# Does CIP Nomenclature Adequately Handle Molecules with Multiple Stereoelements? A Case Study of Vancomycin and Cognates**

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The Cahn – Ingold – Prelog (CIP) system[1–3] is the prevalent set of rules and conventions governing the nomenclature of chemical compounds. Given its simple premise, the CIP system does a remarkable job of providing useful configurational assignments even for molecules with a large number of tetrahedral stereocenters. In an attempt to be generally applicable to the naming of all compounds, stereoelements such as axes and planes were invented and codified.[1] The strict identification of these elements and the conventions for assigning their configurations has been far less "user friendly" than the simple regular tetrahedral stereocenter. Not only has the existence of the whole class of "planar" elements been obviated,[4] the variegated history in the evolution of "axial" elements has resulted in a difficult-to-interpret literature of revisionist and deconstructionist "stereochemical taxonomy". Spirocycles, biaryls, cyclophanes, metallocenes, and allenes have been at times ordained "axes" or "planes" only later to be defrocked as the "theologians" grappled with questions ranging from the role of conformation and connectivity under constraints of time scales and degrees of freedom, to the subtleties of descriptor choice such as *R*/*S* versus *P*/*M*. So much attention has been given to trying to find a concrete definition of the fundamental elements, that little has been said about molecules where multiple "axial" elements need to be confronted; complex issues of directionality leading to cyclostereoisomerism is left to the chemotalmudic scholars.[5] This lack of serious theoretical underpinning is at the root of the recent confusion in the nomenclature of certain glycopeptide antibiotics.[6–9] With the increasing prevalence of compounds containing stereogenic axes, notably in complex natural products, molecular switches[10] and supramolecular constructs,[11] an open discussion of the CIP system within the context of a complex molecule is warranted. We will use vancomycin[6, 12] (**1**, Scheme 1) as a vehicle for discussing molecules with a broad spectrum of stereoelements, in particular multiple stereogenic axes. Consideration of the stereochemistry in this class of natural products motivated us to propose a concise and simple convention for describing stereogenic axes that we feel is an implicit extension of the CIP system[3] and establishes a direct distinction between axial and central elements without recourse to additional descriptors.

Vancomycin and its relatives, the glycopeptide antibiotics, constitute a large and indispensable class of clinical antibiotics; they are the drugs of last resort for the treatment of antibiotic-resistant bacteria.[6, 12] The glycopeptide antibiotics also possess a wealth of stereochemical elements exemplifying some of the most intriguing aspects of stereochemistry. Not only do they possess multiple stereogenic centers and axes, but within their structures one can identify the potential for the subtle and intricate stereochemical feature of directional cyclostereoisomerism,[5, 13–16] an often overlooked and little discussed phenomenon.

The glycopeptide antibiotics contain four principal structural domains (sugar, peptide, biaryl, and diaryl ether) and numerous stereochemical elements. The peptide domains of these molecules have between seven and nine stereogenic centers. Of the seven amino acids that make up the peptide domain of vancomycin (**1**), three possess the *S* configuration and four possess the *R* configuration (Scheme 1). Two of the amino acids present possess a second stereogenic center at their $\beta$-carbon atoms. The cyclopeptide cores of these molecules are adorned with varying numbers of sugar residues, an occurrence that significantly increases their number of stereogenic centers. If one considers only these centers, vancomycin (**1**) has $2^{17}$ (131 072) possible topographical configurations,[17] a remarkable platform for stereochemical-based molecular diversity.[18]

Vancomycin and the glycopeptide antibiotics can also exist, in principle, in two distinct types of *cis*–*trans* stereoisomers. Amide bonds can have either the s-*Z* or the s-*E* configuration. The majority of the amide bonds in the glycopeptide anti-

