

# Dynamics of ligand substitution in labile cobalt complexes resolved by ultrafast T-jump

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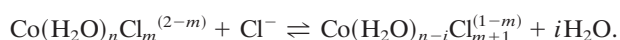
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Contributed by Ahmed H. Zewail, July 15, 2008 (sent for review June 15, 2008)

Ligand exchange of hydrated metal complexes is common in chemical and biological systems. Using the ultrafast T-jump, we examined this process, specifically the transformation of aqua cobalt (II) complexes to their fully halogenated species. The results reveal a stepwise mechanism with time scales varying from hundreds of picoseconds to nanoseconds. The dynamics are significantly faster when the structure is retained but becomes rate-limited when the octahedral-to-tetrahedral structural change bottlenecks the transformation. Evidence is presented, from bimolecular kinetics and energetics (enthalpic and entropic), for a reaction in which the ligand assists the displacement of water molecules, with the retention of the entering ligand in the activated state. The reaction time scale deviates by one to two orders of magnitude from that of ionic diffusion, suggesting the involvement of a collisional barrier between the ion and the much larger complex.

Coordinated metal ions, besides being of fundamental interest in the chemical literature, are central to biological catalysis and function, as in, e.g., metabolism (1, 2). Among these, cobalt complexes are structurally prototypical systems that are biologically relevant in, e.g., vitamin B<sub>12</sub> function (3) and biomedical applications of cancer therapy (4, 5). Ligand substitution reactions (6–8), which involve the replacement of the ligand coordinated to the metal ion by a free one(s) from solution, are multistep processes and part of the hydration mechanism in aqueous media. The exchange, which is temperature- or ligand concentration-sensitive, in many cases is accompanied by dramatic color changes.

The studies reported here focus on the aquachloro complexes of cobalt(II). Steady-state, optical, and x-ray absorption studies (9, 10) have revealed that the complex in aqueous halide solution  $\text{Co}(\text{H}_2\text{O})_m\text{X}_n^{(2-n)+}$  ( $\text{X} = \text{Cl}^-$ ) exists with different number of coordinated chloride, namely,  $[\text{Co}(\text{H}_2\text{O})_6]^{2+}$ ,  $[\text{Co}(\text{H}_2\text{O})_5\text{X}]^+$ ,  $[\text{Co}(\text{H}_2\text{O})_4\text{X}_2]$ ,  $[\text{Co}(\text{H}_2\text{O})_3\text{X}_3]^-$ , and  $[\text{CoX}_4]^{2-}$ ; remaining charge compensation comes from the added chloride salt, in our case LiCl. The first three species have an octahedron configuration, whereas the latter two adopt a tetrahedron configuration because of the crystal field stabilization energy (9, 11). The striking spectroscopic shift from pink to dark blue when increasing  $[\text{Cl}^-]$  or temperature is due to the shift of equilibrium from the octahedral to the tetrahedral structure, each with a characteristic absorption. Upon sudden temperature (e.g., T-jump) or concentration change, the equilibrium changes, and coordinated water molecules gradually get replaced by free chloride ions. Accompanying this change is the structural interconversion from the octahedral to the tetrahedral configuration:



[1]

For this complex reaction, it is important to elucidate the nature of the dynamics and the free energy surface. Here, using the ultrafast T-jump (12, 13), we systematically probed the substitution processes involved over a wide range of concentration, temperature, and time scale. By carefully select-

ing the reactant concentration and the initial temperature, it was possible to capture the elusive intermediates. The experimental results show that along the reaction coordinate, the formation of the final product, tetrachloro tetrahedral species from the hydrated reactant, hexaaqua octahedral species, is a sequential substitution process, with a rate-limiting configurational change from the octahedral to the tetrahedral coordination. We discuss the relevance of the measured rates to the mechanism and to the collision-controlled entry to the activated complexes.

