Bull. Chem. Soc. Jpn., **75**, 365–366 (2002) 365

A Unified Con/Dis Approach to Assigning Stereogenic Axis Configuration

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(Received June 15, 2001)

A new and unifying approach based on a directional relationship between two arcs joining two ligands at either end of the stereogenic axis is presented for assigning stereogenic axis configuration, which is specified as Con (when both arcs are clockwise or counterclockwise) or Dis (when one arc is clockwise and the other counterclockwise). Con and Dis correspond, respectively, to the descriptors axial *R* and axial *S* for a chiral axis, and to *E* and *Z* for an achiral alkene axis.

Stereoisomerism in organic compounds stems from the presence of a stereogenic element (stereogenic center, axis, or plane). Recently, a unified procedure for assigning and correlating the stereogenic center configuration in diverse stereoformulas has been reported.[1] This paper presents a new and unifying approach for assigning the stereogenic axis configuration.

The stereogenic axis in organic molecules exhibits (i) enantiomerism depicting the axial *R*/axial *S* configuration[2,3] or *P*/*M* descriptors[4] in allenes, atropisomers, alkylidenecycloalkanes, and spiranes, wherein the stereogenic axis is a chiral axis;[5] and (ii) diastereomerism depicting the *E*/*Z* configuration[6] in double-bond system such as alkenes. The stereogenic axis is a line joining two atoms, each of which is linked to a pair of different ligands in a particular plane with no restrictions as to the identity of the two pairs attached to the two atoms. The two pairs of ligands lie in mutually perpendicular planes for a chiral axis, which become coplanar for an achiral alkene axis. The priority order of two ligands in each pair is determined, and an arc (clockwise or counterclockwise) is drawn from the ligand of higher priority to that of lower priority for each pair. The stereogenic axis configuration is defined by the relationship between the two arcs: Con (when both arcs are clockwise or counterclockwise) or Dis (when one arc is clockwise and the other counterclockwise).

The configuration for a chiral axis is depicted in Fig. 1A. Two (h, l) pairs are linked to two atoms, X and Y, defining the stereogenic axis, where h and l denote the higher priority and the lower priority ligands, respectively, in each pair. One (h, l) pair lies in the plane of the paper, and the other (h, l) pair is in the perpendicular plane of the paper. For determining the chiral-axis configuration, two h → l arcs (through bond angle) need to be drawn while taking X and Y as the geometric centers. As shown in Fig. 1A, the arcs are to be defined on the top face of the plane of the paper, and on the right face of the perpendicular plane. Because both h → l arcs are clockwise, the chiral-axis configuration is Con, which corresponds to the axial *R* configuration. The correspondence is: Con ≡ *R*; and Dis ≡ *S*. The perpendicular plane of a ligand-pair is shown in four orientations obtained by successively turning the chiral axis by 90° (B1 – B4 in Fig. 1B), in which h → l defines a clockwise arc. These representations lead to a simple and useful mnemonic: if h is in the front, the arc is clockwise; or, if h is in the rear, the arc is counterclockwise.

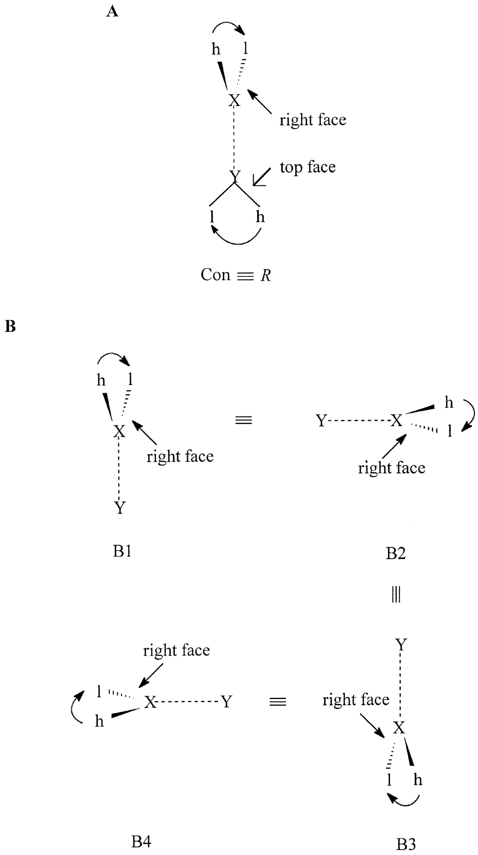

Fig. 1. **A**: Assignment of chiral-axis configuration. X------Y denotes the chiral axis. h and l denote, respectively, the higher priority and the lower priority ligand for a ligand-pair. h → l arcs are defined on the top face of the plane of the paper, and on the right face of the perpendicular plane, taking Y and X as geometric centers respectively. **B**: Four orientations of the perpendicular plane of a ligand-pair (h, l), obtained by turning, in succession, the chiral axis by 90°. The mnemonic is: if h is in the front, the arc is clockwise; or, if h is in the rear, the arc is counterclockwise.