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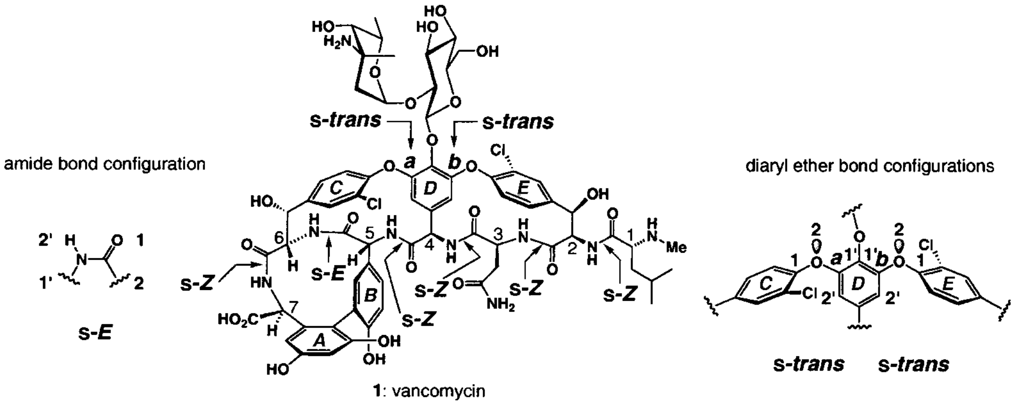
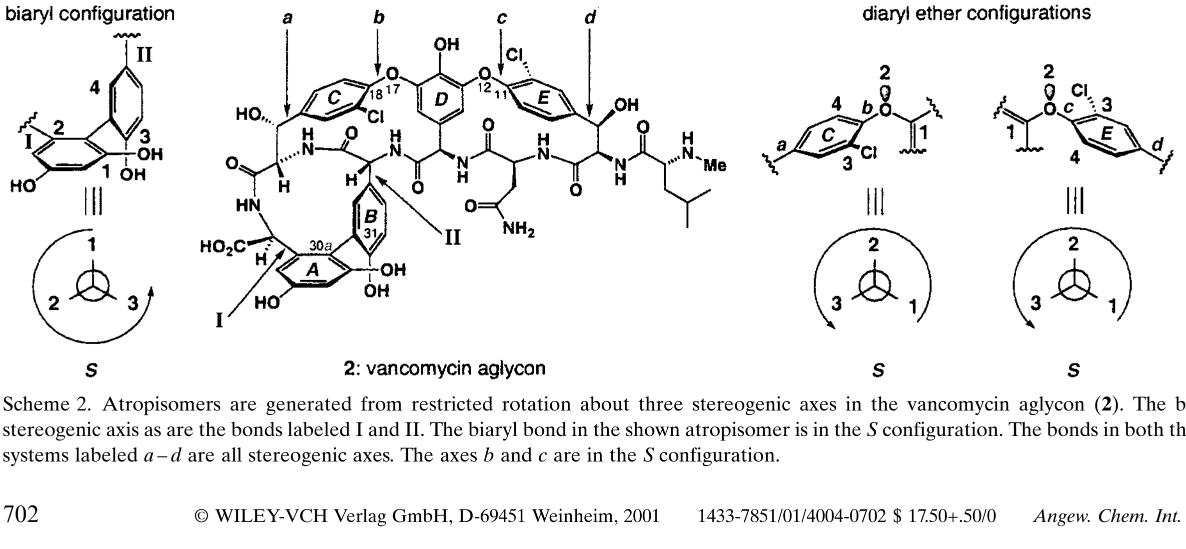


Scheme 1. There are two types of *cis–trans* isomers in the glycopeptide antibiotics as exemplified by vancomycin (**1**). The amide bonds possess both the s-*Z* and s-*E* configurations as shown. The diaryl ether ring systems have two stereochemical elements *a* and *b*. These are constrained by the ring size in the s-*trans* configuration.

biotics are in the s-*Z* configuration. However, the amide bond connecting amino acids 5 and 6 is found in the s-*E* configuration (Scheme 1).[19, 20] A second type of *cis–trans* isomer may manifest itself in the diaryl ether domain. Rigorously speaking, the bonds labeled *a* and *b* are stereochemical elements. These elements could potentially exist in either the s-*cis* or the s-*trans* configuration. The ring size, however, constrains both of these elements into the s-*trans* configuration (Scheme 1).