## Results and Discussion

To understand the mechanism of each individual reaction, the transition state needs to be properly defined. The mechanisms of the reactions between the positive metal ion and ligands in aqueous solution are generally classified to be of three types, as proposed by Lanford and Gray in 1965 (6); associative, dissociative, and interchange. Based on the kinetic studies of activation volume (14), the substitution in octahedral aqua cobalt complexes is generally believed to favor a dissociative interchange activation (15–17); bond breakage is involved in the formation of the activated complex of decreased coordination number. The rates and the activation energies reported here indicate that association is an essential process; the incoming ligand is significantly involved in bond formation and the activated complex, as discussed below.

**Coordination Rates and the Activated State.** The steady-state and the transient behaviors are given, respectively, in Figs. 1 and 2 for various concentrations and initial temperatures. Distinctive transient behavior is observed at different wavelengths. A decay is observed (Fig. 2A) for a probing wavelength of 480 nm, reflecting the depletion of the initial population of hexaaqua complexes with rates that are concentration dependent. For detection wavelength between 550 and 630 nm, a rise or decay is observed (Fig. 2B) depending on the ligand concentration. The behavior in this region is determined by the accumulation or depletion of intermediate populations. For probing wavelengths 630 nm, a rise in absorption is detected (Fig. 2C) due to the formation of the final chloro cobalt complexes.

For more quantification, the datasets of all transients recorded under different conditions were globally fitted with a multiphase exponential model from which we obtained consistently the amplitudes and rate constants (shared as global parameters). The results indicate that three prominent components are present:  $k_{\text{initial}}^{-1}$  (200–1,000 ps),  $k_{\text{limit}}^{-1}$  (1–10 ns), and  $k_{\text{final}}^{-1}$  (200–1,000 ps); the components vary, as discussed below. The first rate process,  $k_{\text{initial}}$ , only appears for samples at low to medium  $[\text{Cl}^-]/[\text{Co}^{2+}]$  ratio (<5.0), representing the relatively fast sub-

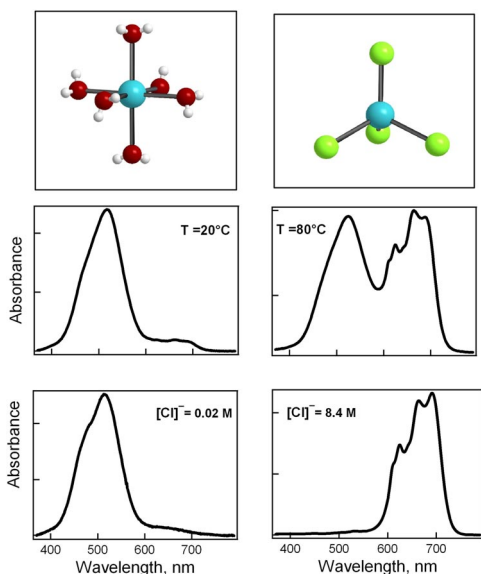
Author contributions: H.M., C.W., and A.H.Z. performed research; and H.M. and A.H.Z. wrote the paper.

The authors declare no conflict of interest.

