

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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December 2021

"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 You's To

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My Amazing Mentor

 Yi Wang

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My Wonderful Professors

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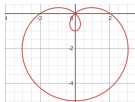
⊗ Andrew Cooper

⊗ Maximilien Péroux

⊗ Brett Frankel

⊗ Irfan Alam

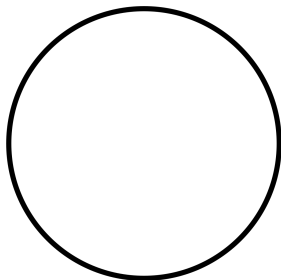
⊗ Amos Smith (Chemistry)



Is This a Knot?



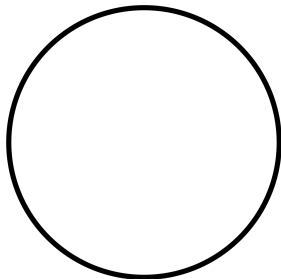
Is This a Knot?



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 composite knot is the composition of 2 knots, neither of which are the trivial knot.

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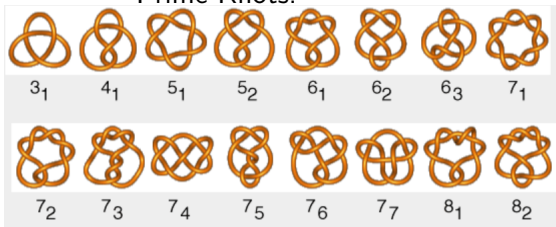
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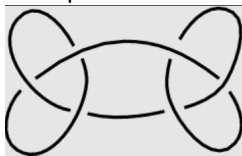
- ⊗ A projection of a knot is a deformation of the original knot.
All deformations of a knot are equivalent to the original knot.
- ⊗ A circle is a trivial knot, the "unknot."
- ⊗ A composite knot is the composition of 2 knots, neither of which are the trivial knot.
- ⊗ A prime knot cannot be constructed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

Prime and Composite Knots

Prime Knots:



Composite Knots:



An Iconic Knot



Reidemeister Moves



Reidemeister Moves

$$\begin{bmatrix} a & b & c \\ d & e & f \\ g & h & i \end{bmatrix} \rightarrow \begin{bmatrix} 1 & 0 & 0 \\ 0 & 1 & 0 \\ 0 & 0 & 1 \end{bmatrix}$$

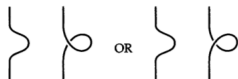


Figure 1.22 Type I Reidemeister move.

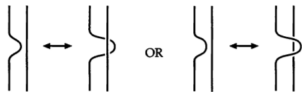


Figure 1.23 Type II Reidemeister move.

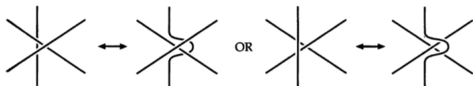


Figure 1.24 Type III Reidemeister move.

Reidemeister Moves

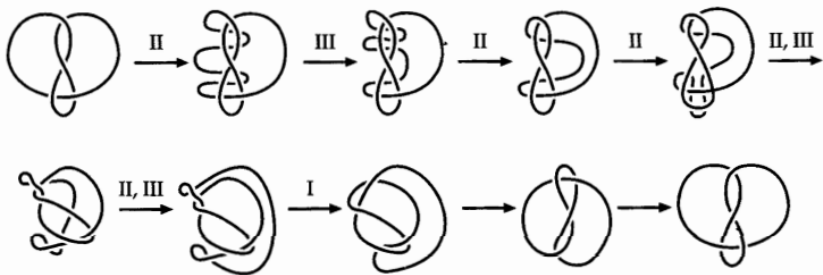


Figure 1.27 The figure-eight knot is equivalent to its mirror image.

