Lecture 15 Apr 11: Substitution Reactions and the Trans Effect

A substitution reaction is one in which an existing ligand on a metal center is replaced by another ligand.

$$ML_n + xP \rightleftharpoons ML_{n-x}P_x + xL$$

Exactly how this occurs depends on the electron count of the metal complex, the ligands on the metal, and their steric and electronic properties.

Ligand substitution reactions occur by associative or dissociative mechanisms. Ligand association is when an incoming ligand coordinates to a metal center that has one or more empty orbitals available. Ligand dissociation is when a ligand coordinated to a metal dissociates. The probability of a specific ligand dissociating depends on how strongly or weakly it is coordinated to the metal center. The simplest cases are:

Saturated, 18e⁻ complex: Dissociative Pathway

Unsaturated, 16e⁻ complex: Associative Pathway (usually)
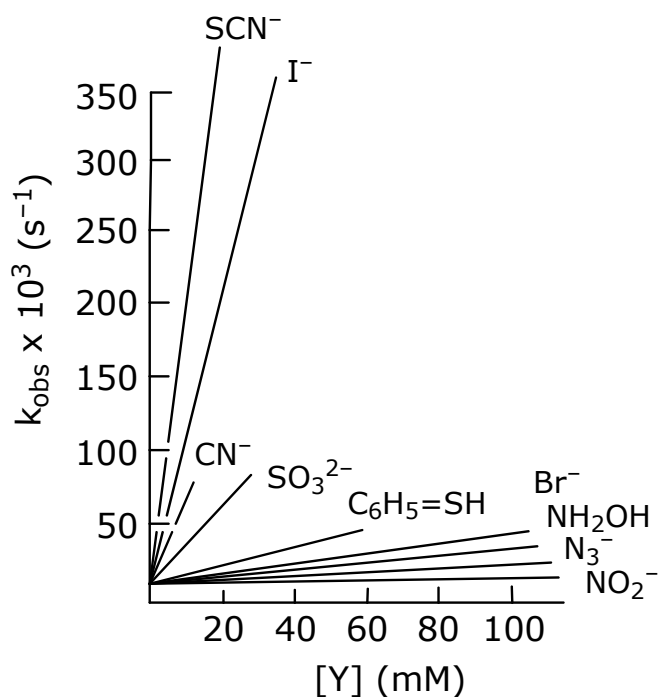   Dissociative pathway (sometimes)

Square Planar Complexes

Low spin d^8 complexes are typical. Substitution of this type of complexes has been most thoroughly studied for Pt(II) complexes. Characteristics of this type of reaction are:

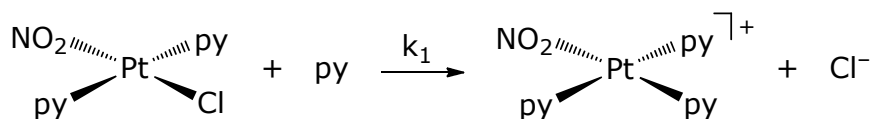**1** reaction proceeds with retention of configuration
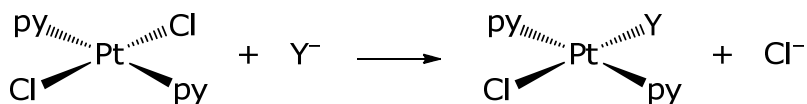
2 the overall observed rate dependence is:

$$\frac{-d[py_2PtCl_2]}{dt} = k_1[py_2PtCl_2] + k_2[py_2PtCl_2][Y]$$

$$= (k_1 + k_1[Y])[py_2PtCl_2]$$

$$\underset{\text{intercept}}{\diagup} \qquad \underset{\text{slope}}{\diagdown}$$

$$NO_2 \cdots Pt \cdots py \atop py \quad Cl \quad + \quad py \quad \xrightarrow{k_1} \quad \left[NO_2 \cdots Pt \cdots py \atop py \quad py \right]^+ \quad + \quad Cl^-$$

Solvent	$k_1 \times 10^4 \ s^{-1}$ at 30 °C
dichloromethane	0.06
methanol	0.7
nitromethane	8
acetone	3100 (at 20 °C)

The rate law is very closely related to **2**. The solvent may be introduced into the rate law as follows:

$$\frac{-d[py_2PtCl(NO_2)]}{dt} = k_D[py_2PtCl(NO_2)] + k_S[py_2PtCl(NO_2)][sol] + k_2[py_2PtCl(NO_2)][Y]$$

where k_D is the intrinsic rate constant accounting for dissociation of the ligand, k_S is the rate constant that accounts for solvent attack on the complex and k_2 is as before, the rate constant accounting for the incoming ligand, Y.

2

Because solvent is in large excess concentration, hence $k_S[S]$ is constant and,

$$\frac{-d[py_2PtCl(NO_2)]}{dt} = k_D[py_2PtCl(NO_2)] + k_S[py_2PtCl(NO_2)][sol] + k_2[py_2PtCl(NO_2)][Y]$$

$$= (k_D + k_S[sol])[py_2PtCl(NO_2)] + k_2[Y][py_2PtCl(NO_2)]$$

$$= k_1[py_2PtCl(NO_2)] + k_2[Y][py_2PtCl(NO_2)]$$

$$= (k_1 + k_1[Y])[py_2PtCl(NO_2)]$$

For a given ligand and complex k_D and $k_2[Y]$ will be the same but k_S will be different for the different solvents. Hence, k_1 (the intercept) will vary for the same reaction run in different solvents. Hence, the result if (**2**) obtained.