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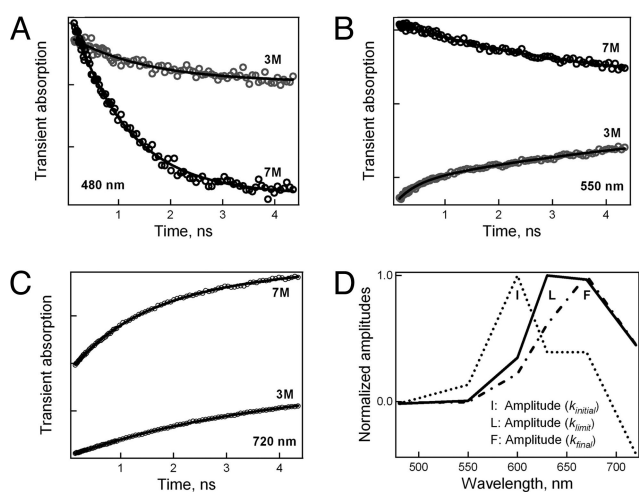
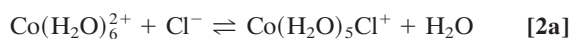
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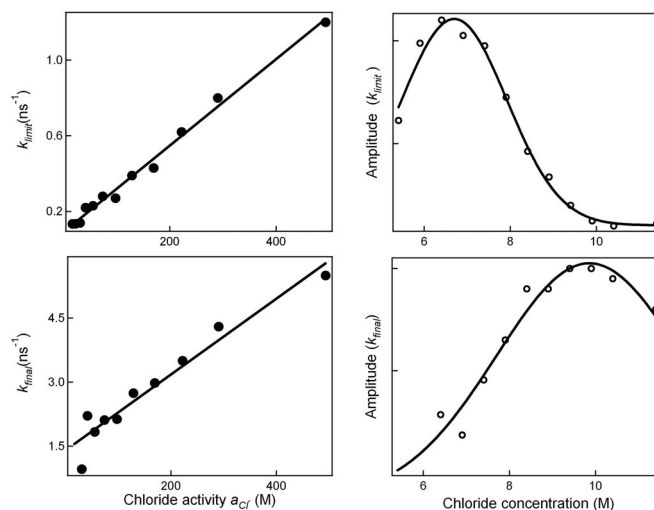


**Fig. 1.** Octahedron and tetrahedron structures and the spectra of the cobalt complexes. Spectroscopic evidence of equilibrium shift at different sample temperatures (*Middle*) and ligand concentration (*Bottom*) are shown with the two structures (*Top*).

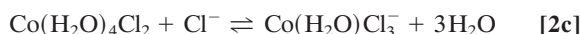
stitution process of the octahedron configuration (Eq. 2a and b). After this initial process, a slower rate step has an amplitude that peaks between  $k_{\text{initial}}$  and  $k_{\text{final}}$  processes (Fig. 2D), and indicates that the octahedral–tetrahedral structural change (Eq. 2c) is the rate-limiting step of the sequential substitution, as discussed below. Study of the concentration dependence of this amplitude (Fig. 3) shows the significant shift of the amplitude with concentration. Finally, at medium to high  $[\text{Cl}^-]/[\text{Co}^{2+}]$  ratios ( $>12$ ), a relatively fast process with rate constant  $k_{\text{final}}$  is recovered, which is assigned to the substitution rate of the tetrahedral chlorocobaltic product (Eq. 2d):



**Fig. 2.** Representative transients for cobalt complexes at different wavelengths. (A) Decay curves, which represent the depletion of initial reactants, the hexaqua octahedral species, with rates depending on concentration of the ligand. (B) Rise or decay curves representing the formation or depletion of the intermediate states. (C) Rising curves represent formation of the final product, the tetrachloro tetrahedral species. (D) The amplitude of the observed rates have distinctive peaks and blue shift from  $k_{\text{initial}}$  to  $k_{\text{final}}$  behavior.



**Fig. 3.** Rates and their amplitude dependencies on concentration. (*Left*) The rates (shown here:  $k_{\text{imit}}$  and  $k_{\text{final}}$ ) follow a linear relationship with chloride activity  $a_{\text{Cl}^-}$ . (*Right*) The amplitude of the observed rates dramatically shifts with concentration.