The above procedure is illustrated in Fig. 2 with four examples. In the substituted allene (Fig. 2A), C=C=C is the chiral axis. The ligand-pair (CO_2H, H) is in the plane of the paper, and the arc CO_2H(h) → H(l) is clockwise. The other ligand-pair (Et, Me) is in the perpendicular plane, and the higher priority ligand Et is in the front. The arc Et(h; front) → Me(l) is clockwise. Therefore, the configuration is Con ≡ *R*. In the biphenyl derivative (Fig. 2B), the bond joining the aryl groups is

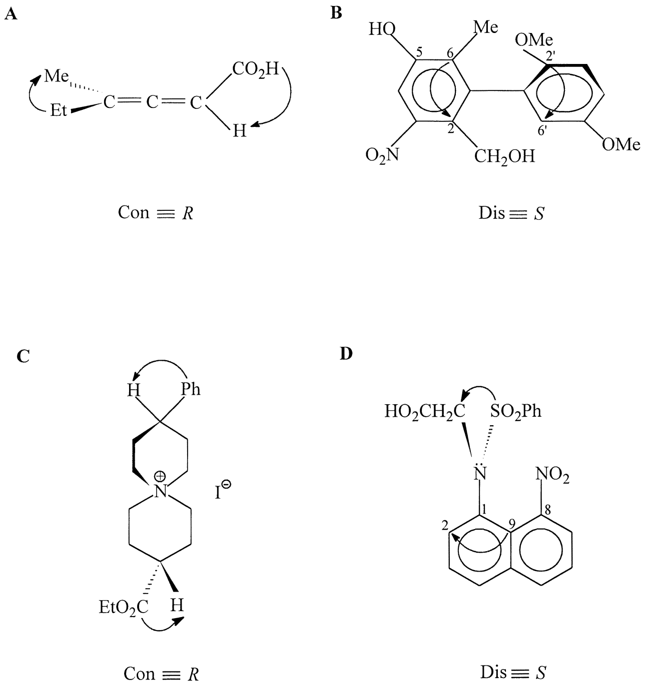

Fig. 2. Assignment of chiral axis descriptors of **A**: a substituted allene; **B**: a biphenyl derivative; **C**: a spirane; and **D**: a substituted 1-naphthylamine.

the chiral axis, and the ligands are explored from the center to outward. The ligand-pair lying in the plane of the paper comprises a C-2 branch and a C-6 branch. Their relative priority has been determined[1] to be C-6 branch [C–O bond and no H at second atom (C-5)] > C-2 branch [C–O bond and 2 H's at second atom (C of CH_2OH)]. The arc C-6(h) → C-2(l) is counterclockwise. The ligands in the perpendicular plane are a C-2′ branch and a C-6′ branch. The arc C-2′(h; front) → C-6′(l) is clockwise. Hence, the configuration is Dis ≡ *S*. The spirane molecule (Fig. 2C) has a chiral axis, C···N···C, in which the arc Ph(h) → H(l) is counterclockwise, and the arc CO_2Et(h; rear) → H(l) is also counterclockwise. Thus, the configuration is Con ≡ *R*. The substituted 1-naphthylamine (Fig. 2D) possesses a chiral axis along the N–C_1 bond, in which the arc C-9 branch(h) → C-2 branch(l) traces clockwise, while the arc SO_2Ph(h; rear) → CH_2CO_2H(l) is counterclockwise. Thus, the configuration is Dis ≡ *S*.

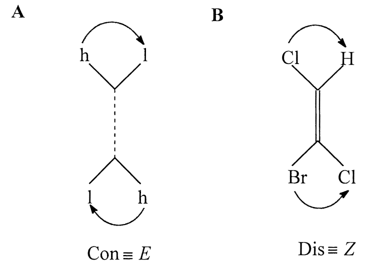

Fig. 3. **A**: Assignment of stereogenic axis configuration of achiral alkene. The dashed line indicates the stereogenic axis. h → l arcs are defined on the same face of alkene plane. **B**: Assignment of descriptor for an alkene.

The Con/Dis approach, as a unifying system, also determines the stereogenic axis configuration of alkenes when the two (h, l) pairs are coplanar (Fig. 3A). The two h → l arcs are clockwise, and the configuration is Con, which corresponds to the *E* configuration. It is notable that Con ≡ *E* and Dis ≡ *Z*. For example, the alkene shown in Fig. 3B has the configuration Dis ≡ *Z*.

The present approach delineates a unifying treatment for assigning the configuration of molecules possessing a stereogenic axis, be it chiral or achiral. The configuration assignments become fast, straightforward and simple in chiral axis cases, no matter which orientation of the 3D structure of the molecule is considered.

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