(**4**) a large positive $\Delta H^{\ddagger}$ and large and negative $\Delta S^{\ddagger}$

Complex	Reagent	k $M^{-1}s^{-1}$	$\Delta H^{\ddagger}$ kJ mol^{-1}	$\Delta S^{\ddagger}$ J K^{-1}mol^{-1}	$\Delta V^{\ddagger}$ cm^3 mol^{-1}
$Pd(H_2O)_4^{2+}$	H_2O	5.6×10^{2a}	50	-26	-2.2
$Pt(H_2O)_4^{2+}$	H_2O	3.9×10^{-4a}	90	-9	-4.6
$Ni(CN)_4^{2-}$	CN^-	$>5 \times 10^5$	—	—	—
$Pd(CN)_4^{2-}$	CN^-	1.2×10^{2b}	17	-178	—
$Pt(CN)_4^{2-}$	CN^-	26^b	26	-143	—
$Au(CN)_4^-$	CN^-	3.9×10^{3b}	28	-100	—
$Pt(dien)Br^+$	H_2O	1.4×10^{-4a}	84	-63	-10
	Cl^-	6×10^{-4}	75	-46	—
	Br^-	6×10^{-3}	67	-63	—
	N_3^-	6.4×10^{-3}	65	-71	-8.5
	py	2.8×10^{-3}	46	-136	-7.7
	NO_2^-	1.4×10^{-3}	72	-56	-6.4
	I^-	0.32	46	-104	—
	NCS^-	0.68	39	-112	—
	$SC(NH_2)_2$	1.3	35	-121	—

$^a s^{-1}$ ^{b}No [CN$^-$]-independent term

Recall that the rate constant is related to $\Delta G^{\ddagger}$ as follows,
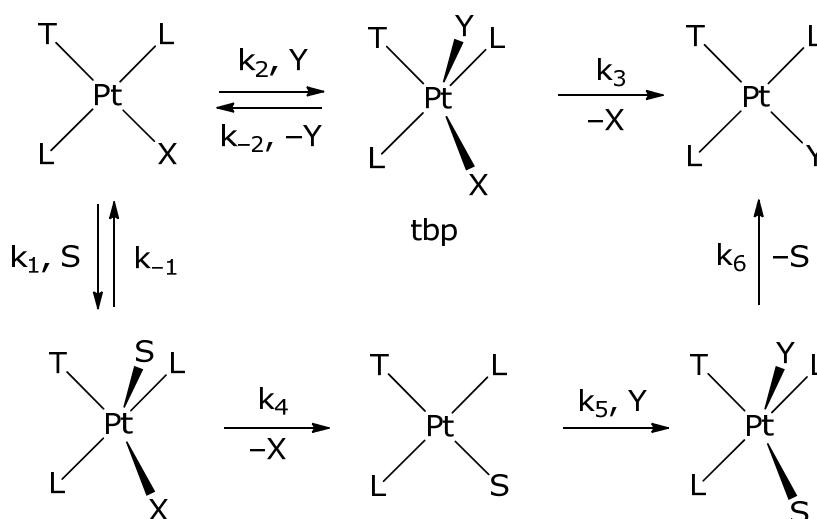
$$k = \frac{k_BT}{h} e^{-\Delta G^{\ddagger}/RT} \quad \text{but } \Delta G^{\ddagger} = \Delta H^{\ddagger} - T\Delta S^{\ddagger}$$

$$k = \frac{k_B T}{h} e^{-\Delta H^\ddagger/RT} e^{\Delta S^\ddagger/R}$$

plot of $\ln\dfrac{k}{T}$ vs $\dfrac{1}{T}$ yields $\Delta H^\ddagger$ from the slope and $\Delta S^\ddagger$ from intercept

$$\ln\left(\frac{k}{T}\right) = \left(\frac{-\Delta H^\ddagger}{RT}\right) + \left[\ln\left(\frac{k_B}{h}\right) + \left(\frac{\Delta S^\ddagger}{R}\right)\right]$$

Experimental observations **1** – **4** are explained by the following mechanism:

tbp

Using the steady state approximation, the rate law of **2** (and **4**) is obtained:

$$\frac{-d[TL_2PtX]}{dt} = k_1[TL_2PtX][S] - k_{-1}[TL_2PtXS] + k_2[TL_2PtX][Y] - k_{-2}[TL_2PtXY]$$

solvent pathway   ligand pathway

Applying the steady-state approximation to $[TL_2PtXS]$ and $[TL_2PtXY]$ for the ligand pathway,

$$\frac{-d[TL_2PtXY]}{dt} = 0 = k_3[TL_2PtXY] + k_{-2}[TL_2PtXY] - k_2[TL_2PtX][Y]$$

$$[TL_2PtXY] = \frac{k_2[TL_2PtX][Y]}{k_3 + k_{-2}}$$

4

$$\frac{-d[TL_2PtX]}{dt} = k_2[TL_2PtX][Y] - \frac{k_2k_{-2}[TL_2PtX][Y]}{k_3 + k_{-2}} + \text{solvent pathway}$$

$$= \frac{k_2k_3[TL_2PtX][Y]}{k_3 + k_{-2}} + \text{solvent pathway}$$

If $k_3 >> k_{-2}$ (implied by irreversibility of the second step), then,

$$\frac{-d[TL_2PtX]}{dt} = k_2[TL_2PtX][Y] + \text{solvent pathway}$$

Following the same approach for the solvent pathway and applying the steady-state approximation to $[TL_2PtXS]$ leads to,

$$\frac{-d[TL_2PtX]}{dt} = k_2[TL_2PtX][Y] + k_1[TL_2PtX][S]$$

but [S] is large and invariant … thus $k_1[S]$ is a constant, $k_1' = k_1[S]$ and therefore,

$$\frac{-d[TL_2PtX]}{dt} = (k_1' + k_2[Y])[TL_2PtX]$$

The result of **2** is obtained.

