What Knot To Do When Synthesizing Medications: The Link Between Topology and Chirality of Organic Molecules

University of Pennsylvania Department of Mathematics Directed Reading Program

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"And isn't it just so pretty to think / All along there was some / Invisible string / Tying you to me?" - Invisible String, Taylor Swift

Some VERY Special Thank Yous To

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My Amazing Mentor

☸ Yi Wang

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My Wonderful Professors

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- ♗ Dennis Deturck

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- ☯ Maximilien Péroux

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- ☋ Brett Frankel
- ☋ Irfan Alam

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⚭ Dennis Deturck

⚭ Andrew Cooper

⚭ Maximilien Péroux

⚭ Brett Frankel

⚭ Irfan Alam

⚭ Amos Smith (Chemistry)
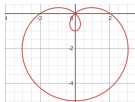
Is This a Knot?

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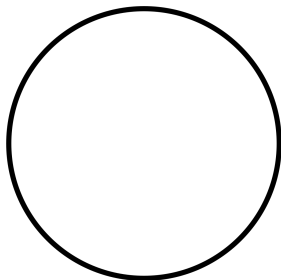
Is This a Knot?

This is (k)NOT a knot.
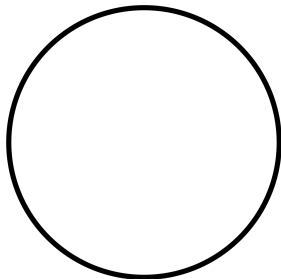
This IS a knot.

What **IS** a Knot?

Definition (Knot)

A *knot* is a knotted loop of string, an embedding of a circle in three dimensional space.

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- ⊗ A circle is a trivial knot, the "unknot."
- ⊗ A composite knot is the composition of 2 knots, neither of which are the trivial knot.
- ⊗ A prime knot cannot be constructed from the composition of any two nontrivial knots.

Prime and Composite Knots

Prime Knots:
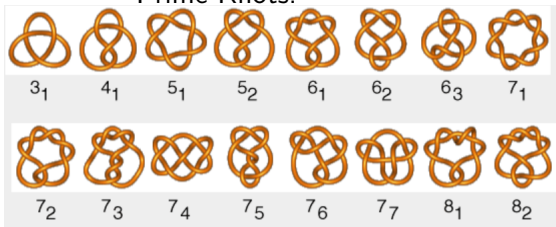
Composite Knots:
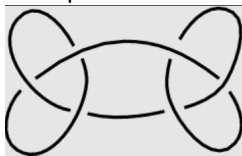
An Iconic Knot

Reidemeister Moves

Reidemeister Moves

$$\begin{bmatrix} a & b & c \\ d & e & f \\ g & h & i \end{bmatrix} \rightarrow \begin{bmatrix} 1 & 0 & 0 \\ 0 & 1 & 0 \\ 0 & 0 & 1 \end{bmatrix}$$
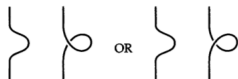
Figure 1.22   Type I Reidemeister move.
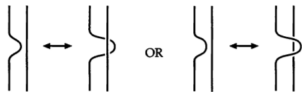
Figure 1.23   Type II Reidemeister move.
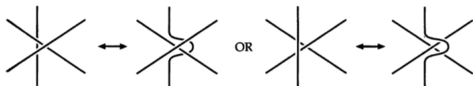
Figure 1.24   Type III Reidemeister move.

Reidemeister Moves
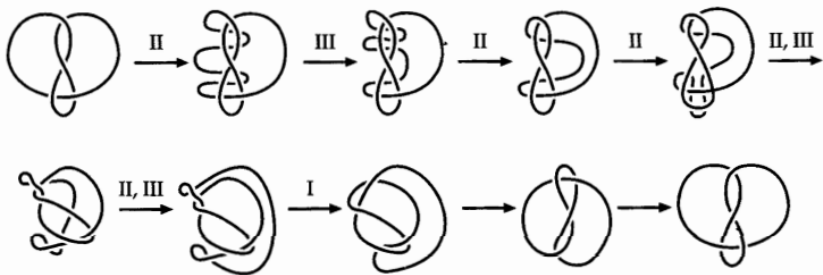
Figure 1.27 The figure-eight knot is equivalent to its mirror image.

Ambient and Planar Isotopy

Definition (Ambient Isotopy)

Ambient Isotopy is a rearranging of the string; movement of the string through three-dimensional space without letting it pass through itself.

⊛ Reidemeister moves are ambient isotopy!

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Definition (Planar Isotopy)

Planar Isotopy is a deformation that deforms the projection plane as if it were made of rubber with the projection drawn upon it.

♾ Reidemeister moves and planar isotopy suffice to get from any one projection of a knot to any other projection of that knot.

What is Chirality?

Definition (Chirality)

A *chiral knot* is a knot that cannot be superimposed on its mirror image.

An *achiral knot* is a knot that can be superimposed on, and is equivalent to, its mirror image.
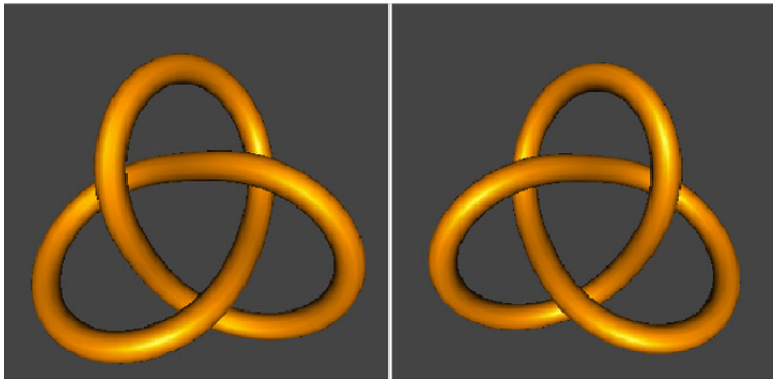
Topological Chirality Implies Chemical Chirality!

