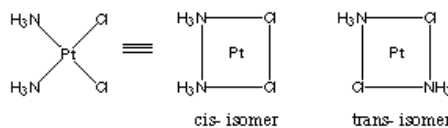


## Lecture 5 - Stereochemistry in Transition Metal Complexes

- Transition metal complexes as drugs- why understanding isomerism is important?
- Stereoisomers - review from previous lecture
- Geometric isomers of octahedral complexes
- Optical isomers of octahedral complexes
- Importance of isomerism - consequences of a racemic drug

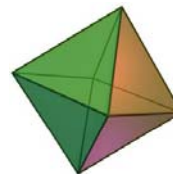
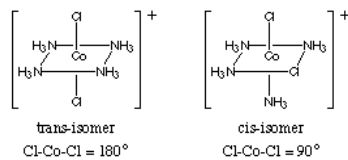
### 2. Stereoisomers in Metal Complexes - Review

- **Geometric Isomers** are found in square planar and octahedral complexes.  
Examples for square planar coordination are the **cis-** and **trans-** isomers of diamminedichloroplatinum(II):

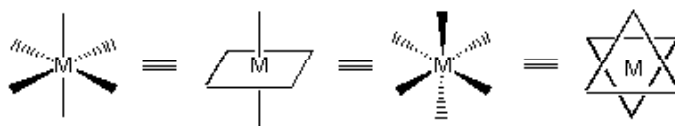


Note the convention of drawing a square with the metal ion in the center and the ligands at the corners of the square.

An example of geometric isomers in octahedral complexes are the **cis**- and **trans**-isomers of the tetraamminedichlorocobalt(III) ion:

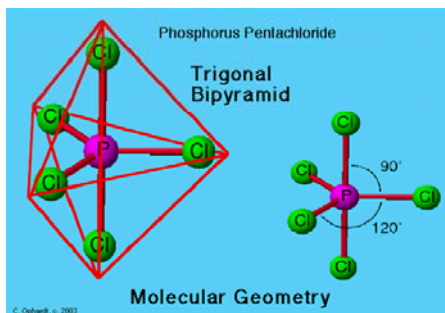


Note that there are several different ways to represent an octahedrally coordinated metal ion; which way you choose depends on what you are trying to show.

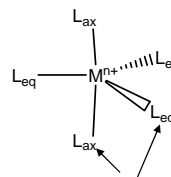


<http://www.chem.purdue.edu/gchelp/cchem/linki.html>

Consider a **trigonal bipyramid**, in this case two positions differ from the other three.



For a coordination compound we draw it as:



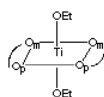
**Not equivalent**

## 1. Transition Metal Complexes as Drugs

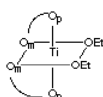
Investigational New Drugs, December 1995, Volume 13, pages 327-332.

- Pt complexes have had the most effective medicinal properties against certain types of cancers, but in 1995 the **first non platinum** transition metal **anticancer agent** (Budotitane) reached phase 2 clinical trials.
- Maximum clinical dose of this compound is 230 mg/m<sup>2</sup> twice weekly because the side effects of larger doses are cardiac arrhythmia.
- **Budotitane** is an **anticancer agent** that is active against a number of tumors but best at reducing the size of **colon/rectal tumors**.

2 **geometric isomers** of Budotitane are known one of which is chiral:



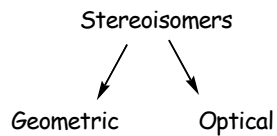
not chiral



chiral

3 isomers known

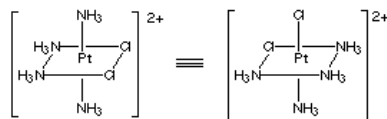
This drug was withdrawn from the market because there were **too many isomers**. (Why are pharmaceutical companies nervous of isomers?)



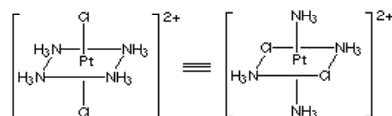
## 3. Geometric Isomerism for Some Common Octahedral Complex Compositions

1. **Composition MA<sub>4</sub>B<sub>2</sub> has 2 geometric isomers, cis and trans.** We have already seen that there are two geometric isomers possible for this composition when the coordination geometry is octahedral: **cis** and **trans**. The key is to not get confused by different ways of drawing these isomers. You should especially remember that all six positions on an octahedron are equivalent: **there are not axial and equatorial positions as there are for a trigonal bipyramid.**

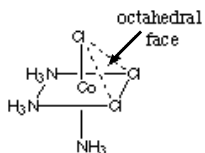
For example, both drawings below represent the *cis*-tetraamminedichloroplatinum(IV) ion, in which the Cl-Pt-Cl bond angle is 90°:



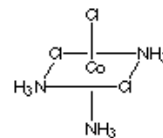
And both of these drawings represent the *trans*-tetraamminedichloroplatinum(IV) ion, in which the Cl-Pt-Cl bond angle is 180°.