The associative mechanism will depend on:

5   Ability of T to direct X to leave

6   Ability of X to leave

7   Nucleophilicity of Y and S

Considering **5** , the ligand trans, T, to the leaving ligand can influence the rate of substitution by perturbing the ground state energy of the reactants, i.e., the ΔG^o or by perturbing the transition state energy, i.e. $\Delta G^{\ddagger}$. The **trans influence**, describes the effect of T on ground state properties, ΔG; it is therefore manifested in changes in bond length and stretching frequencies. The bond length of the $M—L_{trans}$ will be

longer for more trans directing ligands, and the M—L_{trans} frequency will decrease. The **trans effect**, describes the effect of T on the transition state energy, $\Delta G^{\ddagger}$. The kinetics for substitution can vary dramatically with T:
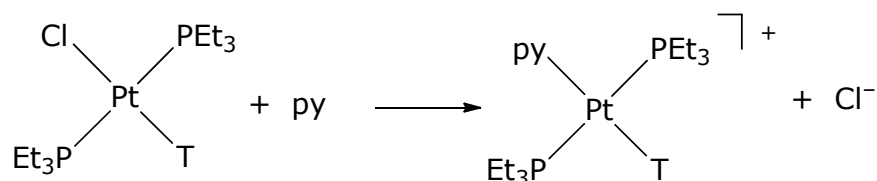
L	$k_1(s^{-1})$	$k_2(M^{-1}s^{-1})$
PEt_3	1.7×10^{-2}	3.8
H^-	1.8×10^{-2}	4.2
CH_3^-	1.7×10^{-4}	6.7×10^{-2}
$C_6H_5^-$	3.3×10^{-5}	1.6×10^{-2}
$p\text{-}ClC_6H_4^-$	3.3×10^{-5}	1.6×10^{-2}
$p\text{-}CH_3OC_6H_4^-$	2.8×10^{-5}	1.3×10^{-2}
Cl^-	1.0×10^{-6}	4.0×10^{-4}

There is a difference of 10^4 in rate! By setting up comparative rate experiments, a relative scaling of the trans directing effect may be established; it is observed to decrease along the series:
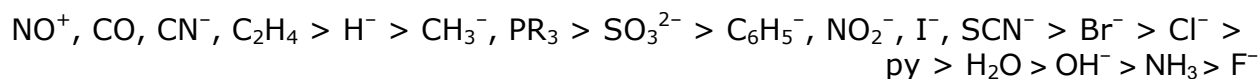
NO^+, CO, CN^-, C_2H_4 > H^- > CH_3^-, PR_3 > SO_3^{2-} > $C_6H_5^-$, NO_2^-, I^-, SCN^- > Br^- > Cl^- > py > H_2O > OH^- > NH_3 > F^-

strong π-acceptors   strong σ donors   weak σ- and π-donors

Rationalization of the above ordering for the T ligand is as follows:

σ-effect: strong σ donor contributes more electron density to the metal that shares the same π orbital. Thus the trans bond is weakened; this may be manifested either in the ground state and/or transition state … so both the trans influence and trans effect may operate here. Note however, the σ-orbitals of the equatorial ligands are not directly pointed at d_{xy} or $d_{x^2-y^2}$ in a tbp geometry, the trans effect is somewhat attenuated (since the transition state assumes a tbp geometry).

**π-effect**: better π-acceptors remove electron density from the metal, thus stabilizing the transition state, especially via the d_{xz} and d_{yz} orbitals along the axial ligand direction and via the d_{xy} and $d_{x^2-y^2}$ in plane π-bonds.

Knowledge of the trans directing effect is useful for synthesis. For example, consider the synthesis of cis- and trans-$PtCl_2(NH_3)_2$.