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

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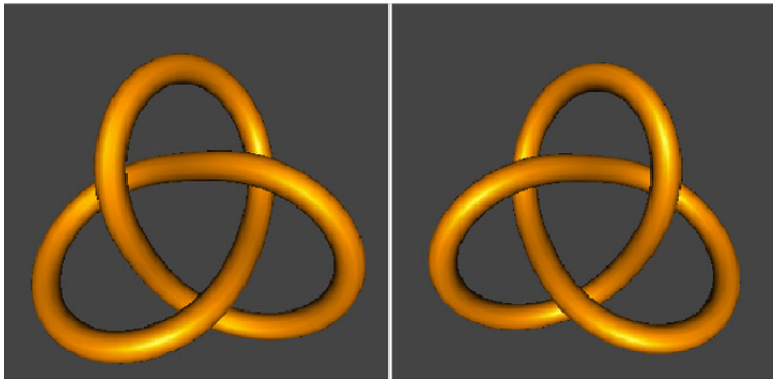
 Reidemeister moves and planar isotopy suffice to get from any one projection of a knot to any other projection of that knot.

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

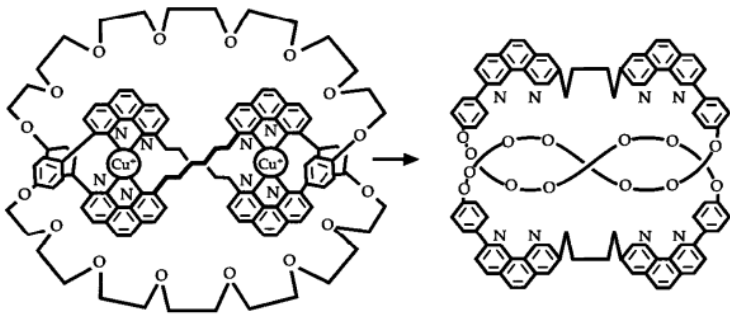
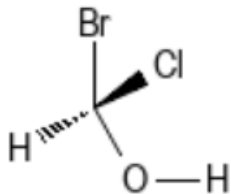
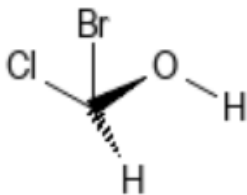


Figure 7.32 The first synthesis of a knotted molecule.

How Do Chemists Assign Stereochemistry?

The Cahn-Ingold-Prelog System



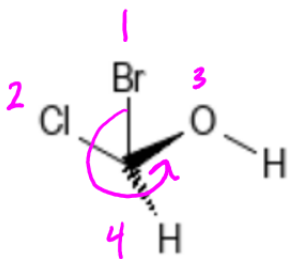
How Do Chemists Assign Stereochemistry?

