Chiral Recognition as Directional Recognition

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A logic of chiral recognition based on the differentiation of directions is more consistent and inclusive than one based on the differentiation of part structures.

Chiral recognition includes enantiomeric and enantiotopic recognition. In the latter, enantiotopic half-spaces are differentiated in the presence of a chiral probe P.[1] A schematic example is illustrated in Figure 1(a), where substrate XYZ reacts with chiral probe ABCD. The preferential formation of one of the enantiomeric products AXYZ is possible because the transition states differ geometrically and can differ, therefore, in energy.[1]

Chiral recognition is the differentiation of enantiomorphs R and S.[1] What are R and S in Figure 1(a)? The term 'enantiotopic recognition' suggests that they are the contents of the enantiotopic half-spaces, half-molecules separated by the XYZ plane. The half-molecules are material objects, since nuclei have finite sizes and electrons fill space, and they are enantiomorphs.

However, enantiotopic recognition remains possible in idealized models with empty enantiotopic regions. Consider molecular models consisting only of point masses at the atomic centres. For an isolated XYZ, the enantiotopic half-spaces are empty. As isolated objects, they are homomorphs; they cannot be R and S. Even so, the transition states illustrated in Figure 1(a) differ geometrically and chiral recognition is possible.

This suggests (i) that the contents of enantiotopic regions are incidental, not fundamental, to recognition and (ii) that there exists a more general logic of chiral recognition. A clue is provided by the common phrase, 'recognition of enantiotopic faces.' The faces of a plane are specified by a point of view, which in turn implies a direction. The logic of chiral recognition described here is based on directions, not sub-

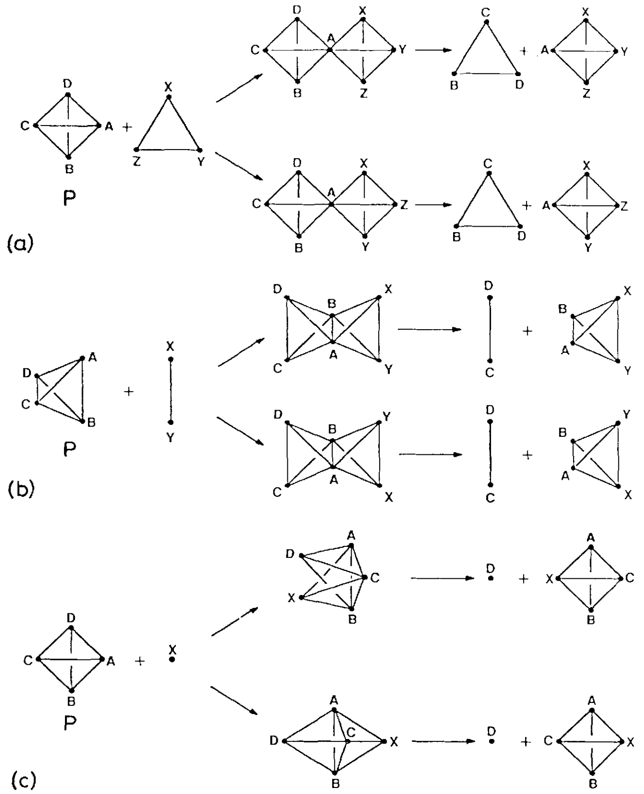

Figure 1. Examples of chiral recognition with substrates that are (a) (pro)^1-chiral, (b) (pro)^2-chiral, and (c) (pro)^3-chiral. Lines are not bonds; they are included to clarify the geometry. P is a chiral probe.

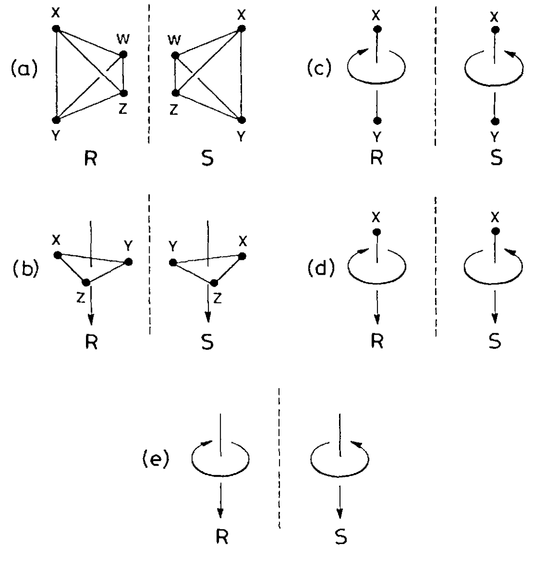

Figure 2. Enantiomorphs R and S that are differentiated in chiral recognition with the simplest possible (a) (pro)^0-, (b) (pro)^1-, (c) (pro)^2-, and (d) (pro)^3-chiral substrates. The vectors represent supplementary linear and rotational directions that combine with the substrates to give a chiral objects R and S, which are differentiated in the presence of a chiral probe. (e) Vector definitions of opposite chiral senses.

spaces. Chiral recognition is directional recognition. This concept allows a unified treatment that includes examples of chiral recognition not previously recognized as such.

