

The Computer Derivation of Stereochemical Relationships from the Chirality of Ring Atoms

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Most stereochemical information not involving torsional isomerism¹ is tersely described by stating the chirality of each chiral centre. Programs that deal with stereochemical problems have to derive the concepts of *cis*, *trans*, axial, equatorial, alpha, beta, *exo*, *endo*, etc., from knowledge of the chirality. A fast algorithm has been devised which finds the *cis*- and *trans*-relationships of substituents in the same ring, knowing the chirality of the relevant two ring atoms. The other steric relationships can then be simply derived from the *cis*-*trans* relationships.

SOME stereochemical relationships can be altered by an actual or a hypothetical rotation around a single or double bond. Those which cannot be so altered are relationships involving configuration at saturated atoms. Almost all such relationships can be conveyed by indicating the chirality of the chiral atoms concerned.¹ An exception is the case of molecules which have steric relationships in a plane of symmetry. The plane of symmetry can be permanent, as in 1-bromo-3-chlorocyclobutane, or time-averaged, as in *cis*-decalin. In the latter situation there is no instantaneous plane of symmetry, but the rapid interchange of *R,R* and *S,S* chiralities for the junction atoms gives rise to an effective plane of symmetry.

In the overwhelming majority of cases, then, the information about the three-dimensional stereochemistry of a molecule is completely as well as conveniently stored in the form of the chirality of the chiral atoms. Given such a representation of stereochemical information in a computer memory, the problem arises of how to determine such matters as whether or not substituents of adjacent ring atoms are *trans*-diaxial to each other or which is the *endo*-side of a molecule. The key task is the determination of the *cis* and *trans*-relationships of substituents in the same ring. If the rings of the molecule have been found by a procedure which involves traversing the ring at some stage, e.g. Esack's,² so that the sequence of atoms in the ring is known and if, in addition, the neighbouring atoms of each ring are listed in the same canonical order that defines the chirality, then this problem can be solved.

The Parity Rule of Petrarca, Lynch, and Rush.—This solution depends on the parity rule of Petrarca, Lynch, and Rush.³ The rule states that when the atom numbers of the four neighbouring atoms of a chiral atom are written in an ordered list, any even permutation of the list represents a physical operation that preserves the indicated chirality and any odd permutation of the numbers in the list represents a physical operation that inverts the chirality. The list will originally be ordered according to some criterion, e.g. the Cahn-Ingold-Prelog sequence rules,⁴ which ranks the atoms. This criterion can be used to order the atoms of the molecule. In the examples below, the highest-ranking atoms have the lowest numbers.

Validity of the Parity Rule.—Suppose that in a certain molecule a particular chiral atom is numbered as atom

5 and suppose, further, that the neighbours of atom number 5 are numbered 2, 4, 6, and 8. Then the list 2, 4, 6, 8 is evidently in canonical order, i.e. the highest ranking atom has its number listed first, the next highest second, etc. The list 2, 4, 6, and 8 obviously conveys nothing to us of the chirality; we have to be separately informed that the chirality of atom number 5 is, let us say, *R*. Once we are so informed we can mentally construct a tetrahedron at the vertices of which we place the atoms numbered 2, 4, 6, and 8. This means that each position in the list now has a definite meaning; it refers to a definite vertex of a definite tetrahedron. When we view the ligands from the side opposite atom 8 we shall see the atoms 2, 4, and 6 are arranged in clockwise order. Now if we interchange the numbers 4 and 6, for example, then the new list 2, 6, 4, 8, conveys an arrangement of

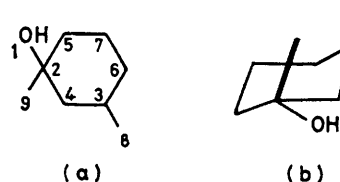


FIGURE 1 (a) 1,3-Dimethylcyclohexanol, with the chiralities indicated but the *cis*-*trans* relationships not shown; (b) 1,3-dimethylcyclohexanol, with the stereochemistry shown

the four ligands which differs from the original arrangement by the interchange of atoms 4 and 6. Evidently the chirality must be reversed. The information conveyed by the new list plus the fact that the old list had *R* chirality is that the atom now has *S* chirality. This explains why the parity rule holds.

