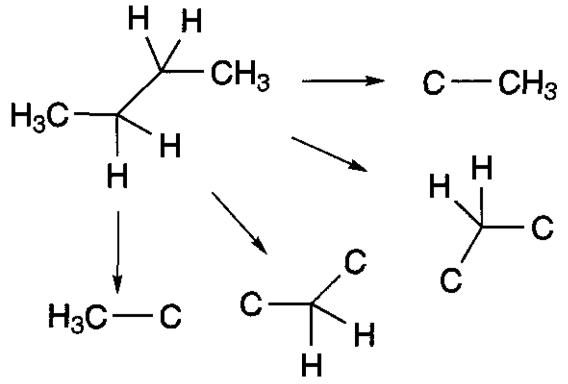

Figure 3.4. Decomposition of *n*-butane molecule into aggregates.