**2. Composition  $MA_3B_3$  has two geometric isomers, *fac* and *mer*.** The *fac*- isomer (short for "**facial**") gets its name because all three chlorides are coordinated on **one face** of the octahedron. The *mer*- isomer (short for "**meridional**") has the three chloride ions coordinated **in a plane** that includes the metal ion. (This corresponds to the meridian on a sphere, which is any plane through the sphere that contains the center.)



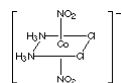
**fac**-triamminetrichlorocobalt(III)  
All three Cl-Co-Cl bond angles are 90°.



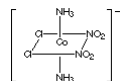
**mer**-triamminetrichlorocobalt(III)  
Two Cl-Co-Cl bond angles are 90°,  
the other is 180°.

**3. Composition  $MA_2B_2C_2$  has five geometric isomers.** It's just a matter of working out all the **cis** and **trans** possibilities for each pair of ligands.

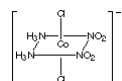
Consider the cobalt complex  $[Co(NH_3)_2Cl_2(NO_2)_2]^-$ .



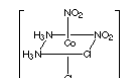
*cis*-diammine-*cis*-dichloro-*trans*-di-N-nitritocobaltate(III) ion



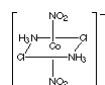
*trans*-diammine-*cis*-dichloro-*cis*-di-N-nitritocobaltate(III) ion



*cis*-diammine-*trans*-dichloro-*cis*-di-N-nitritocobaltate(III) ion

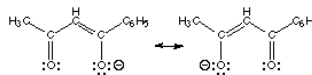


*cis*-diammine-*cis*-dichloro-*cis*-di-N-nitritocobaltate(III) ion

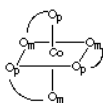


*trans*-diammine-*trans*-dichloro-*trans*-di-N-nitritocobaltate(III) ion

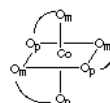
**4. Composition  $M(A-B)_3$  has two geometric isomers, *fac* and *mer*.** Here, A-B represents an unsymmetrical bidentate chelating agent such as the aminoethanethiolate ion,  $NH_2CH_2CH_2S^-$ , or the benzoylacetate ion whose resonance forms are shown below. The donor atoms are different for aminoethanethiolate so it is clearly unsymmetrical. However, even though the donor atoms are same (both oxygens) for benzoylacetate, the two "ends" of the chelating anion are different: one oxygen is close to a methyl group, the other to a phenyl group.



resonance structures for benzoylacetate



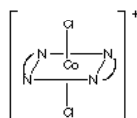
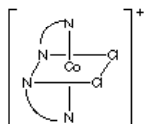
**fac**-isomer,  $Co(bzac)_3$ .  $O_p$  is the oxygen closest to the phenyl group,  $O_m$  is the oxygen closest to the methyl group. i.e. all O-Co-O angles are  $90^\circ$ .



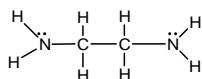
**mer**-isomer,  $Co(bzac)_3$ . Here the  $O_m$ 's are all meridional, as are the  $O_p$ 's i.e. two O-Co-O angles  $90^\circ$  and one  $180^\circ$ .

**5. Composition  $M(A-A)_2B_2$  has two geometric isomers, cis and trans.**

Here, A-A represents a symmetrical bidentate ligand such as acetylacetonate (acac), oxalate (ox), or ethylenediamine (en). The isomers for  $[Co(en)_2Cl_2]^+$  are shown below. The N-N is ethylenediamine.



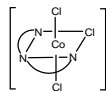
*cis*-dichlorobis(ethylenediamine)cobalt(III) ion      *trans*-dichlorobis(ethylenediamine)cobalt(III) ion



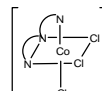
ethylenediamine (en)  
1,2-diaminoethane IUPAC

**6. Composition  $M(A)_3B_3$  has two geometric isomers, fac and mer.**

Here, A represents a tridentate ligand such as diethylenetriamine. The isomers for  $[Co(dien)_2Cl_3]$  are shown below. The N-N-N is diethylenetriamine.