The biaryl and diaryl ether domains of the glycopeptide antibiotics possess no less than seven stereogenic axes, which are associated with the phenomenon of atropisomerism.[21] One stereogenic axis is located in the biaryl ring system (*AB*, Scheme 2). Restricted rotation about the biaryl bond, as a result of constrictions imposed by the macrocycle's ring size and the substitution of the aromatic rings, gives rise to two possible isomers. All biogenic glycopeptide antibiotics possess the same configuration as seen in Scheme 2,[6] although models of the biaryl ring system have been synthesized with both atropisomeric configurations.[20] Two additional axes stem from the connection of the biaryl ring to the 12-membered macrocycle. These are correlated with the biaryl axis by the tight ring constraints, but are nonetheless stereochemically unique. The diaryl ether domains of the glycopeptide antibiotics (*C-O-D* and *D-O-E*, Scheme 2) can also display atropisomerism. Thus, as a consequence of the chlorine substituents on the aromatic rings and constraints imposed by the macrocycle's ring size, the bonds labeled *a–d* (Scheme 2) are stereogenic axes. Both of the diaryl ether ring systems in the vancomycin aglycon (**2**, Scheme 2) bear the same configurations.[6] In fact, the diaryl ether ring systems in all of the naturally occurring glycopeptide antibiotics possess the same configurations. Synthetic intermediates of vancomycin with either atropisomeric configuration have, however, been reported.[7, 8, 22–25]

The identification and naming of this multitude of stereogenic axes presents a considerable nomenclature problem. The selection of an appropriate descriptor and identification of its location are not transparent operations because of historical inconsistencies in the CIP system. The classification of stereogenic units into centers, axes, and planes was introduced by Cahn, Ingold, and Prelog in their seminal treatise on stereochemistry in 1956.[1] Since that initial description, stereogenic axes and planes have stimulated a great deal of discussion.[2–4, 26] Stereogenic axes and planes were devised in the CIP system to describe systems that could not be adequately defined by stereogenic atoms alone.[2, 27] The stereochemical descriptors *R* and *S* were prescribed in 1966 for the description of all stereogenic units. The prefixes *a* and *p* were introduced to distinguish stereogenic axes and stereogenic planes, thus *aR* and *aS* would define a stereogenic axis and *pR* and *pS* would be used to define a stereogenic plane.[2] Hirschmann and Hanson simplified matters by showing that axes and planes could be resolved into a single element.[4] The essence of their argument was stipulated by Prelog and Helmchen in 1982.[3] Nonetheless, nomenclature for the stereogenic axis remained ill-applied in the community.[28]



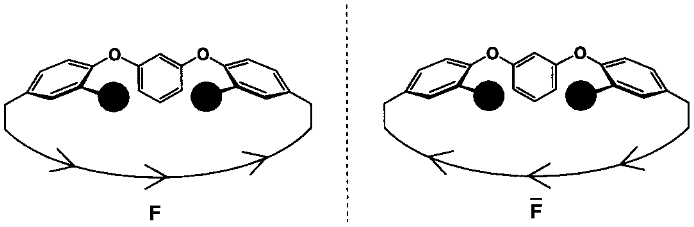
Scheme 2. Atropisomers are generated from restricted rotation about three stereogenic axes in the vancomycin aglycon (**2**). The biaryl bond is one stereogenic axis as are the bonds labeled I and II. The biaryl bond in the shown atropisomer is in the *S* configuration. The bonds in both the diaryl ether ring systems labeled *a–d* are all stereogenic axes. The axes *b* and *c* are in the *S* configuration.

Cahn, Ingold, and Prelog introduced a further distinction among stereogenic axes[2] in their discussion of configurational versus conformational stereoisomers.[29] Configurational stereogenic axes were to be defined with the *aR* and *aS* descriptors, whereas conformational stereogenic axes were to be described by the *P* and *M* descriptors. Cahn, Ingold, and Prelog, however, loosened their conviction by stating that "both methods of specifying the chirality of (conformational stereogenic axes) would be regarded as available."[2] They also implied that a distinction between configurational and conformational stereogenic elements should not be a basis for stereochemical terminology. Recently, this view has been boldly reasserted by Helmchen.[30] Surprisingly then, in the 1982 revision of the CIP system, stereogenic axes were considered conformational and as such it is prescribed that they should be defined by the helical descriptors *P* and *M*.[3] Nonetheless, many substances, such as chiral biaryls and allenes, have remained defiantly unchanged by this vicissitude.