France, 1988 Catenane synthesis by Christina Dietrich-Buchecker and Jean-Pierre Sauvage
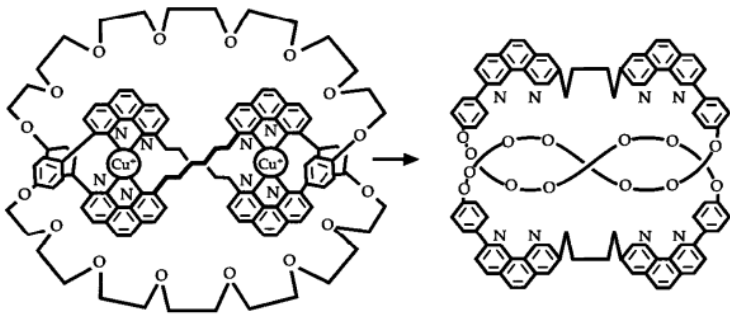
Figure 7.32 The first synthesis of a knotted molecule.

How Do Chemists Assign Stereochemistry?

The Cahn-Ingold-Prelog System
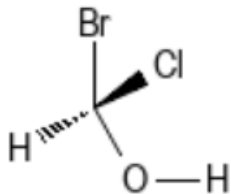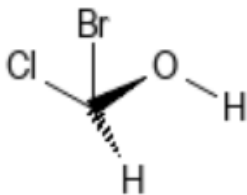
How Do Chemists Assign Stereochemistry?

Our Best Friend the Periodic Table

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The Cahn-Ingold-Prelog System
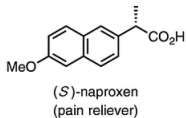

S-Bromochloromethanol
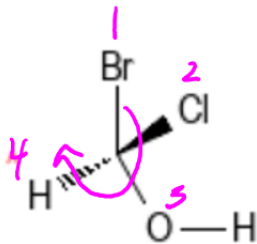
R-Bromochloromethanol
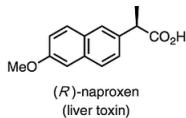
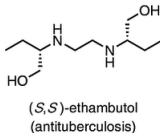# Interesting Enantiomeric Differences
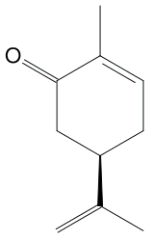
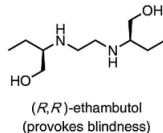(R)-carvone
(spearmint)
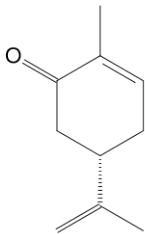
(S)-carvone
(caraway)

(S)-naproxen
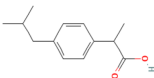(pain reliever)

(R)-naproxen
(liver toxin)

(S,S)-ethambutol
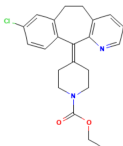(antituberculosis)

(R,R)-ethambutol
(provokes blindness)
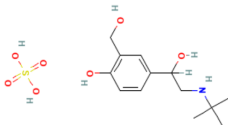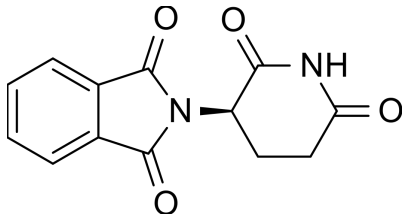
Chiral Medications

Ibuprofen (Advil, Motrin)

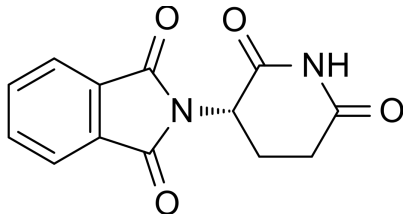Loratadine (Claritin)

Albuterol Sulfate (Asthma Inhalers)

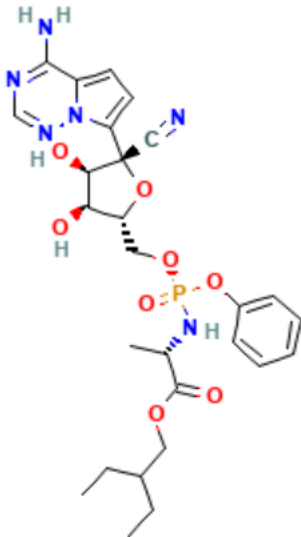# Case Study of the 1950s-1960s Thalidomide Scandal

(R)-thalidomide

(S)-thalidomide

Sedative or teratogen?

Modern Medicine

Remdesivir: the first US Food and Drug Administration Approved treatment for COVID-19

References and Citations

American Chemical Society
Khan Academy
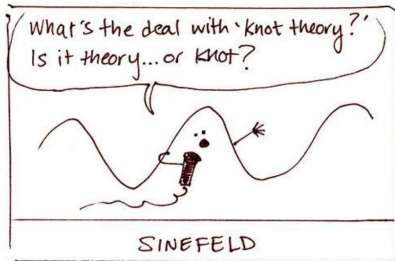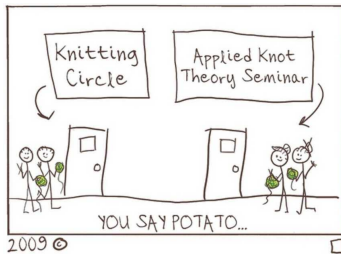The Knot Book by Colin Adams
Professor Amos Smith
PubChem
PubMed
When Topology Meets Chemistry A Topological Look at Molecular
Chirality by Erica Flapan

Knot, Knot, Who's There?