The Axial Chirality Problem

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Abstract

Axial chirality results, not from a tetrahedral chiral center, but from a chiral axis. This form of chirality most frequently occurs in biaryls and allenes. The importance of axial chirality to organic chemistry was recognized in 2001, when Ryoji Noyori was co-awarded the Nobel Prize in Chemistry, in part for his work with highly selective catalysts derived from the axially-chiral BINAP ligand.

Keywords

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> *… To discover high-performance asymmetric catalysts, developing an excellent chiral ligand is crucial. Attracted by its molecular beauty [Chemica Scripta **1985**, 25, 83], we initiated the synthesis of BINAP (2,2'-bis(diphenylphosphino)-1,1'-binaphthyl) [J. Am. Chem. Soc. **1980**, 102, 1932] in 1974 at Nagoya with the help of H. Takaya, my respected long-term collaborator. BINAP was a new fully aromatic, axially dissymmetric C_2 chiral diphosphine that would exert strong steric and electronic influences on transition metal complexes. Its properties could be fine-tuned by substitutions on the aromatic rings. …*
>
> *Ryoji Noyori*

Axial chirality results, not from a tetrahedral chiral center, but from a chiral axis. This form of chirality most frequently occurs in biaryls and allenes. The importance of axial chirality to organic chemistry was recognized in 2001, when Ryoji Noyori was co-awarded the Nobel Prize in Chemistry, in part for his work with highly selective catalysts derived from the axially-chiral BINAP ligand.

Since the early 1980s, axial chirality has played an increasingly significant role in organic chemistry. Much of this research has focused on catalysis; consider two recent reviews, one on modified BINOLs, and one on modified BINAPs. But axial chirality isn't just restricted to catalysts; it's also a feature of numerous natural products.

Once merely a curiosity, axial chirality now plays a role in virtually every subdiscipline of organic chemistry. At the same time, this important concept is alien to most molecular languages and toolkits. Consider, for example, that the specifications of all four of the most popular molecular languages (SMILES, InChI, Molfile, and CML) are silent on the representation of axial chirality. In other words, axial chirality is undefined in these languages. Although support for axial chirality could be "hacked" into these languages, this would require nonstandard conventions that would be unintelligible to any third party.

This situation poses a significant problem for those needing to discriminate axially chiral stereoisomers in molecular databases or other applications. For example, PubChem's entry on the axially-chiral drug gossypol is devoid of stereochemical information. If PubChem used an internal representation of molecular structure capable of encoding axial chirality, coupled with a suitable molecular language to be used by depositors, separate entries for each gossypol enantiomer would be feasible. After all, PubChem users have come to expect the same of other chiral drugs containing stereogenic atoms.

To address this problem, a new XML-based molecular language called FlexMol has been developed. Recent articles have highlighted FlexMol's use with the multi-atom bonding found in metallocenes, and E/Z alkene geometrical isomerism. Based on a specification by Andreas Dietz, Flexmol can represent all forms of axial chirality using a single flexible formalism..

Chemical informatics is beginning to embrace the concepts of Open Source and Open Data already in widespread use elsewhere. This shift will bring into sharp focus the need for robust and open methods for accurately encoding molecular structure. Existing technologies have not kept up with the chemists themselves, as the axial chirality problem demonstrates. Future articles in this

series will show how FlexMol can offer a solution to this and other important molecular representation problems.

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