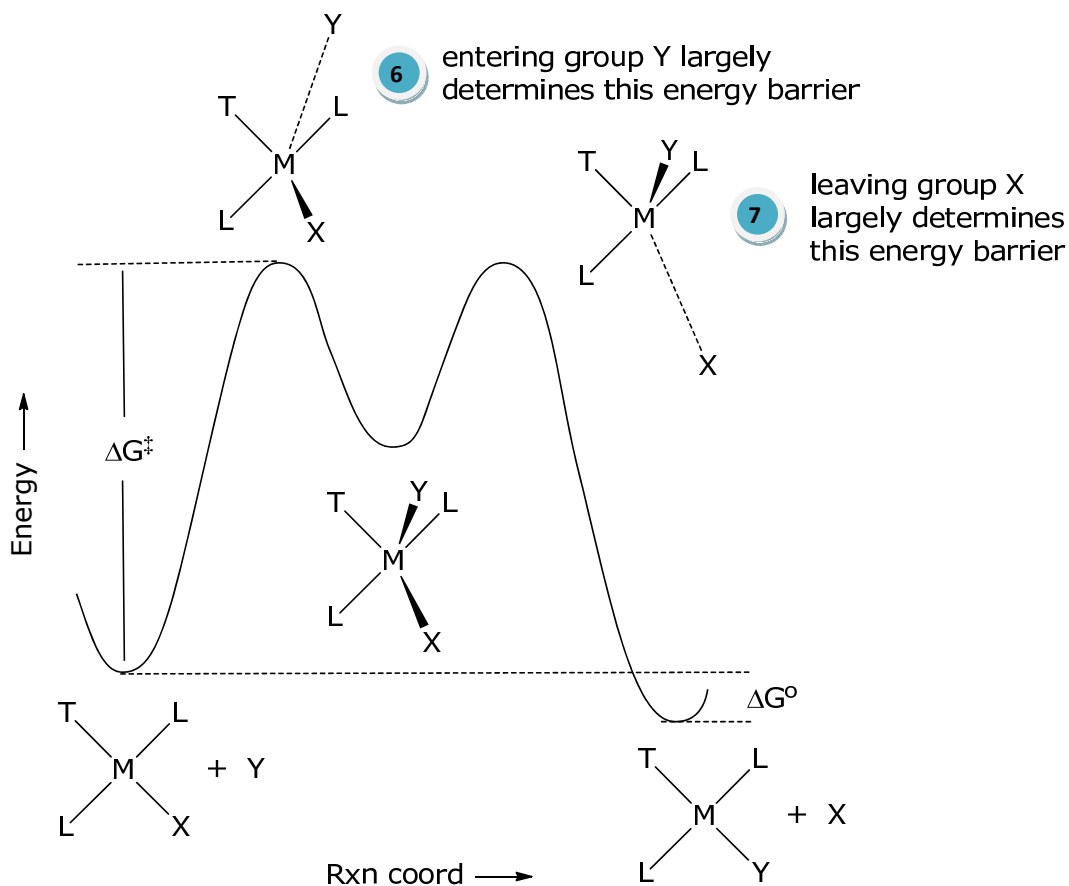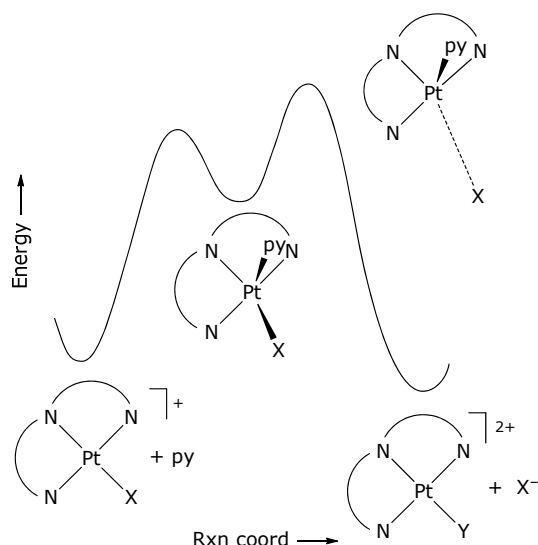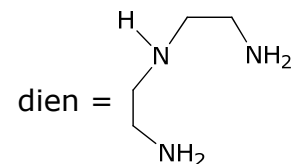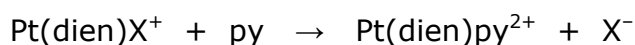*trans*-platin
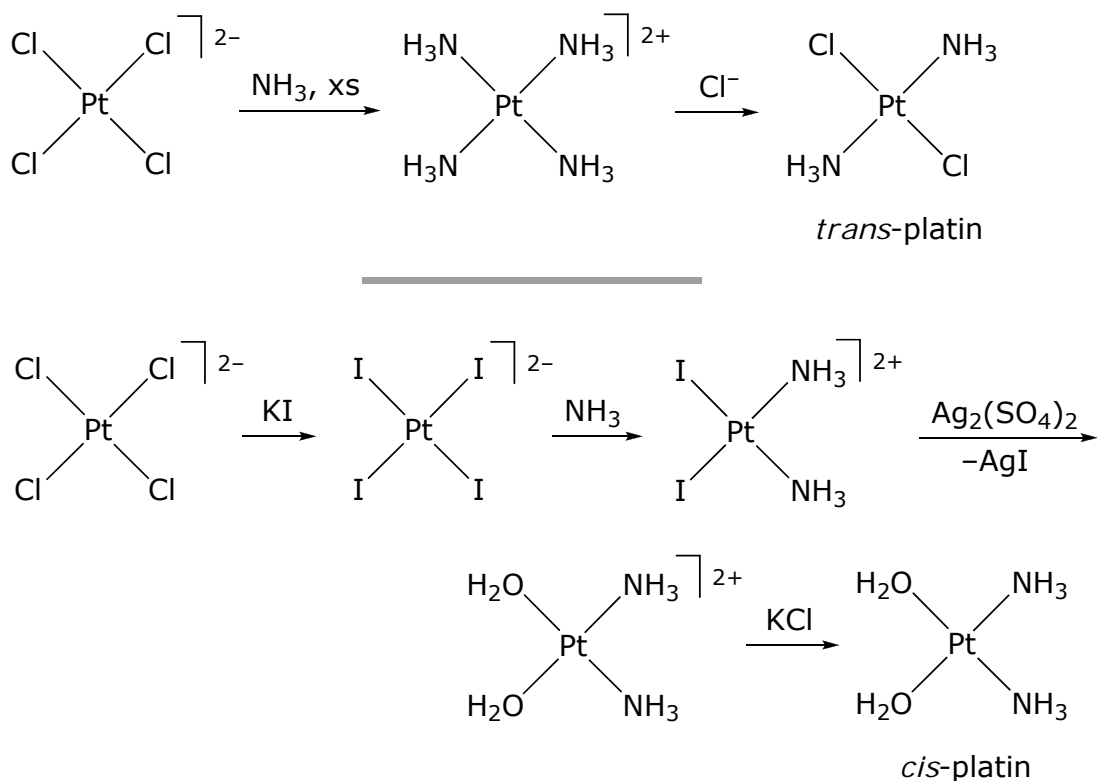
cis-platin

