

Figure 3.5. Distance between atoms (1–7) and atom 10 separated by a single rotatable bond T can be described with a transformation of the equation of a circle describing the locus of atom 10 as bond T is rotated. Notice that distance D between any atom (1–7) and center of circle of rotation of atom 10 that is on axis of rotation is fixed, regardless of value of T .

ecule (set A), previously constructed, that have been found to be in a sterically allowed partial conformation. For each possible addition of the aggregate, the atoms of the aggregate (set B) must be checked against those in the partial molecule. If one uses the concept of a rigid body rotation, then one can describe the locus of possible positions of any atom in set B as a circle whose center lies on the axis of rotation T_i (the interconnecting bond) at a distance along the axis that can be calculated. The formula for a circle can be transformed to represent the possible distances between the atom b in set B and any atom a in set A, as shown in Fig. 3.5. An equation with scalar coefficients that describes the variable distance between two atoms as a function of a single torsional variable was derived (111), which has a discriminant whose evaluation can be used to determine whether atom a and atom b will:

- be in contact, despite changes in the value of the torsional rotation of the aggregate, which implies that the current partial conformation has to be discarded, given that there is no possible way to add the aggregate that is sterically allowed;
- never come in contact for any value of the torsional rotation, so that this pair of atoms can be removed from consideration regarding this aggregate; or
- come in contact for some values of the torsional rotation that can be calculated for that pair and that removes a segment of the

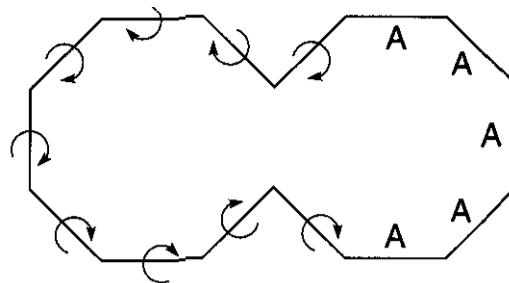


Figure 3.6. Scheme for combining systematic search with analytical solution for closure. Bonds indicated by arrows were systematically scanned, whereas those indicated by **A** were analytically determined. Dotted bond **can** represent either chemical bond or experimental distance determination (NOE, etc.).

torsional circle from consideration for other atom pairs. If all segments of the torsional circle are disallowed by combinations of the angular requirements of different atom pairs, then the partial conformation of the molecule is disallowed because further construction is not feasible. As a first approximation, this removes a degree of torsional freedom from the problem, reducing T to $T - 1$ torsional degrees of freedom. At a 10° torsional scan, an approximate reduction in computational complexity of a factor of 36 results.

2.1.4.5 The Concept and Exploitation of, Rings. Realization that many of the relevant constraints in chemistry can be expressed as interatomic distances, VDW interactions, nuclear Overhauser effect constraints, and so forth allows use of the concept of a virtual ring in which the constraint forms the closure bond. Small rings up to six members can be solved analytically (112), so that one can search the torsional degrees of freedom associated with a constraint until only five remain and then solve the problem **analytically** (Fig. 3.6). The torsional angles for those degrees of freedom are no longer sampled on a grid, thus removing the problem of grid tyranny, in which valid conformations are missed by the choice of increment and starting conformation. This approach is then a hybrid because only part of the conformational space is searched with regular torsional increments. It is, however, much more efficient to solve a set of equations than search 5 torsional degrees of freedom.