It is of little surprise then that many investigators are left somewhat confused by the vast array of choices provided by the CIP system in naming stereogenic axes. Our recommendation is to stick to the simplest naming scheme that will identify the location and configuration of each element. For that, *R* and *S* retain primacy and a locator is used to distinguish an axis from a center and specify the location in the molecule. Thus, (30*a*:31*S*) clearly identifies the location and sets the configuration of the biaryl axis.[31–33] The use of the *P* and *M* descriptors is superfluous as a result of the ability of the *R* and *S* descriptors to adequately and unambiguously define these stereogenic elements. In fact, the use of *P* and *M*, which still require a locator, only confuses matters by introducing conformational versus configurational issues.

It is the opinion of the authors that the helical descriptors *P* and *M* be retained for systems in which *R* and *S* are inadequate in describing the stereochemical elements, such as with helical double-stranded DNA (the B form of DNA possesses the *P* configuration while the *Z* form possess the *M* configuration). This recommendation resonates well with the guiding principles Prelog and Helmchen[3] outlined in their revision of the CIP system. That is that "... previously assigned descriptors should remain unchanged as far as possible ...," and that there be "... self-restraint in introducing yet more to the already existing surfeit of new stereochemical terms ..."[3]

Lastly, the family of glycopeptide antibiotics contains an element of directionality in their peptide backbones which can give rise to cyclostereoisomerism.[5, 13–16] This type of isomerism is quite subtle and often overlooked. It was initially proposed[13] and investigated[14] by Prelog and co-workers and critically revised to be consistent with a proper symmetry analysis.[5, 15, 16] Cyclostereoisomers are directional isomers;[5, 15] that is, they rely on the directionality of the constituent chemical bonds (namely, a peptide bond could be -C(O)N(H)- or -N(H)C(O)-) to give rise to isomers. Examination of the diaryl ether macrocycles of the glycopeptide antibiotics shows that these structures exhibit many of the features necessary for cycloisomerism. The hypothetical glycopeptide antibiotic shown in Scheme 3 is used to illustrate this phenomenon. The *meso*-like configuration of the atropisomers in the diaryl ether ring systems without the directional element of the peptide bonds would be invariant under reflection. The addition of the directional element arising from the peptide bonds, however, gives rise to cyclostereoisomers. This condition is maintained even if the peptide backbone is void of any stereocenters (for example, in an all-glycine backbone).[34]



Scheme 3. This hypothetical glycopeptide antibiotic exhibits cyclostereoisomerism. The directionality of the peptide bonds differentiates one cyclostereoisomer from the other.

As masterpieces of molecular engineering by nature, the glycopeptide antibiotics contain a wealth of intriguing stereochemical elements. In this essay, we have attempted to delineate a variety of these stereochemical elements and to present a nomenclature that should facilitate communication among researchers in the field. In particular, we have proposed a convention for naming stereogenic axes. Following this convention the stereogenic axes in vancomycin (**1**) are named (11:12*S*, 17:18*S*, 30*a*:31*S*)-vancomycin (see Scheme 2 for numbering).[33] In addition, we have shown that the glycopeptide antibiotics provide an interesting starting point for the exploration of cyclostereoisomerism and its potential impact on biologically active molecules.

Recent advances in chemistry, biology, and material science are requiring that the CIP system be applied to molecules that are currently beyond its scope. The CIP system has performed admirably thus far, but it is time to revisit its treatment of stereogenic axes and bring it up to date with recent scientific advances. While, we recommend adoption of our proposed convention, our primary motivation in writing this article was to initiate discourse that will lead to a clarification of the treatment of stereogenic axes by the CIP system.

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[14] H. Gerlach, J. A. Owtschinnikow, V. Prelog, *Helv. Chim. Acta* **1964**, *47*, 2294–2302.

[15] M. D. Singh, J. Siegel, S. E. Biali, K. Mislow, *J. Am. Chem. Soc.* **1987**, *109*, 3397–3402.

[16] R. Cruse in *Stereochemie der Kohlenstoffverbindungen* (Ed.: E. L. Eliel), Verlag Chemie, Weinheim, **1966**, pp. 215–225.