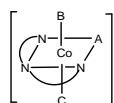
**mer** isomer



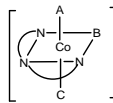
**fac** isomer (all on one face)

Consider  $[Co(dien)ABC]$  where ABC are three different ligands:

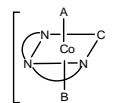
The mer isomer has three possibilities



B trans to C



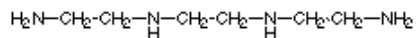
A trans to C



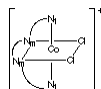
A trans to B

The fac isomer also has three possibilities so there are a total of 6 geometric isomers for  $[Co(dien)ABC]$

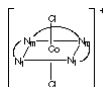
**7.  $M(\text{trien})\text{B}_2$  has 3 geometric isomers. Trien is a linear tetradentate ligand, .**



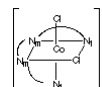
The flexible trien ligand can coordinate to an octahedral center in 3 different ways as shown below for  $[\text{Cr}(\text{trien})\text{Cl}_2]^+$ . Nm and Nt designate the middle NH groups and the terminal  $\text{NH}_2$  groups, respectively, on the ligand



Isomer A: both chlorides are trans to the middle nitrogens



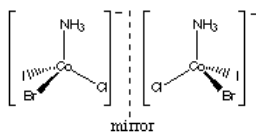
Isomer B: the chlorides are trans to each other



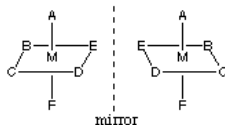
Isomer C: one chloride is trans to a middle nitrogen, the other is trans to a terminal nitrogen.

**4. Optical Isomerism**

**Optical Isomers** are usually associated with tetrahedral or octahedral geometries. The  $[\text{Co}(\text{NH}_3)\text{ClBrI}]^-$  ion is tetrahedral, with four different groups bonded to the cobalt, and has two **nonsuperimposable mirror images**:



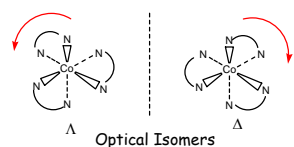
Thus this complex is exactly analogous to carbon compounds. It is also true that an octahedral metal ion bonded to 6 different ligands would be chiral (there are no known examples of such a complex as far as I know):



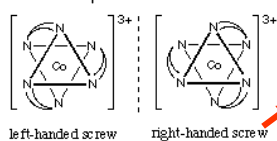
### Optical Isomerism for Some Common Octahedral Complex Compositions

There are instances of chirality and optical isomerism **that do not depend** on having four different groups attached to a tetrahedral central atom.

**1.  $M(A-A)_3$  has optical isomers.** This means that any octahedral tris chelate, whether with a symmetrical or an unsymmetrical bidentate ligand, is chiral and will have optical isomers. For example, the tris(ethylenediamine)cobalt(III) ion is chiral, in spite of the fact that the three ethylenediamine ligands are all the same and are themselves symmetrical:



$[Co(en)_3]^{3+}$  - the ligands are identical but they are chiral molecules

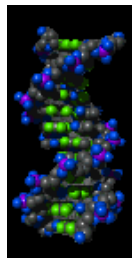


One of the alternate ways of showing the octahedron shows the right/left handed nature of these two isomers more clearly:

The chelates define either a right handed helix  $\Delta$  (delta) or a left handed helix  $\Lambda$  (lambda).

### Remember the "twist" of chirality

On your cover a very rare sight,  
a helix that gave me a fright.  
Did you forget that this spiral  
called DNA is chiral,  
and it normally twists to the right?



[Chemical & Engineering News, Aug 14, 2000, 8](#)

As shown in the figures to the left and right, most DNA of living things on the earth twists as a "right-hand screw". This is the same direction as a regular wood or metal screw.





## Chirality and fun

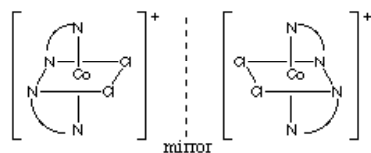
A **helter skelter** is an **amusement park** ride with a slide built in a **spiral** around a high tower. Users climb the tower and slide down usually on a mat. It is the precursor to the **water slide**. The term is primarily (but not exclusively) found in **British English**.