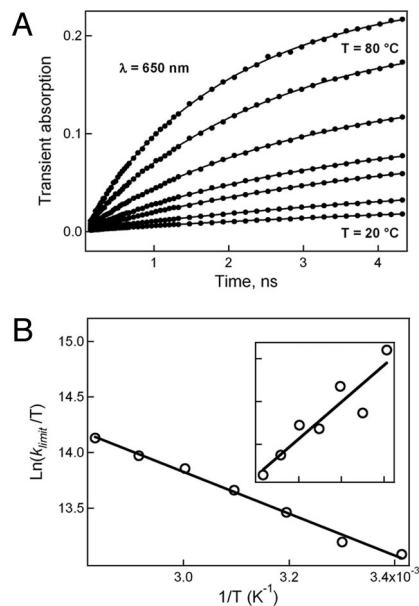


In Fig. 3, we plot the concentration dependence of the reaction rates which follows a linear relationship with the chloride activity ( $a_{\text{Cl}^-}$ );  $k = k_{\text{ligand}} \times a_{\text{Cl}^-} + k_{\text{water}}$ . Here, the slope ( $k_{\text{ligand}}$ ) and intercept ( $k_{\text{water}}$ ) denote the rate constant of ligand (chloride) or water attack, respectively. The mean activity of chloride  $a_{\text{Cl}^-}$  is given by  $a_{\text{Cl}^-} = [\text{Cl}^-]10^{0.19[\text{Cl}^-]-0.53}$  (10) and is significant for solutions of high concentration ( $>5$  M). It was anticipated that the substitution in octahedral complexes would follow a dissociative interchange pathway (15–17) in which the rate of leaving water molecule(s) becomes a determining step. However, the observed linearity studied over a wide range and up to 13 M, suggests that the chloride anion is the rate-limiting step of the bimolecular process. Thus, it is an interchange mechanism in which the bond-making association is essential.

Further support of this notion comes from the study of the temperature dependence and energetics of the activated state. The activation energy ( $E_a$ ) and entropy ( $\Delta S^\ddagger$ ) is measured from the Eyring relationship (Eq. 3) of observed rate constants vs. temperature,

$$k = \frac{k_B T e}{h} e^{-E_a/RT} e^{\Delta S^\ddagger/R}, \quad [3]$$

where  $e$  is expressed to calculate the activation energy, not enthalpy ( $\Delta H^\ddagger = E_a - RT$ ). Here  $k_B$  denotes the Boltzmann constant,  $R$  the gas constant, and  $T$  the absolute temperature. The data shown in Fig. 4 give the activation energy  $E_a$  and the entropy  $\Delta S^\ddagger$  as  $\approx 15.6 \pm 0.6$  kJ/mol and  $\approx -43.7 \pm 2.0$  J/mol·K, respectively. The negative entropy value suggests that in the activated complex, the entering ligand and departing water are rotationally and translationally confined. The nearly 16 kJ/mol activation energy deduced from the Eyring relationship is nearly threefold smaller than the hydration energy of cobalt complexes ( $\approx 47$  kJ/mol) (14). The origin of the low activation energy can be explained as due to ligand-assisted labilization process, for which the activation energy is compensated by the energy of chloride in the coordinated position, to assist the leaving water.



**Fig. 4.** Temperature dependence of reaction rates. (A) The transients measured by absorption change at different temperatures in the range of 20°C–80°C. (B) The Eyring plot of  $\ln(k_{\text{limit}} T^{-1})$  vs.  $T^{-1}$  gives the activation energy of 16 kJ/M. (Inset) The temperature dependence in  $\ln(k_{\text{initial}} T^{-1})$  vs.  $T^{-1}$  has a negative activation energy.