Cis-platin and Cancer

Cis-platin is one of the most successful anticancer drugs ever discovered. The drug was discovered by biophysicist Barnet Rosenberg from Michigan State, who was examining the effect of strong electric fields on cell division. He was interested in determining the effect of large electric fields on aging. To examine if there was an effect, he applied current through an "inert" Pt electrode to E. coli in $NH_4^+Cl^-$ buffer. He noted that cell division was inhibited. In performing control experiments, he determined that the effect was not due to an electric field but rather to Pt hydrolysis products formed at the electrode that was the responsible agent for cell inhibition. It was then decided that Pt complexes should be tested for anticancer activity, and in short order he ascertained that cis-platin had potent antitumor activity. Since this discovery in the 1960s, most of all the important mechanistic work to determine the action of cis-platin has been performed at MIT in Professor Stephen Lippard's group. A synopsis of decades of work is shown below.
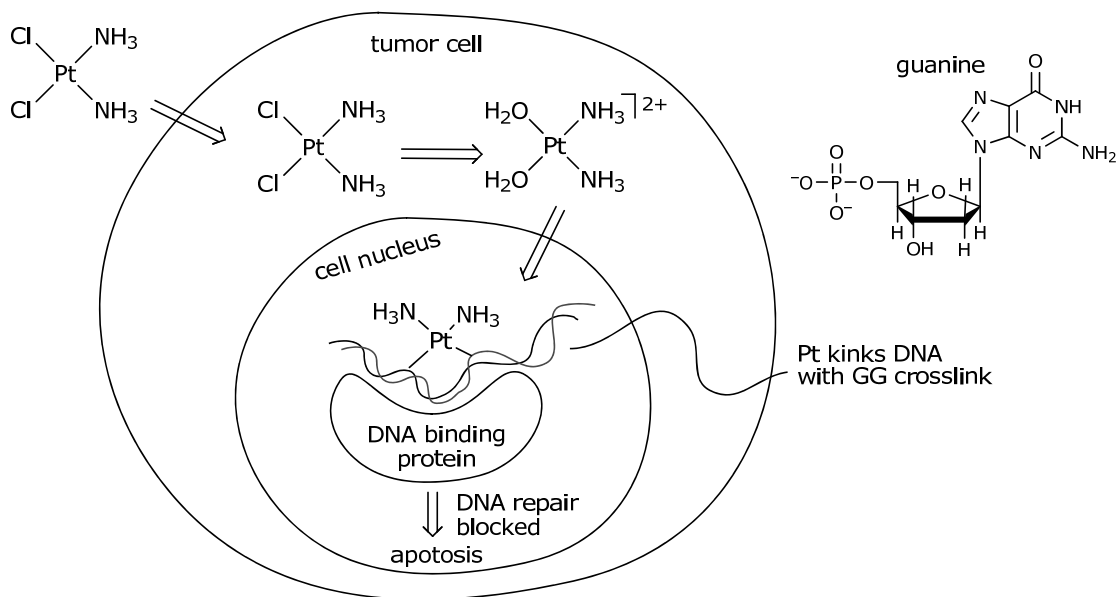
Considering **6** and **7**, the potential free energy landscape determines the differentiation between entering and leaving group effects
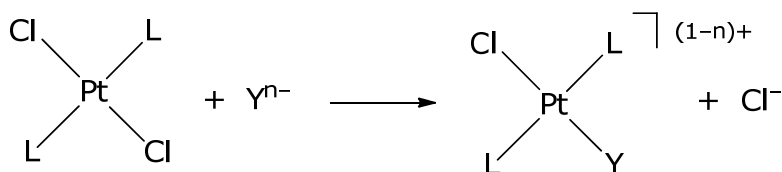

6 entering group Y largely determines this energy barrier

7 leaving group X largely determines this energy barrier

$\Delta G^{\ddagger}$

ΔG^{o}

Energy →

Rxn coord →

Pt(dien)X$^+$ provides an example of **6** ,

$$Pt(dien)X^+ \;+\; py \;\rightarrow\; Pt(dien)py^{2+} \;+\; X^-$$

dien =

X	k_{obs}
NO_3^-	very fast
H_2O	1900
Cl^-	35
Br^-	23
I^-	10
N_3^-	0.8
SCN^-	0.3
NO_2^-	0.05
CN^-	0.02

Rate varies by 10^6! Note, the stronger π-bonding inhibits dissociation of X^- from the 5-coordinate transition state

PtL$_2$Cl$_2$ complexes provide an example of **7** ,

Y	$L = Py^b$	$L = PEt_3^c$	$\eta_{Pt}^{\circ\,b}$
Cl^-	0.45	0.029	3.04
NH_3	0.47	—	3.07
NO_2^-	0.68	0.027	3.22
N_3^-	1.55	0.2	3.58
Br^-	3.7	0.93	4.18
I^-	107	236	5.46
SCN^-	180	371	6.65
PPh_3	249,000	—	8.93

