# Unit 2

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## 2.1 Lecture 4: Substitution Reactions

- Association/dissociation reactions.

- Fairly related to organic $S_N2$ and $S_N1$ reactions, respectively.

- General form:
$$ML_6 + L' \rightleftharpoons ML_5L' + L$$

- We investigate the position of the equilibrium with the three main characteristics that determine reactivity.

  1. Sterics.
     - Related to the metal coordination number.
       - C.N. $> 6$ is typically disfavored.
       - C.N. $< 6$ is possible.
     - The size of L' is also important: If L' $= PPh_3$ for example, this is hard to get to C.N. $> 4$.
  2. Ligand character.
     - In nonpolar media, dissociation of charged groups (e.g., $Cl^-$) will be disfavored. However, the opposite is true in polar media.
       - This is because of the issue of making charge/ionizing.
     - The match between M and L (e.g., hard/soft, electron rich/poor) is also important.
       - For example, $Fe^0$ will bind CO strongly since $Fe^0$ is electron rich and CO is a $\pi$ acceptor.
       - However, $Fe^{IV}$ will not (as a hard, electron-poor metal center).
  3. Electronic structure of the metal center (whether or not the metal is electronically saturated [has 18 electrons]).
     - $18\,e^-$: it will not want to coordinate an additional L'.
     - $20\,e^-$: it will want to dissociate.
     - $16\,e^-$: it *can* associate.
       - However, it may not want to given that $16\,e^-$ square-planar complexes are fairly stable.
       - The associated state may be a transition state in a square-planar ligand substitution or otherwise not a ground state.

- Ligand substitution reactions terms: **Kinetic** and **thermodynamic**.

- **Kinetic** (considerations): Elements are inert (slow) or labile (fast).

- **Thermodynamic** (considerations): Which side of an equilibrium will be favored. Elements are stable or reactive.

- In ligand substitution reactions, there are two limiting regimes:

    1. Associative substitution.
        - See the related discussion in Labalme (2021).
        - This is the most general reaction type, even for coordinatively saturated complexes.
        - Rate law:
        $$\frac{d[ML_5L']}{dt} = k_{obs}[ML_6][L']$$

    2. Dissociative mechanism.
        - See the related discussion in Labalme (2021).
        - There are many things that look dissociative that are associative (e.g., instead of forming a 5-coordinate species, you could just have a molecule of the solvent displace a ligand).
        - This mechanism is rare and hard to prove.
        - Rate law:
        $$\frac{d[ML_5L']}{dt} = \frac{k_2 k_1 [ML_6][L]}{k_{-1}[L] + k_2[L']}$$
        - Experimentally, we swamp the reaction with L' so that $[L'] >>>$ than all other reagents. This makes it so that the rate is just $k_{obs}[ML_6]$, i.e., pseudo-first order conditions.

- Unfortunately, much like in orgo, very few cases are at these extremes and we can have hybrids called. . .

    3. Interchange mechanisms.
        - See the related discussion in Labalme (2021).
        - Within this category, we can have $I_a$ (associative interchange) and $I_d$ (dissociative interchange).
        - In the transition state, we have L' coming in and L leaving at the same time.

- Kinetics and rates of these mechanisms.

- Several categories (measure with water exchange rates; see Labalme (2021)):

    I) Very fast.
        - Alkali metals (species that primarily engage in ionic bonding; little covalent character).
        - $10^8 \, s^{-1}$; close to the diffusion limit.
    II) Fast.
        - Higher valent ions; often $M^{3+}$ such as $Al^{3+}$.
            ■ Higher charge $\Rightarrow$ higher ligand affinity $\Rightarrow$ slightly slower but still pretty fast.
        - $10^3$-$10^8 \, s^{-1}$.
    III) Slower.
        - Getting into the transition metals: $Fe^{3+}$, $V^{3+}$, $Ti^{3+}$.
            ■ $d$-orbital splitting + covalency $\Rightarrow$ stronger bonding $\Rightarrow$ slower exchange rate.
        - $10^1$-$10^4 \, s^{-1}$.
    IV) Inert.
        - $Co^{3+}$, $Cr^{3+}$, $Pt^{2+}$, and $Fe^{2+}$(L.S.).
        - $10^{-8}$-$10^{-4} \, s^{-1}$.

- The overlap between the rates reflects the fact that there is no hard and fast cut off between categories.

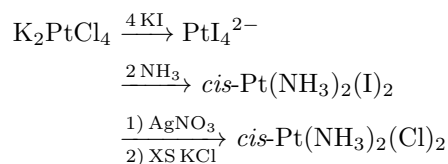- The identity of L' also influences rates.

    - Reaction rates increase with the ligand field strength of $L'^{[1]}$.

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[1]Goes over Table IX.1 from Labalme (2021).

