

Simplified Nomenclature and Projection Diagrams of Chiral Cubane Analogs

John L. Krstenansky*

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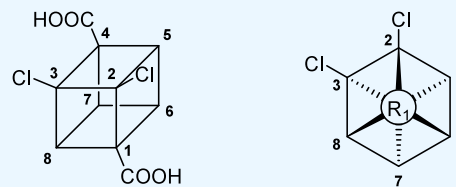
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ABSTRACT: A simplified nomenclature for chiral cubane analogs is proposed where analogs with a clockwise systematic continuous numbering of the cubane core are designated as (C)-, and analogs with an anticlockwise continuous numbering of the cubane core are designated as (A)-. This method is accurate, allows for the rapid conversion of the chemical name to a structure, and it eliminates the need to designate the stereochemistry of each of the 8 carbons of cubane.



(1R,2S,3S,4R,5S,6S,7S,8S)-2,3-dichlorocubane-1,4-dicarboxylic acid
(C)-2,3-dichlorocubane-1,4-dicarboxylic acid

INTRODUCTION

The polycyclic alkane, pentacyclo[4.2.0.0.^{2,5}0.^{3,8}0^{4,7}]octane (cubane), has advanced from a theoretical synthetic challenge that was solved in 1964 to a component of a wide variety of useful molecules.^{1,2} The synthesis of cubane containing intermediates and substituted analogs has advanced significantly in recent years and they are seeing application in medicinal chemistry bioisosteres and as functional elements themselves.^{3–7} While simple analogs of cubane present little challenge in naming or quickly interpreting the structure from the name, polysubstituted chiral analogs can present a challenge in naming accurately or conversely interpreting the complex IUPAC name.

There have been a couple of reports discussing approaches to understanding the symmetry aspects of cubanes;^{8,9} however, there is still a need for a simple and more intuitive way to analyze and compare chiral cubane substitution patterns. The field of carbohydrates employ Haworth projections and Fisher diagrams,¹⁰ organic stereochemistry uses Newman projections,¹¹ fullerenes can be visualized with Schlegel diagrams,¹² and peptide chemistry makes use of helical net diagrams¹³ and helical wheels.¹⁴ Each of these representations simplifies the relationship between substitutions and makes comparison of related analogs relatively simple. Herein we propose a simplified nomenclature for chiral cubanes and a perspective on depicting and thinking about chiral, polysubstituted cubane-containing analogs.

RESULTS AND DISCUSSION

In applying the IUPAC nomenclature to cubane (pentacyclo[4.2.0.0.^{2,5}0.^{3,8}0^{4,7}]octane) there are only two ways of numbering the molecule by moving from atom to atom continuously for all 8 carbon atoms. If the perspective is taken of looking along the axis of position 1 to position 4, in the opposite corner of the

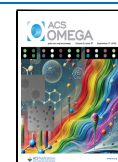
molecule, then going from carbon 3 to carbon 8 can be seen as appearing either in the clockwise or anticlockwise (aka counterclockwise) direction (Figure 1a and b, respectively). The numbering shown in the IUPAC Blue Book P-23.7 Table 2.6 corresponds to Figure 1b.¹⁵ Some cubane analogs in the literature do not use standard numbering, possibly in an effort to provide the lowest position number to a substituent. This can result in a discontinuous and incorrect numbering of the cyclooctane carbons. At the time of this writing, one vendor of cubane precursors labeled their 1,4-substituted compounds, which are substituted on opposite corners of the cubic molecule, as 1,8- indicating the use of a nonstandard numbering system. Using nonuniform numbering can obscure the similarities and differences of analogs particularly when comparing them to other reports in the literature. As a caution, it should be noted that other continuous numberings of cubane are possible; however, close inspection shows that using such numbering does not result in the correct connectivity indicated by the accepted IUPAC name (Figure 1c,d). Therefore, consistency demands that continuously numbered approaches to ring numbering be utilized, as depicted in Figure 1a,b. While the anticlockwise numbering of Figure 1b corresponds to the figure shown in the official IUPAC document, the clockwise numbering, Figure 1a, is also consistent with the official chemical name. The proper naming of substituted cubanes uses either clockwise or anticlockwise numbering, whichever results in the lowest position numbering of the substituents. A