The trend in rates is consistent with HSAB concepts (see Lecture module 4/6), Pt(II) is a soft metal and therefore forms better Lewis acid-base adducts with a soft ligand. Thus the polarizability of the incoming ligand is important. A measure of this polarizability is given by the nucleophilic reactivity constant, η.
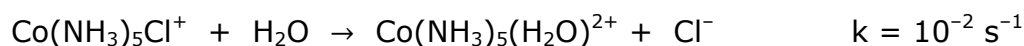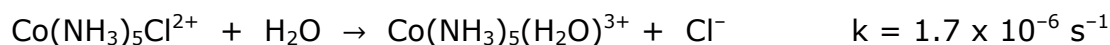
Octahedral Complexes

The most thoroughly studied systems are $Cr^{3+}(d^3)$, Co^{3+} (d^6) and Ni^{2+} (d^8). The characteristics of the reaction are:

8 substitution rate is independent of Y^-

$$Ni(H_2O)_6{}^{2+} + L^{n-} \rightarrow Ni(H_2O)_5L^{(2-n)+} + H_2O$$

L	$k \times (10^4 \text{ s}^{-1})$[a]
SO_4^{2-}	1.5
CH_3COO^-	3
SCN^-	0.6
F^-	0.8
H_2O	3.0
NH_3	3
Py	3

9 increased charge on complex, decreased substitution rate

$$Co(NH_3)_5Cl^{2+} + H_2O \rightarrow Co(NH_3)_5(H_2O)^{3+} + Cl^- \qquad k = 1.7 \times 10^{-6} \text{ s}^{-1}$$

$$Co(NH_3)_5Cl^+ + H_2O \rightarrow Co(NH_3)_5(H_2O)^{2+} + Cl^- \qquad k = 10^{-2} \text{ s}^{-1}$$

10 increase in substitution rate with increased steric crowding

$$Co(NH_3)_5Cl^{2+} + H_2O \rightarrow Co(NH_3)_5(H_2O)^{3+} + Cl^- \qquad k = 1.7 \times 10^{-6} \text{ s}^{-1}$$

$$Co(NMe_2H)_5Cl^{2+} + H_2O \rightarrow Co(NMe_2H)_5(H_2O)^{3+} + Cl^- \quad k = 3.7 \times 10^{-4} \text{ s}^{-1}$$
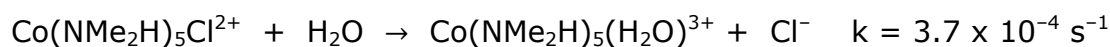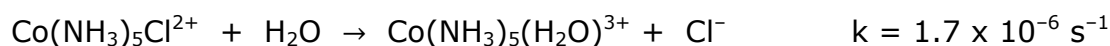
11 substitution rate increases with decrease in M—X BDE

$$Co(NH_3)_5X^{2+} + H_2O \rightarrow Co(NH_3)_5(H_2O)^{3+} + X^-$$
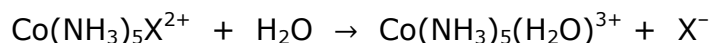
X	$k(\text{s}^{-1})$	$K_{eq}(M^{-1})$
NCS^-	4.1×10^{-10}	3.7×10^{-4}
N_3^-	2.1×10^{-9}	1.2×10^{-3}
F^-	8.6×10^{-8}	0.040
Cl^-	1.7×10^{-6}	0.90
Br^-	6.5×10^{-6}	2.9
I^-	8.3×10^{-6}	8.3
NO_3^-	2.7×10^{-5}	12.

A dissociative (S_N1) mechanism is consistent with the above data,
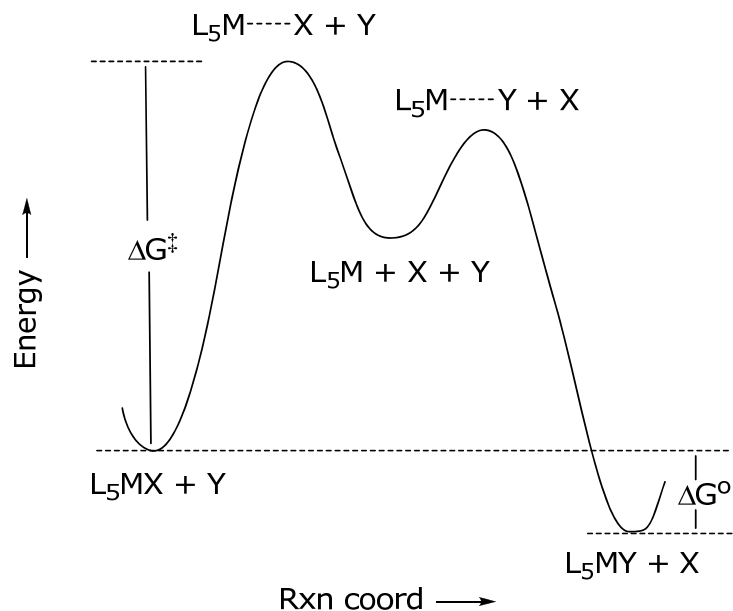
The intermediate is 5-coordinate and the rate law is independent of Y, i.e., the first barrier dominates the reaction (is highest). A rate law that accounts for this independence in Y is as follows,