Our Best Friend the Periodic Table

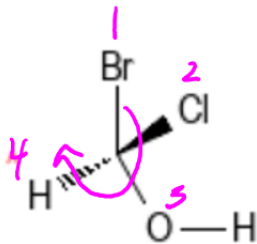
	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18		
1	1 H Hydrogen 1.008	Atomic Symbol Name Weight																	2 He Helium 4.0026	
2	3 Li Lithium 6.94	4 Be Beryllium 9.0122	<div style="display: flex; justify-content: space-around;"> <div style="border: 1px solid black; padding: 5px;">C Solid</div> <div style="border: 1px solid black; padding: 5px;">Hg Liquid</div> <div style="border: 1px solid black; padding: 5px;">H Gas</div> <div style="border: 1px solid black; padding: 5px;">Rf Unknown</div> </div>																	10 Ne Neon 20.180
3	11 Na Sodium 22.990	12 Mg Magnesium 24.305	<div style="display: flex; justify-content: space-around;"> <div style="border: 1px solid black; padding: 5px;">Alkali metals</div> <div style="border: 1px solid black; padding: 5px;">Alkaline earth metals</div> <div style="border: 1px solid black; padding: 5px;">Lanthanoids</div> <div style="border: 1px solid black; padding: 5px;">Actinoids</div> <div style="border: 1px solid black; padding: 5px;">Transition metals</div> <div style="border: 1px solid black; padding: 5px;">Post-transition metals</div> <div style="border: 1px solid black; padding: 5px;">Metalloids</div> <div style="border: 1px solid black; padding: 5px;">Nonmetals</div> <div style="border: 1px solid black; padding: 5px;">Reactive nonmetals</div> <div style="border: 1px solid black; padding: 5px;">Noble gases</div> </div>																	18 Ar Argon 39.948
4	19 K Potassium 39.098	20 Ca Calcium 40.078	21 Sc Scandium 44.956	22 Ti Titanium 47.867	23 V Vanadium 50.942	24 Cr Chromium 51.996	25 Mn Manganese 54.938	26 Fe Iron 55.845	27 Co Cobalt 58.933	28 Ni Nickel 58.693	29 Cu Copper 63.546	30 Zn Zinc 65.38	31 Ga Gallium 69.723	32 Ge Germanium 72.630	33 As Arsenic 74.922	34 Se Selenium 78.971	35 Br Bromine 79.904	36 Kr Krypton 83.798		
5	37 Rb Rubidium 85.468	38 Sr Strontium 87.62	39 Y Yttrium 88.906	40 Zr Zirconium 91.224	41 Nb Niobium 92.906	42 Mo Molybdenum 95.95	43 Tc Technetium (98)	44 Ru Ruthenium 101.07	45 Rh Rhodium 102.91	46 Pd Palladium 106.42	47 Ag Silver 107.87	48 Cd Cadmium 112.41	49 In Indium 114.82	50 Sn Tin 118.71	51 Sb Antimony 121.76	52 Te Tellurium 127.60	53 I Iodine 126.90	54 Xe Xenon 131.29		
6	55 Cs Cesium 132.91	56 Ba Barium 137.33	57-71	72 Hf Hafnium 178.49	73 Ta Tantalum 180.95	74 W Tungsten 183.84	75 Re Rhenium 186.21	76 Os Osmium 190.23	77 Ir Iridium 192.22	78 Pt Platinum 195.08	79 Au Gold 196.97	80 Hg Mercury 200.59	81 Tl Thallium 204.38	82 Pb Lead 207.2	83 Bi Bismuth 208.98	84 Po Polonium (209)	85 At Astatine (210)	86 Rn Radon (222)		
7	87 Fr Francium (223)	88 Ra Radium (226)	89-103	104 Rf Rutherfordium (267)	105 Db Dubnium (268)	106 Sg Seaborgium (269)	107 Bh Bohrium (270)	108 Hs Hassium (277)	109 Mt Meitnerium (278)	110 Ds Darmstadtium (281)	111 Rg Roentgenium (282)	112 Cn Copernicium (285)	113 Nh Nihonium (286)	114 Fl Flerovium (289)	115 Mc Moscovium (290)	116 Lv Livermorium (293)	117 Ts Tennessine (294)	118 Og Oganesson (294)		
For elements with no stable isotopes, the mass number of the isotope with the longest half-life is in parentheses.																				
	57 La Lanthanum 138.91	58 Ce Cerium 140.12	59 Pr Praseodymium 140.91	60 Nd Neodymium 144.24	61 Pm Promethium (145)	62 Sm Samarium 150.36	63 Eu Europium 151.96	64 Gd Gadolinium 157.25	65 Tb Terbium 158.93	66 Dy Dysprosium 162.50	67 Ho Holmium 164.93	68 Er Erbium 167.26	69 Tm Thulium 168.93	70 Yb Ytterbium 173.05	71 Lu Lutetium 174.97					
	89 Ac Actinium (227)	90 Th Thorium 232.04	91 Pa Protactinium 231.04	92 U Uranium 238.03	93 Np Neptunium (237)	94 Pu Plutonium (244)	95 Am Americium (243)	96 Cm Curium (247)	97 Bk Berkelium (247)	98 Cf Californium (251)	99 Es Einsteinium (252)	100 Fm Fermium (257)	101 Md Mendelevium (258)	102 No Nobelium (259)	103 Lr Lawrencium (266)					

How Do Chemists Assign Stereochemistry?