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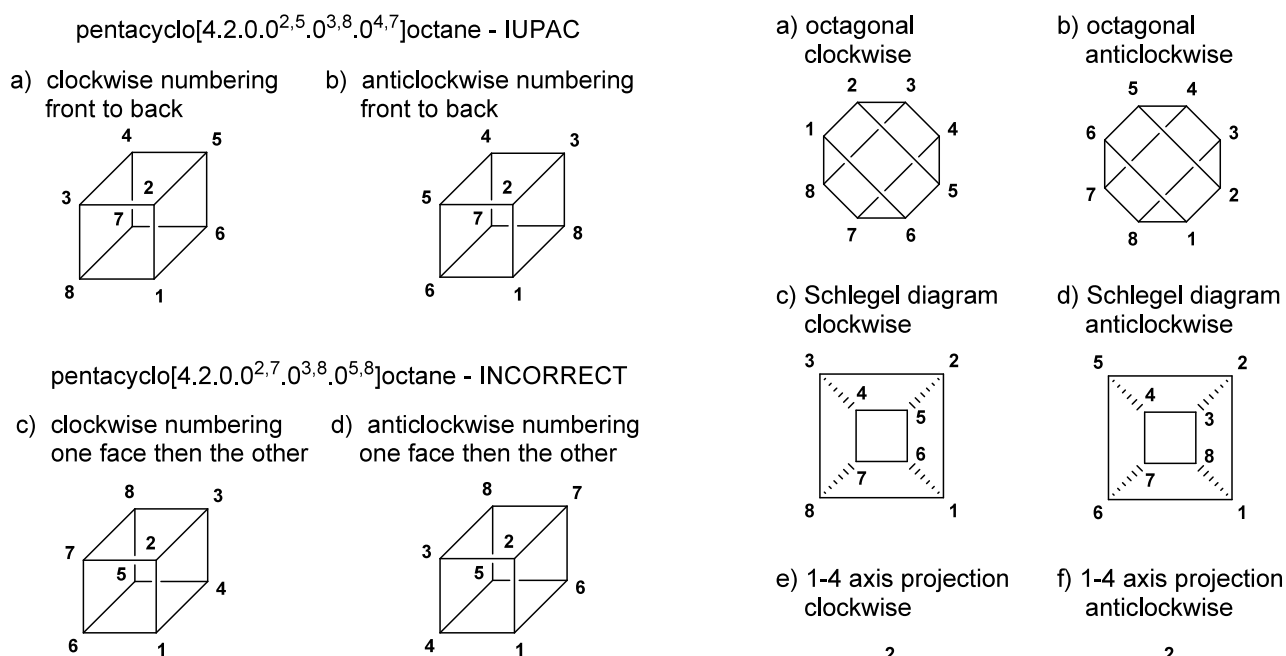


Figure 1. Cubane numbering possibilities: correct (a, b) and incorrect (c, d).

recent literature example of this appears in the numbering of the substituents for the enantiomers (1*S*,2*R*,3*R*,4*S*,5*R*,6*R*,7*R*,8*R*)-2,3-dichlorocubane-1,4-dicarboxylic acid ((-)-**2a**) and (1*R*,2*S*,3*S*,4*R*,5*S*,6*S*,7*S*,8*S*)-2,3-dichlorocubane-1,4-dicarboxylic acid ((+)-**2a**) (Figure 4).¹⁶

Figure 2 depicts a variety of alternative perspectives or projections that can be used to visualize cubane and its substituted analogs. The octagonal representations (Figure 2a,b) most clearly depict the logic and connectivity described by the IUPAC name, pentacyclo[4.2.0.0^{2,5}.0^{3,8}.0^{4,7}]octane. The Schlegel diagrams (Figure 2c,d) display the pentacyclic nature of the molecule. Finally, the projection obtained by observing the molecule down the the position 1 to position 4 axis provides a perspective that more clearly indicates the relationship of the stereochemistry of polysubstituted cubanes relative to the 1, 2, 4, and 7 planes (Figure 2e,f). Note: In each case the clockwise and anticlockwise numberings are presented.

ACHIRAL CUBANES

Using the 1–4 axis projection, where position 1 represents a fixed position of interest, the stereochemical aspects of mono-, di-, and trisubstitution at positions 2, 6, 8 or 3, 5, 7 can be described. In a monosubstituted cubane, the substitution is a position 1, by definition. In any disubstituted cubane, there are only three possibilities, 1,2-, 1,3-, and 1,4-substitution and all are achiral. Achiral compounds can be numbered with either of the two correct numbering directions due to the symmetry that makes them achiral. With three or more nonidentical substitutions, chiral analogs result.