$$L_5MX \underset{k_{-1}}{\overset{k_1}{\rightleftharpoons}} L_5M + X$$

$$L_5M + Y \overset{k_2}{\longrightarrow} L_5MY$$
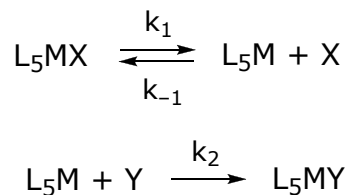
Keying on the 5-coordiante intermediate,

$$\frac{d[L_5MY]}{dt} = k_2[L_5M][Y]$$

and applying the steady-state approximation gives,

$$\frac{d[L_5MY]}{dt} = 0 = k_1[L_5MX] - k_{-1}[L_5M][X] - k_2[L_5M][Y]$$

$$[L_5M] = \frac{k_1[L_5MX]}{k_{-1}[X] + k_2[Y]}$$

11

Substitution for [L₅M] in the original expression gives,

$$\frac{d[L_5MY]}{dt} = \frac{k_1 k_2 [L_5MX][Y]}{k_{-1}[X] + k_2[Y]}$$

and if $k_2[Y] \gg k_{-1}[X]$, then the result is

$$\frac{d[L_5MY]}{dt} = k_1[L_5MX]$$

Thus the appearance of product (and disappearance of reactant) is independent of [Y], consistent with observations for substitution at most octahedral metal complexes.

On the basis of this mechanism, revisiting **8** – **11**,

8   little [Y] dependence since energy needed to surmount the initial energy barrier is sufficient to carry the reaction over the second barrier

9   removing ligand, especially an anionic one, from a positively charged complex will have a significant electrostatic contribution to the first barrier

10   increased steric congestion will destabilize the ML_6 ground state, hence the activation barrier will be decreased with increasing steric congestion about the metal

11   for a given complex, the transition state is always the same, L_5M, but the ground state energy of the complex will scale with stability of the M—X bond
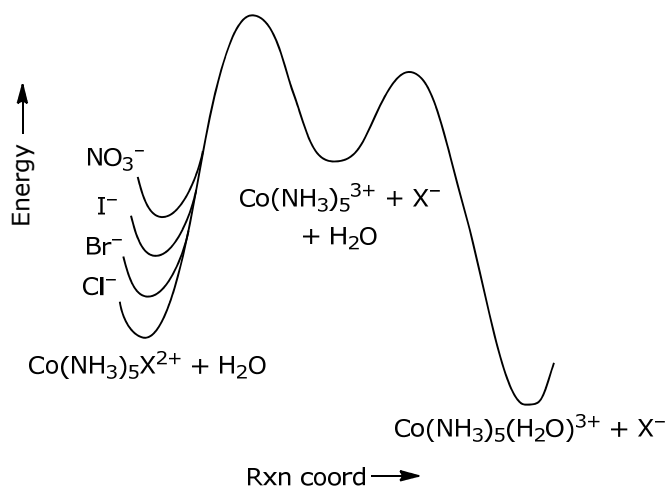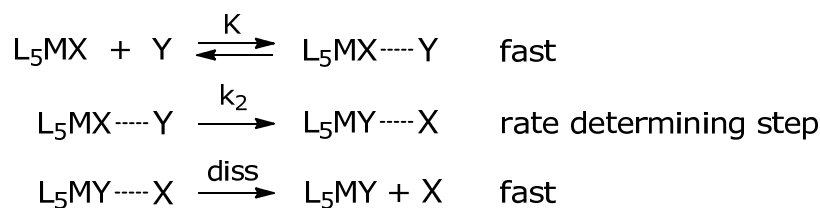

If this picture is correct, then reaction run in reverse (i.e., called anation of $Co(NH_3)_5(H_2O)^{3+}$) should be independent of X^-, this is experimentally observed.

There are some complications for the dissociative mechanism in a S_N1 limiting form. For instance, activation parameters are not consistent with a dissociative mechanism. This is especially true for $\Delta S^\ddagger$, which should be large and negative. But this is not the case.

complex	$\Delta H^\ddagger$	$\Delta S^\ddagger$	$\Delta V^\ddagger$	reference	product
$Cr(H_2O)_5NO_2^{2+}$	19.8	9	—	13	$Cr(H_2O)_6^{3+}$
$Cr(H_2O)_5SO_4^{+}$	26.5	−1	—	13	$Cr(H_2O)_6^{3+}$
$Cr(H_2O)_5N_3^{2+}$	23.2	−8	—	13	$Cr(H_2O)_6^{3+}$
$Cr(H_2O)_5CN^{2+}$	20.2	−6	—	13	$Cr(H_2O)_6^{3+}$
$Cr(H_2O)_6^{3+}$	30.3	9	—	14	$Cr(H_2O)_5Cl^{2+}$
$Cr(en)(H_2O)_4^{3+}$	27.1	−3	—	15	$Cr(H_2O)_6^{3+}$
$Mn(H_2O)_6^{2+}$	8.1	3	—	16	$Mn(H_2O)_6^{2+}$
$Fe(H_2O)_6^{2+}$	7.7	−3	—	16	$Fe(H_2O)_6^{2+}$
$Co(H_2O)_6^{2+}$	10.4	5	6−10	16,19	$Co(H_2O)_6^{2+}$
$Ni(H_2O)_6^{2+}$	13.9	9	7	16,18	$Ni(H_2O)_6^{2+}$
$Co(NH_3)_5(H_2O)^{3+}$	26.6	6.7	1.2	17	$Co(NH_3)_5(H_2O)^{3+}$
$Rh(NH_3)_5(H_2O)^{3+}$	24.6	0.8	−4.1	17	$Rh(NH_3)_5(H_2O)^{3+}$
$Ir(NH_3)_5(H_2O)^{3+}$	28.1	2.7	−3.2	17	$Ir(NH_3)_5(H_2O)^{3+}$
$Co(NH_3)_5Cl^{2+}$	23.3	−6.8	−10.6	17	$Co(NH_3)_5(H_2O)^{3+}$
$Co(NH_3)_5Br^{2+}$	23.2	−3.8	−9.2	17	$Co(NH_3)_5(H_2O)^{3+}$
$Co(NH_3)_5(NCS)^{2+}$	30.1	−0.8	−4.0	17	$Co(NH_3)_5(H_2O)^{3+}$
$Co(NH_3)_5(NO_3)^{2+}$	24.3	1.9	−6.3	17	$Co(NH_3)_5(H_2O)^{3+}$
$Co(NH_3)_5(N_3)^{2+}$	33.2	13.1	16.8	17	$Co(NH_3)_5(H_2O)^{3+}$

