Pergamon

Tetrahedron: *Asymmetry* 9 (1998) 539–541

TETRAHEDRON:
ASYMMETRY

A potential ambiguity in the stereochemical description of complex paracyclophanes

P. J. Pye * and K. Rossen*
Merck Research Laboratories, Department of Process Research, Rahway, NJ 07090, USA

Received 12 December 1997; accepted 6 January 1998

Abstract

Potential ambiguities in the assignment of the absolute stereochemistry of complex paracyclophanes are avoided by applying the formal description developed by Prelog and Helmchen. © 1998 Elsevier Science Ltd. All rights reserved.

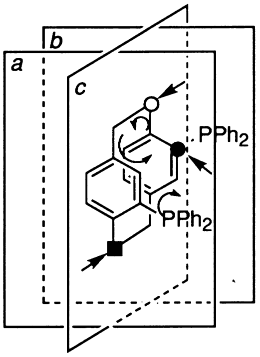
The description of stereoisomers in organic chemistry follows a set of rules proposed by Cahn, Ingold and Prelog in a series of seminal articles.[1] These rules, especially with the formalization provided by Prelog and Helmchen in 1982,[2] support a logical and comprehensive system of stereochemical descriptors. Nevertheless, the synthesis of stereochemically more complex systems gives rise to apparent ambiguities that deserve comment,[3] especially when such a class of compounds is gaining in importance.

One such system is the pseudo-ortho disubstituted paracyclophane [2.2]PHANEPHOS (**1**), which we have successfully used in Rh, Pd and Ru catalyzed reactions.[4] Following the rules set forward by Cahn et al.,[1] the naming starts by choosing a chiral plane containing a maximum number of atoms. This plane must also arise by desymmetrization of a plane of symmetry. Following the examples given in by Cahn et al.[1] the choice would fall on the planes *a* or *b*, which are equivalent due to the C_2 symmetry of the molecule. Neither of these planes are planes of symmetry in the unsubstituted D_{2h}-symmetric [2.2]paracyclophane and the desymmetrization is instead viewed as bringing plane *a* alongside plane *b* or vice versa.

---

* Fax: 732 594 1499; e-mail: philip_pye@merck.com or kai_rossen@merck.com.

PII: S0957-4166(98)00041-X



1, [2.2]PHANEPHOS

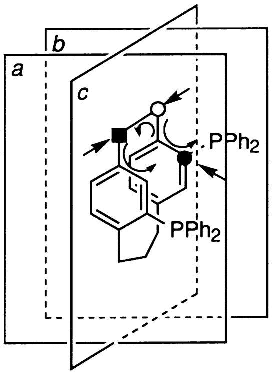
R using plane *a* or plane *b*

S using plane *c*

○ Pilot atom for plane *a*

■ Pilot atom for plane *b*

● Pilot atom for plane *c*



2

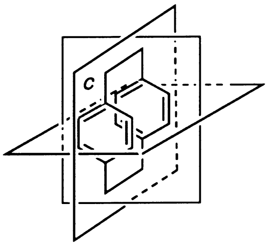
R using plane *a* but S using plane *b*

S using plane *c*

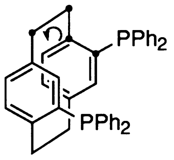
After the selection of the plane, an atom of highest priority outside of the plane, but directly connected to the plane, is used as the pilot atom. Looking down on the plane from the pilot atom and following the sequence of atoms of highest priority clockwise or counterclockwise leads to the chiral descriptor. In structure **1**, the assignment is *R* using either plane *a* or *b*.

However, in a molecule like the disubstituted [2.3]paracyclophane **2** (no longer C_2 symmetric), the choice of plane determines the stereochemical descriptor! Assuming either plane *a* or *b* as the desymmetrizing plane, then the highest priority atom outside of the planes are as marked. Looking down on the respective plane results in ambiguous assignments, that could only be determined if additional rules were created.

The issue is resolved as soon as one considers the source of the chirality: rather than desymmetrizing plane *a* or *b* by bringing in the second plane, we prefer to look at the symmetry of the unsubstituted parent, in the case of **1** the D_{2h}-symmetric [2.2]paracyclophane **3**. It contains three planes of symmetry, but of these only plane *c* has atoms lying in it. Desymmetrization of this plane by placement of diphenylphosphino groups[5] in the 4 and 12 positions as in **1** results in a chiral molecule. The choice of this plane is unambiguous and logical for non-C_2 symmetrical molecules as the priority rules will enable an assignment of a pilot atom.[6]



3, D_{2h} - Symmetric



M or S
[2.2]PHANEPHOS

Use of this plane leads to the *S* configuration for **1** and **2**. Additionally, the choice of this plane does not require drastic assumptions about the geometry of the molecule. An X-ray structure of the phosphineoxide analogue of **1** reveals that the aromatic rings are strongly bent and additionally tilted to accomodate the strain of the diphenylphosphine oxide. Thus, the use of plane *a* or *b* requires idealizations of the real structure.

Most importantly, the choice of the dissecting plane *c* is equivalent to the description offered by Prelog and Helmchen.[2] In that description the helicity of the path going from the aromatic methine connected to the P of the diphenylphosphino group to the adjacent methylene bridge is examined. In the above example a left handed helix results, thus the description *M* or *S*. This description obviously does not depend on assumptions about the geometry of the molecule and unambiguously assigns the stereochemical descriptor also in non-C_2 symmetric cases.

In summary, care should be taken in the stereochemical description of complex paracyclophanes. Use of the definitions offered by Prelog and Helmchen avoids ambiguities and does not require the use of drastic simplifications of the molecular geometry.

Acknowledgements

We would like to acknowledge the helpful discussion with Prof. Helmchen.

References

1. (a) Cahn, R. S.; Ingold, C. K.; Prelog, V. *Experimentia* **1956**, *12*, 81. (b) Cahn, R. S.; Ingold, C. K.; Prelog, V. *Angew. Chem. Int. Ed. Engl*. **1966**, *5*, 385. (c) Eliel, E. L.; Wilen, S. H. *Stereochemistry of Organic Compounds*, Wiley, New York, 1994.
2. (a) Prelog, V.; Helmchen, G. *Angew. Chem. Int. Ed. Engl*. **1982**, *21*, 567. (b) Helmchen, G. In *Methods of Organic Synthesis (Houben–Weyl)*, *Stereoselective Synthesis* (Ed. G. Helmchen, R. W. Hoffmann, J. Mulzer, E. Schaumann), Thieme Verlag, Stuttgart, 1996, Chapter 1.
3. Mata, P.; Lobo, A. M.; Marshall, C.; Johnson, A. P. *Tetrahedron: Asymmetry* **1993**, *4*, 657.
4. (a) Pye, P. J.; Rossen, K.; Reamer, R. A.; Tsou, N. N.; Volante, R. P.; Reider, P. J. *J. Am. Chem. Soc*. **1997**, *119*, 6207. (b) Rossen, K.; Pye, P. J.; Maliakal, A.; Volante, R. P. *J. Org. Chem*. **1997**, *62*, 6462.
5. This desymmetrization is obviously also obtained for groups other than the PPh_2 group.
6. The choice of plane *c* in the previously described and named mono-substituted [2.2]paracyclophanes[1] does *not* lead to a change in stereochemical descriptor. Although compound **1** can be unambiguously assigned as *S*-, it may be helpful to designate the pilot atom thus arriving at the chiral descriptor 4*S*-. The Cram convention is the more commonly used numbering system.