CHIRAL CUBANES: PSEUDOTETRAHEDRON

The symmetry inherent in the cubane structure provides some interesting stereochemical possibilities. Considering positions 1, 3, 5, and 7 as a pseudotetrahedron, such polysubstituted analogs can be analyzed and designated as *S*- or *R*-configuration overall.¹⁷ Standard CIP nomenclature can be used to describe these analogs, but they can also be simply described as requiring

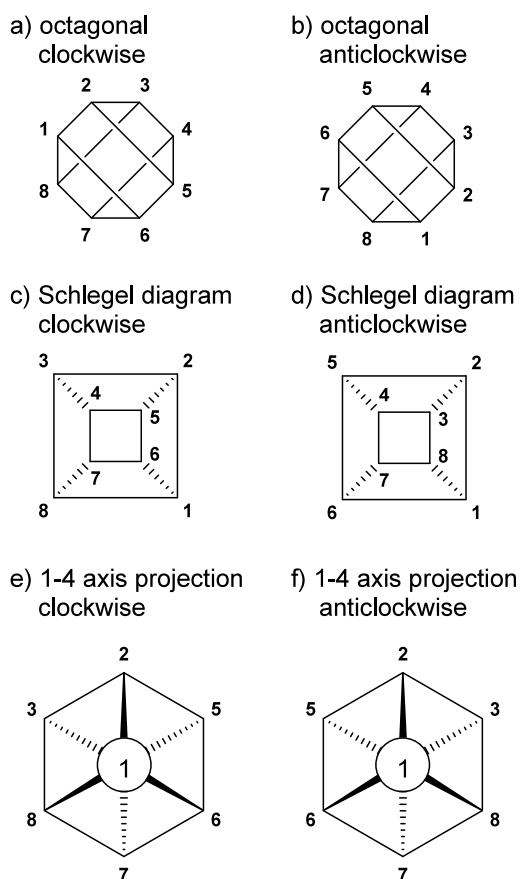


Figure 2. Alternative cubane perspectives and projections with IUPAC numbering. In the 1–4 axis projection, carbon 4 is directly behind and obscured by carbon at position 1. Carbons 1, 2, 4, and 7 are in the same plane in either numbering direction.

clockwise or anticlockwise numbering. It is proposed that the clockwise numbering of cubanes be designated as (C)- and the anticlockwise numbering of cubanes be designated as (A)- (Figure 3). This follows the precedent proposed for the naming of chiral fullerenes.¹⁸ Since the designation refers to the nature of the numbering required for the cubane and not the stereo-configuration of any particular position, it avoids confusion. Note that in the two examples shown, the position numbers in alphabetical preference (bromo > iodo) do not follow the CIP priorities (I > Br). Therefore, stereochemistry of an analog cannot be correlated with the “handedness” of the numbering required. Correct nomenclature for these *S*-pseudotetrahedron analogs shown in Figure 3 requires either the clockwise or anticlockwise cubane numbering depending on the naming. This shorthand nomenclature contains information not readily apparent from the IUPAC name. Reconstructing the molecule from the IUPAC name would be a time-consuming process without an automated chemical drawing program. The C/A shorthand permits an accurate and rapid manual or potentially automated reconstruction of the molecule from the name.

OTHER CHIRAL CUBANES

Chiral cubanes that are not pseudotetrahedra cannot be readily designated *R* or *S* based on their overall configuration. Figure 4 depicts other substitution patterns of chiral polysubstituted cubanes. Here the utility of the shorthand notation can be seen in that it is unambiguous and allows for the rapid interpretation