An explanation for this anomalous observation is the occurrence of an interchange mechanism,

$$L_5MX + Y \underset{}{\overset{K}{\rightleftharpoons}} L_5MX\text{-----}Y \qquad \text{fast}$$

$$L_5MX\text{-----}Y \xrightarrow{k_2} L_5MY\text{-----}X \qquad \text{rate determining step}$$

$$L_5MY\text{-----}X \xrightarrow{diss} L_5MY + X \qquad \text{fast}$$

Also, electronic factors must be considered. For instance, H_2O exchange data for trivalent and trivalent cations cannot be explained solely on the basis of charge.

$$M(OH_2)_6^{n+} + \text{*}OH_2 \xrightarrow{k} M(OH_2)_5(\text{*}OH_2)^{n+} + OH_2$$

labeled water (^{18}O)

13
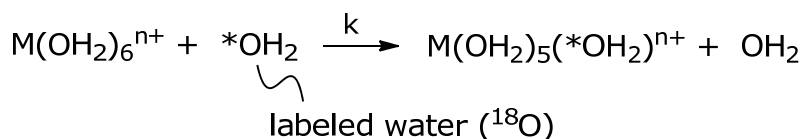
Divalent ions:

	V^{2+}	Mn^{2+}	Fe^{2+}	Co^{2+}	Ni^{2+}	Ru^{2+}
k, s^{-1}	89	2.1×10^7	4.4×10^6	3.2×10^6	3.2×10^4	1.8×10^{-2}
$\Delta H^{\ddagger}$, kJ mol^{-1}	62	33	41	47	57	88
$\Delta S^{\ddagger}$, J K^{-1}mol^{-1}	-0.4	$+6$	$+21$	$+37$	$+32$	$+16$
$\Delta V^{\ddagger}$, cm^{3}mol^{-1a}	-4.1	-5.4	$+3.8$	$+6.1$	$+7.2$	-0.4
Electronic Config.	t_{2g}^3	$t_{2g}^3 e_g^2$	$t_{2g}^4 e_g^2$	$t_{2g}^5 e_g^2$	$t_{2g}^6 e_g^2$	t_{2g}^6
Ionic Radius, Å^b	0.79	0.83	0.78	0.74	0.69	0.73

Trivalent ions:

	Ti^{3+}	V^{3+}	Cr^{3+}	Fe^{3+}	Ru^{3+}	Ga^{3+c}
k, s^{-1}	1.8×10^5	5.0×10^2	2.4×10^{-6}	1.6×10^2	3.5×10^{-6}	4.0×10^2
$\Delta H^{\ddagger}$, kJ mol^{-1}	43	49	109	64	90	67
$\Delta S^{\ddagger}$, J K^{-1}mol^{-1}	$+1$	-28	$+12$	$+12$	-48	$+30$
$\Delta V^{\ddagger}$, cm^{3}mol^{-1a}	-12.1	-8.9	-9.6	-5.4	-8.3	$+5.0$
Electronic Config.	t_{2g}^1	t_{2g}^2	t_{2g}^3	$t_{2g}^3 e_g^2$	t_{2g}^5	$t_{2g}^6 e_g^4$
Ionic Radius, Å^b	0.67	0.64	0.61	0.64	0.68	0.62

The exchange rates are explained by crystal field activation energies (CFAE). The CFAE does not explicitly account for $\Delta G^{\ddagger}$— it is the energy difference between the ML_6 octahedral complex and the ML_5 square pyramidal complex (C_{4v}). Though not rigorously $\Delta G^{\ddagger}$, it very nicely scales with $\Delta G^{\ddagger}$.

electron configuration	octahedral CFSE	square pyramidal CFSE	CFAE
d^0	0	0	0
d^1	4	4.6	-0.6
d^2	8	9.1	-1.1
d^3	12	10.0	2
d^4(strong field)	16	14.6	1.4
d^4(weak field)	6	9.1	-3.1
d^5(strong field)	20	19.1	0.9
d^5(weak field)	0	0	0
d^6(strong field)	24	20.0	4
d^6(weak field)	4	4.6	-0.6
d^7(strong field)	18	19.1	-1.1
d^7(weak field)	8	9.1	-1.1
d^8	12	10	2.0
d^9	6	9.1	-3.1
d^{10}	0	0	0