Consider Figure 1. A canonical numbering of the atoms of 1,3-dimethylcyclohexanol is displayed in Figure 1(a). The atoms numbered 2 and 3 are chiral atoms and we are given that both of them have *R* chirality. We would like to know whether the two methyl groups are *cis* or *trans* to each other. The chiral reader, with his built-in knowledge of what is clockwise and what is counterclockwise, can infer by inspection that with the indicated *R* chirality both methyl groups will be pointing up towards us away from the plane of the ring. In other words they are *cis* to each other in this ring and the hydroxy-oxygen is *trans* to methyl atom 8 [cf. Figure 1(b)]. The achiral computer can infer the same information by the use of the method which we now describe.

The computer program has previously traversed the ring and hence it has equipped itself with a list of the ring atoms. The list of ring atoms could be 2, 4, 3, 6, 7, 5 or 5, 7, 6, 3, 4, 2 or 7, 6, 3, 4, 2, 5, etc. It does not matter which list is used. For convenience we write the list twice, *i.e.* 2, 4, 3, 6, 7, 5, 2, 4, 3, 6, 7, 5.

Consider atom number 2. The first occurrence of its neighbour, atom number 5, in the list of ring atoms given above is to the left of atom number 2. Therefore we will say that atom 5 is the 'left atom'. Denoting it as the left atom says nothing about its actual location in space; we merely mean that it lies to the left of atom 2 in the list of the ring atoms. Its other ring neighbour, atom number 4, is the first atom on the right of atom 2 in the same list. Let us call atom number 4 the 'right' atom, again only because it lies immediately to the right of 2 in the list of ring atoms. In the list of neighbours of atom 2 there are four possible positions for the left atom. Since the ascending canonical order in this specific case is 1, 4, 5, 9, it follows that the position of the left atom happens to be the third. It will be convenient here to number the positions as 0, 1, 2, and 3 rather than 1, 2, 3, and 4. Hence, in this case the left atom, atom 5, is in position 2 in the list. Now let us delete atom 5 from the list. We now have a list of three atoms, neighbours of atom 5. There are three possible positions of the right atom, atom 4, in this list. In this specific case the right atom is the second on the list of the remaining three atoms. Again, taking the positions to be numbered as 0, 1, and 2, the position of atom 4 in the list 1, 4, 9 is position 1. We add the two positions 2 and 1 and obtain the sum 3. This is the number of interchanges of two ligands required to bring the original list, 1, 4, 5, 9 into the form 5, 4, 1, 9. This is a particular example of the general form: left ring atom, right ring atom, higher-ranking substituent, lower-ranking substituent.

We then do the same for the other chiral atom, number 3. We find that the left atom, number 4, has position number 0 in the list of neighbours 4, 6, 8, H. The right atom, number 6, has position number 0 in the list 6, 8, H. The sum of these two numbers is zero. That is the number of interchanges of pairs of ligand atoms required to bring the list 4, 6, 8, H into the standard form as described above: left atom, right atom, higher-ranking substituent atom, lower-ranking substituent atom. In other words the list was in the standard order to begin with. On adding 3, the number for chiral atom 2, to zero, the number for chiral atom 3, we obtain 3 which is an odd number. This is another way of saying that the parity of the permutation required to bring the list of ligands of atom 2 into the standard form is different from the parity of the permutation required to bring the list of ligands of atom 3 into standard form. In such a case, according to the rule to be stated below, the higher ranking of the substituents of atom 2 must be *trans* to the higher-ranking substituent of atom 3. In other words the hydroxy-oxygen is *trans* to the methyl carbon,

number 8. Evidently the methyl groups are *cis* to each other.

The Rule for Deriving cis-trans Relationships from Chirality.—We now state the rule formally. The higher ranking substituents of two chiral ring atoms in the same ring are *cis* to each other if, and only if, the following two statements are both true or both false: (1) The chiralities of the two atoms are the same. (2) The parity (evenness or oddness) of the permutations required to bring the canonically ordered list of their ligands into the standard form is the same. The canonical order uses the same criteria that rank the ligands to determine chirality.

Let us consider another example, 1-methylcyclopentane-1,2-diol; it is shown in Figure 2. A list of ring atoms, repeated, is 7, 5, 3, 4, 6, 7, 5, 3, 4, 6. The canonically ordered list of neighbours of atom 3 is 1, 4, 5, 8. The left atom is 5 and the right atom 4. Applying the method described above we find that the left atom is in position 2 and the right atom in position 1. The sum of these is 3. The list of neighbours of atom 4 is 2, 3, 6, H. The left atom is 3 and the right atom 6.