The helter skelter is chiral like DNA!

Britain's first indoor office helter skelter sees staff slide down three floors in just seven seconds

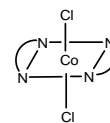


2. ***cis*-M(A-A)<sub>2</sub>X<sub>2</sub>** has optical isomers. It follows that ***cis*-M(A-B)<sub>2</sub>X<sub>2</sub>** is chiral and will also have optical isomers. The optical isomers of **[Co(en)<sub>2</sub>Cl<sub>2</sub>]<sup>+</sup>** are shown below.



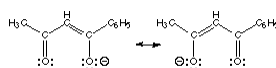
Left handed screw

Right handed screw



trans is not chiral

**Budotitane** is a 6-coordinate octahedral titanium complex that has been developed for treating **colon cancer**. Its formula is **[Ti(bzac)<sub>2</sub>(OEt)<sub>2</sub>]**, where **bzac** is the **benzoylacetone** ligand. The **OEt** ligand is **ethoxide**, **CH<sub>3</sub>CH<sub>2</sub>O-**.



benzoylacetone ligand

### Biological activities of titanium compounds

- Most anticancer titanium compounds act against tumors in the gastrointestinal tract. Activity towards breast, lung and skin (melanoma) cancers is shown by some as well. Among their appealing properties is that they do not show common side effects of widely used cytostatic agents such as alopecia or bone marrow impairment. These features make titanium compounds interesting for combined therapy and further study.

2 geometric isomers of Budotitane are known one of which is chiral:



Not chiral



chiral

3 isomers known

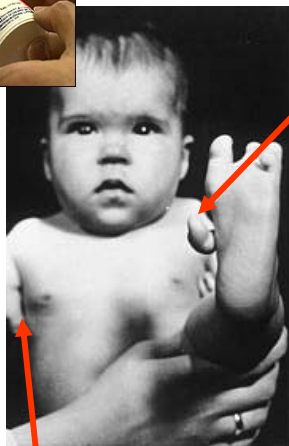
This drug was dropped from the market because there were too many isomers.

### 5. Why is isomerism important?

- The reason that isomers are so important in drug design is that normally, only one particular isomer is effective in treating the condition.
- Other isomers are less effective or even harmful!
- The classic example is thalidomide, where one enantiomer helped women overcome morning sickness associated with the early weeks of pregnancy, and the opposite enantiomer caused the horrendous birth defects (lack of arms and legs) seen in what are now known as the **"thalidomide babies."**
- It was developed by a German pharmaceutical company and sold between 1957 to 1961 in 50 countries.



### A Thalidomide Baby

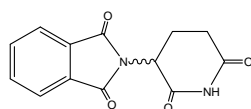


Missing/deformed arm

1962 photo of a baby born with an **extra appendage** connected to the foot caused by the pregnant mother taking the drug Thalidomide. This condition is known as "**phocomelia**".

Thalidomide - 2-(2,6-dioxo-3-piperidyl)isoidole-1,3-dione.

Prescribed as the racemic mixture of S and R-enantiomers



Thalidomide,  $C_{13}H_{10}N_2O_4$

### The consequences of isomerism - BBC News - Friday, 7 June, 2002 UK



**Geoff Adams-Spink** provides a personal insight into thalidomide.

I had a more fortunate start in life, though my mother, too, was initially numbed. I was born with very short arms, no right eye and 10 per cent vision in my left eye. My mother had taken **one thalidomide tablet**. "When you were born it was a very big shock. In fact for the first three days I didn't really want to know," my mother admitted.

In the late 1950s and 1960s pregnant women across the globe reached for a recommended remedy for bouts of morning sickness - **thalidomide**.

Around 10,000 babies were born with disabilities as a result of their mothers taking the thalidomide drug. Just under half of those survived - 456 of them in the UK.

In 1962, a Belgian woman was found not guilty of murdering her thalidomide baby.

The drug was not only administered as a treatment for morning sickness: it was also marketed as a "harmless" sedative.

One pregnant mother had taken it following a nervous breakdown. When she gave birth to a son without arms, health professionals didn't think that she could stand the shock. Forty years later, I suppose many of us "thalidomiders" see ourselves as guardians of the drug's heritage - anxious that no scientists or medical practitioner should forget, and that pharmaceutical giants are held firmly in check.