[17] One should note that vancomycin (**1**) and all other glycopeptide antibiotics are composed of both proteinogenic and nonproteinogenic amino acids as well as common and uncommon sugars, thus $2^{17}$ is a true measure of the molecular diversity possible from the 17 stereogenic centers.

[18] *Combinatorial Chemistry and Molecular Diversity in Drug Discovery* (Eds.: M. Gordon, J. F. Kerwin, Jr.), Wiley, New York, **1998**.

[19] It should be noted that the *cis*–*trans* configurations of the amide bonds in the glycopeptide antibiotics have been frequently misassigned.[6, 20] The correct assignment is shown in Scheme 1.

[20] a) D. A. Evans, C. J. Dinsmore, D. A. Evard, K. M. DeVries, *J. Am. Chem. Soc.* **1993**, *115*, 6426–6427; b) D. A. Evans, C. J. Dinsmore, *Tetrahedron Lett.* **1993**, *34*, 6029–6032.

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[24] D. L. Boger, S. Miyazaki, S. H. Kim, J. H. Wu, O. Loiseleur, S. L. Castle, *J. Am. Chem. Soc.* **1999**, *121*, 3226–3227.

[25] The configuration of the diaryl ether ring systems in the glycopeptide antibiotics have been frequently misassigned.[6–8] The correct assignments are given here.

[26] K. Mislow, J. Siegel, *J. Am. Chem. Soc.* **1984**, *106*, 3319–3328.

[27] It is somewhat surprising that Cahn, Ingold, and Prelog prescribed factorization of structures into centers, axes, and planes. They stated in 1966 that a “chiral centre that is not the seat of an atom can be contemplated.”[2] Following this train of thought, it is easy to eliminate the need for both stereogenic axes and planes, certainly within all the examples described by Cahn, Ingold, and Prelog.[1, 2] All stereogenic elements can, thus, be viewed as stereogenic centers.[4, 26]

[28] It is noteworthy that even in Eliel's stereochemical compendium[9] it is difficult to find an unambiguous naming for an axial element as simple as a chiral allene.

[29] “By configuration is meant the space-arrangement of a model representing a molecular state with neglect of the distinctions between varieties of that state which differ only as after relative rotations of groups directly bonded together, about internuclear lines of their intervening, formally single bonds; and by a conformational molecular state … is meant a space-arrangement which signalises such a distinction, and identifies such a variety-state.”[2]

[30] “Stereoselective Synthesis”: G. Helmchen, *Methoden Org. Chem. (Houben-Weyl) 4th ed. 1952-*, Vol. E 21/a, **1983**, pp. 1–63.

[31] To correctly determine the absolute configuration of a stereogenic axis it is necessary to rank the substituents using the CIP sequence rules.[32] First the atoms of the axis are ranked. The groups on the higher ranking side of the axis are given the ranks of 1 and 2, while the groups on the other side of the axis are then given the ranks of 3 and 4. If the atoms of the axis are of the same rank the overall highest priority group is ranked 1. Its geminal substituent is ranked 2. The groups on the other side of the axis are then ranked 3 and 4. These four groups, with the stereogenic axis as the center, are envisioned to form an elongated tetrahedron and can now be assigned as *R* or *S*, as is shown in Scheme 2.

[32] P. Mata, A. M. Lobo, C. Marshall, A. P. Johnson, *Tetrahedron: Asymmetry* **1993**, *4*, 657–668.

[33] The complete numbering system for vancomycin (**1**) can be found in ref. [6]. In designating the stereogenic axes, each axis is defined by the atoms at the two ends of the structural unit defining the axis; the numbers defining the atoms are separated by a colon; and the stereochemical descriptor *R* or *S* follows.

[34] While it is true that the two isomeric forms shown in Scheme 3 can be distinguished through appropriate numbering and assignment of stereochemical descriptors, this in no way precludes them from being cyclostereoisomers. In fact, any two cyclostereoisomers can be distinguished by appropriate numbering and assignment of stereochemical descriptors. Thus, at the simplest level the two isomers of *cis*-3,5-dimethylcaprolactam can be considered cyclostereoisomers.