All cases, regardless of the nature of the substrate, are treated by the same logic, as follows:

(i) The enantiomorphs R and S are combinations of substrate molecules with supplementary linear or rotational directions, represented by vectors in Figure 2, sufficient to define chiral senses. A chiral sense can be defined by a linear direction and a rotational direction around it [Figure 2(e)].[2] (Pro)^0-chiral substrates define both linear and rotational directions and are themselves enantiomorphs R and S [Figure 2(a)].[3][†] (Pro)^1-chiral molecules define rotational directions and combine with supplementary linear directions to give R and S [Figure 2(b)], (pro)^2-chiral molecules define linear directions and combine with supplementary rotational directions [Figure 2(c)], and (pro)^3-chiral molecules define only a point and combine with supplementary linear and rotational directions [Figure 2(d)].

(ii) When the chiral probe P is at a sufficient distance from the substrate that no interaction occurs, pairs PR and PS differ geometrically. There are no placements of P relative to R and S such that all internal distances and angles in PR and PS, including measurements on vectors as well as atoms, are the same. Thus, R and S are differentiated in the presence of P (chiral recognition). Non-interacting pairs PR and PS are considered because the capacity for chiral recognition (geometric difference between PR and PS) can be lost along the mechanistic pathway of a reaction.

(iii) The differentiation of R and S implies the differentiation of the directions that define their chiral senses. For achiral substrates, the supplementary directional components of R and S are differentiated. In each case, interactions and reactions of P with R and S can have different chemical consequences for these directions.

Illustrative schematic examples for achiral substrates are given in Figure 1. In Figure 1(a), the linear directions perpendicular to the face of (pro)^1-chiral substrate XYZ are differentiated. In Figure 1(b), the rotational directions around the axis of (pro)^2-chiral substrate XY are differentiated. In Figure 1(c), the rotational directions around the axis of a radial direction from (pro)^3-chiral substrate X are differentiated. The substrates for the examples illustrated in Figures 1(b) and 1(c) do not delineate enantiotopic spaces and such reactions have not been recognized previously as examples of chiral recognition.

An S_N2 reaction of I^- with $CR^1R^2R^3Cl$ is an analogue of the reaction in Figure 1(c). $CR^1R^2R^3Cl$ is the chiral probe P and I^- is the substrate X. In transferring $CR^1R^2R^3$ from $CR^1R^2R^3Cl$ to I^-, the two directions of rotation about a radial direction from I^- are differentiated, one direction being selected. The differentiation of the enantiomorphs R and S of Figure 2(d) underlies the directional discrimination.

The particular (pro)^2- and (pro)^3-chiral substrates of Figures 1(b) and 1(c) do not delineate enantiotopic regions, but other (pro)^2- and (pro)^3-chiral substrates do.[3][‡] Of all

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[†] The linear directional component of R or S can be chosen arbitrarily, but it must be consistently defined in R and S. It may be convenient to identify it with a rotational axis or with a direction perpendicular to a plane of symmetry. For chiral molecules, a convenient choice is along a line of centres between two atoms. Two atoms off this line can be chosen to define the rotational direction.

[‡] For example, the symmetry planes of a formaldehyde molecule, which is (pro)^2-chiral, divide space into enantiotopic half-spaces consisting of four quadrants. Labelling corresponding points in enantiotopic quadrants defines opposite rotational directions around the axis of the molecule, analogous to Figure 2(c). Thus, enantiotopic recognition and directional recognition are equivalent in this case, as in all similar cases.

reactions of $(pro)^2$- and $(pro)^3$-chiral substrates that give enantiomeric products with a preference, the concept of enantiotopic recognition counts some, but not all, as examples of chiral recognition. This distinction seems inappropriate and does not appear in the direction-based concept of chiral recognition.

In summary, the direction-based logic given here treats all cases of chiral recognition in a simple manner that (i) is applied consistently to all substrates, (ii) includes enantiomeric and enantiotopic recognition, (iii) includes previously unrecognized cases, and (iv) treats $(pro)^2$- and $(pro)^3$-chiral substrates that delineate enantiotopic regions in the same manner as those that do not.

Chiral recognition can be classified by the nature of the substrate. Let 'CR*p*' be chiral recognition with a $(pro)^p$-chiral substrate. Then CR0 is enantiomeric recognition and Figures 1(a)—(c) illustrate CR1, CR2, and CR3.

For CR0, at least 8 atoms are required, four in the probe and four in a substrate molecule, as previously shown.[4] For CR1, seven atoms are required, for CR2 six, and for CR3 five. Thus, the minimum number of atoms required for chiral recognition is five.

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References

1 See J. Rétey and J. A. Robinson, 'Stereospecificity in Organic Chemistry and Enzymology,' vol. 13 of 'Monographs in Modern Chemistry,' ed. H. F. Ebel, Verlag Chemie, Weinheim, 1982, pp. 9—11 and 21—25, for example. Objects differ geometrically if they are neither congruent nor mirror images; p. 4. Enantiomeric and enantiotopic recognition are discussed in almost all textbooks of organic chemistry or stereochemistry.

2 This is the basis of Cahn–Ingold–Prelog configurational ('*RS*') nomenclature: R. S. Cahn, C. Ingold, and V. Prelog, *Angew. Chem., Int. Ed. Engl.*, 1966, **5**, 385.

3 For '$(pro)^p$-chiral,' see K. Mislow and J. Siegel, *J. Am. Chem. Soc.*, 1984, **106**, 3319.

4 S. Topiol and M. Sabio, *J. Am. Chem. Soc.*, 1989, **111**, 4109.