- Characteristics of the metal that control the observed rates.

  - Ranking L.S. metal centers (slowest to fastest): $\text{Co}^{\text{III}} < \text{Cr}^{\text{III}} < \text{Mn}^{\text{III}} < \text{Fe}^{\text{III}} < \text{Ti}^{\text{III}} < \text{V}^{\text{III}}$.
  - Considering the $d$ counts, we have $d^6 < d^3 < d^4 < d^5 < d^1 < d^2$.
  - Now think of this in terms of the $d$-orbitals splitting diagram (Figure 1.7b).
    - ■ As the antibonding orbitals get filled, $\sigma$ bonds will weaken, promoting a faster exchange.
    - ■ Full and half-full $t_{2g}$ also provides stability.

- Thus, we list the following configurations as inert and labile (see the related discussion in Labalme (2021)):

  - Inert: $d^3$, L.S. $d^{4,5,6}$, and square planar $d^8$.
  - Labile: $d^0$, $d^1$, $d^2$, H.S. $d^{4,5,6}$, $d^7$, $d^9$, $d^{10}$.

- Other important kinetic factors:

  1. Oxidation state.
     - As oxidation state increases, exchange rate decreases (becomes more inert).
  2. Size.
     - Smaller ions are more inert.
     - However, first row ions are almost always labile (because they more readily populate higher spin states).
  3. Chelate effect.
     - Reviews some info from Labalme (2021).
     - Chelating ligands form a ring or a **metallacycle** (this is why 4,5-membered ligands are stable; because 5,6-membered rings are favorable).
     - Binding of a chelating ligand is typically favored, primarily due to entropic reasons (effective concentration is secondary).
     - Example: Gives actual $\Delta G = \Delta H - T\Delta S$ thermodynamic data for the formation reaction of $\text{Cu(MeNH}_2)_4{}^{2+}$ vs. $\text{Cu(en)}_2{}^{2+}$ to emphasize the importance of entropy (see the related discussion in the notes on Chapter 10 in Labalme (2021)).
     - EDTA is a hexadentate ligand that is commonly used in biology to pull all metal centers out of solution.
       - ■ For $\text{Fe}^{3+}$ for example, $K_f = 10^{25}\,\text{mol}^{-1}$. What is $\text{mol}^{-1}$ and why is it here?
       - ■ Sidenophones and euterobactin are biology's own chelaters ($K_f = 10^{52}\,\text{mol}^{-1}$).
       - ■ These chelaters involved because if bacteria are going to invade a host, they need to scavenge iron, but iron is pretty tightly regulated. Thus, there has been an arms race of molecules that can scavenge iron or prevent iron from being scavenged.
     - Chelation therapy: If exposed to a heavy metal, you will be given chelating agents that will bind to metal ions and cause them to be excreted from the body.
  4. Trans effect.
     - Reviews some info from Labalme (2021).
     - Helps predict the **regiochemistry** of where a given ligand will substitute.
     - Cis-platin reaction mechanism: $cis\text{-Pt(NH}_3)_2(\text{Cl})_2 \longrightarrow cis\text{-Pt(NH}_3)_2(\text{H}_2\text{O})_2$ in the body, which binds to DNA on the $cis$-water side, causing a kink, stopping transcription, and initiating apoptosis.
       - ■ Cis-platin is quite toxic (people are trying to develop formulations that are less so), but highly effective at stopping cancer.
       - ■ Can't have $trans$ because it doesn't have the $cis$-water side. Thus, this synthesis mechanism doesn't work: $[\text{PtCl}_4]^{2-} \xrightarrow{2\,\text{NH}_3} trans\text{-Pt(NH}_3)_2\text{Cl}_2$.

■ Therefore, we synthesize it as follows.

$$K_2PtCl_4 \xrightarrow{4\,KI} PtI_4{}^{2-}$$
$$\xrightarrow{2\,NH_3} \textit{cis-}Pt(NH_3)_2(I)_2$$
$$\xrightarrow[2)\ XS\,KCl]{1)\ AgNO_3} \textit{cis-}Pt(NH_3)_2(Cl)_2$$

   ■ Note that we start from tetrachloroplatinate because it is the most common form of platinum.
   ■ Also note that XS stands for "excess."
  – Trans-effect order listed.
  – The trans-effect is kinetic; concerned with rates of exchange.
   ■ Stronger *trans*-directors **labelize** the ligands opposite them.
  – The trans influence is thermodynamic.
   ■ It influences the ground state structure, causing lengthening of bonds *trans* to a strong-field ligand (think of this in terms of competition for electrons on the central atom; a strong-field ligand will attract more of these, making the other bond weaker).

• Note that intramolecular reactions (such as a second binding of a bidentate chelating ligand) are highly favored.