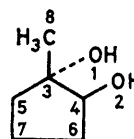


FIGURE 2 1-Methylcyclopentane-1,2-diol, with the atoms numbered in Cahn-Ingold-Prelog canonical order

Here we obtain 2 as the sum of the positions of the left and right atoms in the appropriate lists. The parities of the number of interchanges required to bring the neighbour lists into the same standard form are different. We are given, let us say, that the chiralities of both atoms are *S*. Then we know from the rule stated above that the higher-ranking substituent of atom 3 is *trans* to the higher-ranking substituent of atom 4. In other words the two hydroxy-groups are *trans* to each other.

The problem solved by this algorithm is almost the inverse of the problem of deriving the unknown chirality of a ring atom from the known chirality of another ring atom together with stereochemical relationships of the substituents of the chiral atoms.⁵

The reader may wonder why the rule is valid no matter which way the list of ring atoms reads. For example, the list for 1-methylcyclopentane-1,2-diol might just as well have read 6, 4, 3, 5, 7, 6, 4, 3, 5, 7. This has to do with the fact that the *cis-trans* relations are the same if both chiral atoms have *R* chirality or both have *S* chirality. If the chiralities are different it does not matter which one is *S* and which is *R*. We note that the *cis-trans* relationships are derived from the relationship between the chiralities, not the absolute value of the chiralities. Reflection in a plane does not alter the relationship between chiralities and hence does not alter *cis-trans* relationships. Taking the list of ring atoms in the opposite direction is equivalent to reflecting the molecule in a plane.

Derivation of other Stereochemical Properties from the cis-trans Relationships.—The other stereochemical properties which are definite consequences of *cis*- and *trans*-relationships can then be easily derived by a computer program. For example, in a bicyclo[2.2.1] system, if a ring substituent is *cis* to the bridge atom, then it is *exo*. Also, we know that when small- and medium-sized rings are *trans*-fused to a six-membered ring, the two ring substituents of the six-membered ring must both be equatorial. As we can see in Figure 3, it is easy for a computer program to derive that atom X must be equatorial since it is *trans* to equatorial atom Z. Atom Y must also be equatorial since it is *trans* to atom X. In the program we write that substituents are axial in a *trans*-fused ring system if they are *trans* to an equatorial substituent and separated from it by three ring atoms. They are also axial if they are *cis* to an equatorial substituent and separated from it by two or four ring atoms or *cis* to an axial substituent and separated from it by three ring atoms.

The foregoing algorithm has been incorporated into the computer program of the author which generates synthetic routes conforming to input requirements on number of steps and minimum overall yield without interacting with a chemist during the operation of the program.⁶ The structure of the desired goal molecule is conveyed to the program *via* a connection table⁷ which contains the chiralities for each chiral atom. Thus for α -cholestan-3-ol, the input structural information could be depicted mentally as in Figure 4(a), in which there is no concept of α , β , *cis*, *trans*, etc. However after application of the above rule the program derives all the common stereochemical relationships, infers that the

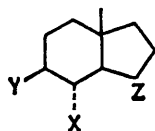


FIGURE 3 Example to show the inference of axial and equatorial information from *trans*-fusion of the rings

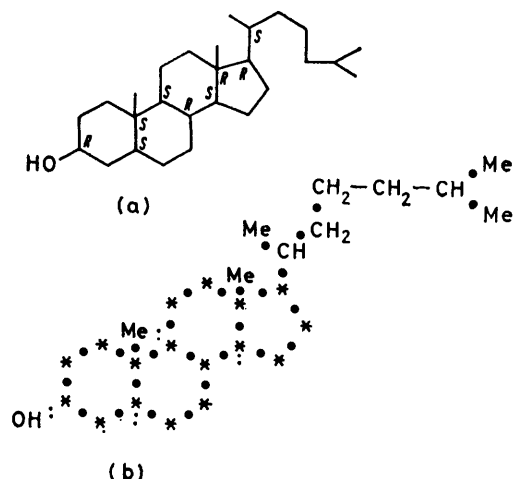


FIGURE 4 (a) The input data on the structure of α -cholestan-3-ol as it appears to the computer program; (b) the structure of α -cholestan-3-ol, as output by the computer program after deducing the *cis-trans* relationships

alcohol is axial, a fact of synthetic importance, infers that the angular methyl groups are on the α -side, etc. The actual structure drawn by the program after this process is shown in Figure 4(b). Exocyclic bonds to α and β substituents are represented by a colon and a dot, respectively.

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