The Cahn-Ingold-Prelog System

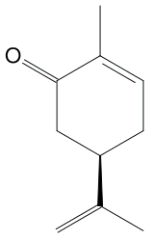


S-Bromochloromethanol

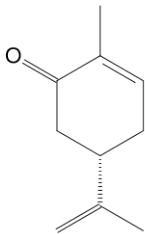


R-Bromochloromethanol

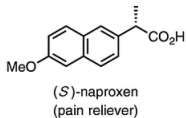
Interesting Enantiomeric Differences



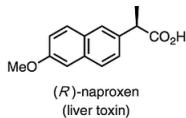
(R)-carvone
(spearmint)



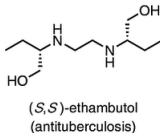
(S)-carvone
(caraway)



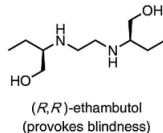
(S)-naproxen
(pain reliever)



(R)-naproxen
(liver toxin)



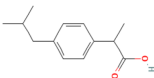
(S,S)-ethambutol
(antituberculosis)



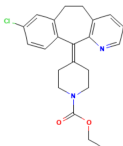
(R,R)-ethambutol
(provokes blindness)

Chiral Medications

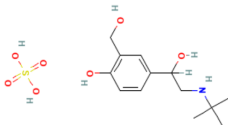
Ibuprofen (Advil, Motrin)



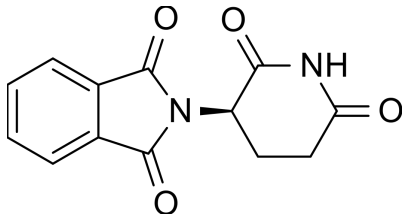
Loratadine (Claritin)



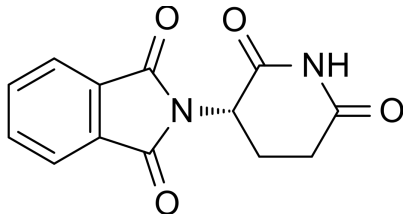
Albuterol Sulfate (Asthma Inhalers)



Case Study of the 1950s-1960s Thalidomide Scandal



(R)-thalidomide

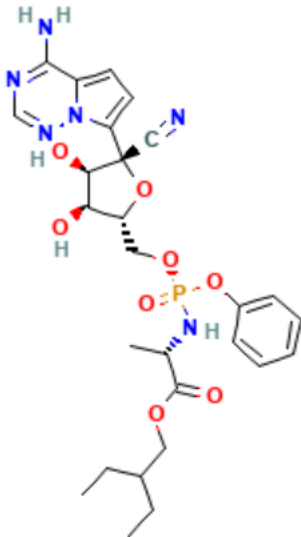


(S)-thalidomide

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

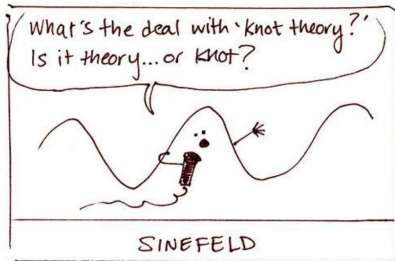
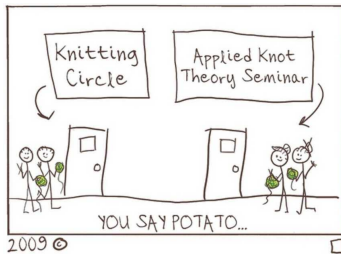
When Topology Meets Chemistry A Topological Look at Molecular Chirality by Erica Flapan

Knot, Knot, Who's There?



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