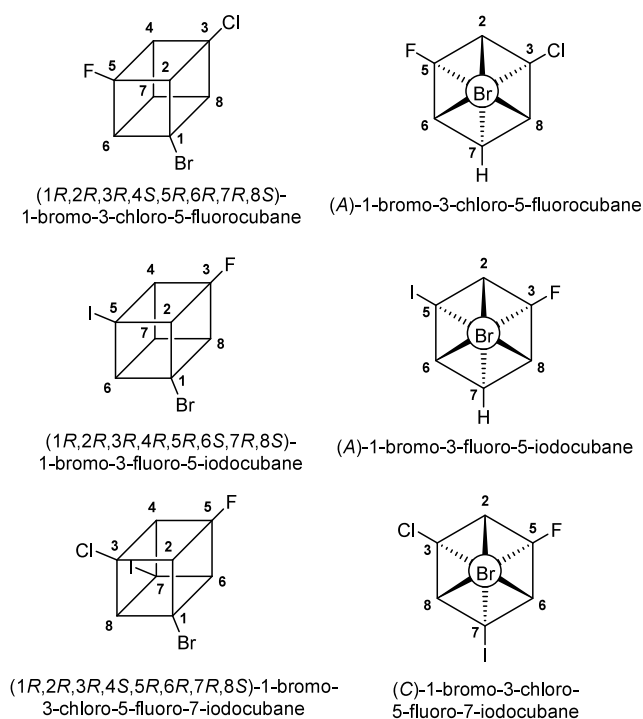


Figure 3. (Left) IUPAC stereochemical nomenclature for some example *S*-pseudotetrahedral polyhalocubanes¹⁷ and (Right) 1–4 axis projections of those compounds and the proposed stereochemical shorthand for such molecules.

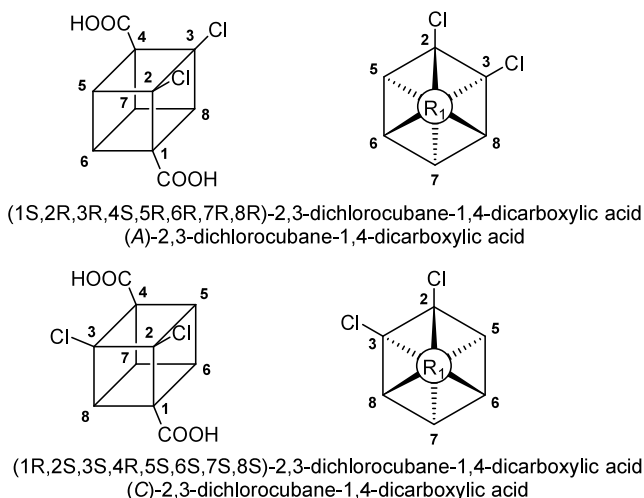


Figure 4. Chiral 2,3-dichlorocubane-1,4-dicarboxylic acids¹⁶ with the IUPAC and proposed shorthand nomenclature depicted by their standard projections and the 1–4 axial projections.

of its three-dimensional structure. The IUPAC name does not provide information about the numbering direction that will result in the correct configuration. The shorthand notation allows for the immediate transference of the substituent information in a stereochemically correct manner to accurately depict the molecule.

The 1–4 axial projection functions much like a helical wheel diagram of a peptide, allowing for the facile observation of facial characteristics of the molecule that might be important for a ligand as it binds to a receptor.

This clockwise/anticlockwise nomenclature originally proposed for fullerenes¹⁸ is applicable to classes of molecules that

have two numbering schemes that are mirror images of one another, such as the Platonic hydrocarbons tetrahedrane, cubane, and dodecahedrane. Additionally, this can apply to some related analogs such as buta-1,3-diyne expanded cubanes.¹⁹ Tetrahedrane is already rather simple, and chiral forms can readily be described as overall *R* or *S*, as mentioned for the pseudotetrahedral cubanes.

SUMMARY

An expansion in the interest in and application of substituted cubanes has resulted in the development of methods allowing for selective substitution of all positions in cubane, and the complexity of the compounds appearing in the literature has correspondingly increased. Polysubstitution can result in chiral analogs requiring stereochemical designation of the 8 stereocenters of a chiral cubane molecule. There are two ways of numbering a cubane, clockwise and anticlockwise, that provide a pair of enantiomers for any substitution pattern. The IUPAC name does not readily indicate which of the two ring numbers will result in the correct stereochemistry. Therefore, a nomenclature that simply indicates a clockwise, (*C*)-, or anticlockwise, (*A*)-, can accurately allow for the rapid reconstruction of the correct stereoisomer. This nomenclature was chosen because it is clear and intended to not be confused with *R*, *S*, *d*, *l*, + or −, since there is no correlation with the type of numbering needed for a stereoisomer and any physical stereochemical designation. Only chiral cubanes would utilize this designation, since the symmetry of an achiral cubane allows for numbering in either a clockwise or anticlockwise direction.

AUTHOR INFORMATION

Corresponding Author

John L. Krstenansky – Keck Graduate Institute, School of Pharmacy, Claremont, California 91711, United States;
 orcid.org/0000-0003-3773-2523;
 Email: john_krstenansky@kgi.edu

Complete contact information is available at:
<https://pubs.acs.org/10.1021/acsomega.4c04267>

Notes

The author declares no competing financial interest.

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