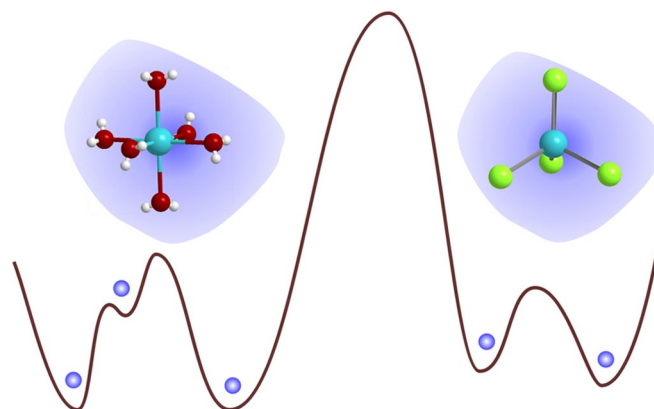
Swift (18) studied the conversion of cobalt aqua ions,  $\text{Co}(\text{H}_2\text{O})_4^{2+} + 2\text{H}_2\text{O} \rightleftharpoons \text{Co}(\text{H}_2\text{O})_6^{2+}$ , and observed the relaxation time of the structural conversion to be  $\approx 50$ – $200$  ms. A comparison can be made between the relaxation time for the above process and the chloride-assisted structural conversion (Eq. 2c); over the broad range of concentrations studied here, chloride ion participation enhances the rate by seven to eight orders of magnitude. The labilization effect of the ligand arises from the significant reduction in the activation barrier (both enthalpic and entropic), in accord with an associative interchange process.

**Ionic Diffusion and Collisions.** Because the reactions involve bimolecular collisions in solution, one should consider the effect of diffusion. At low electrolyte concentration, the diffusion of two ions with charges  $Z_1$  and  $Z_2$  may be estimated by using Debye's theory,

$$k_D = 4\pi N_0 D r \left( \frac{U_e / k_B T}{e^{(U_e / k_B T)} - 1} \right) \quad [4]$$

where  $D = D_1 + D_2$ ,  $D_1$  and  $D_2$  denote the diffusion coefficients of the ions,  $U_e = z_1 z_2 e^2 / 4\pi\epsilon r$  the electrostatic potential,  $N_0$  Avogadro's number,  $\epsilon$  the dielectric constant, and  $r$  the distance of closest approach of the two ions (19). From the Stokes–Einstein equation [ $D_0 = k_B T / 6\pi\eta r$ ], the diffusion coefficient for  $\text{Cl}^-$  in water is estimated to be  $4.4 \times 10^{-5} \text{ cm}^2 \text{ s}^{-1}$ ; the contribution of the complex to the diffusion rate can be neglected because its size is much larger than that of the chloride ion. The estimated typical diffusion-controlled rate is in the range of  $1$ – $50 \times 10^9 \text{ M}^{-1} \text{ s}^{-1}$ . When compared with the observed reaction rates, it is faster by one to two orders of magnitude. Therefore, the process must take into consideration the efficiency of collisions and the geometrical constrain between the large complex and small chloride ion (20).

**Mechanism.** From the above results, the following picture of a two-step process can be painted (Fig. 5). First, the ligand diffuses into the second coordination sphere and forms an ion pair by



**Fig. 5.** Schematic of the free energy surface of the ligand substitution in labile cobalt complexes, with the rate-determining step being that of structural change.

electrostatic interactions. This is a preassociation process that follows the notion of Eigen and Wilkins (21, 22). The reaction takes place when successful collisions are made. Because the cobalt complexes become more negatively charged and less sterically crowded as the reaction proceeds toward the product, we would predict that the kinetics of water attack should accelerate and that of the chloride should slow down. Indeed, the observed trend of the rate constants (Table 1) supports this simple picture. Chloride is anated to the complex in a stepwise manner along the reaction coordinate, with the rate-limiting step being the structural conversion from octahedral to tetrahedral coordinate. The dynamical bottleneck may arise from the large desolvation enthalpy (two extra water molecules are removed when the substitution is coupled with the structural change) as well as possible contributions of entropic penalty from rearrangement of the activated complex configuration. Without ligand assistance, water exchange is orders of magnitude slower ( $\mu\text{s}$  or longer) (14, 17).

## Conclusion

The ultrafast T-jump study reported here shows that the substitution of the Co(II) ion in aqueous solution occurs in multiple steps, with the rate-limiting step being the octahedral-to-tetrahedral structural change. The reaction shows features of an associative interchange mechanism, where the ion in the coordination shell is critical for the liberation of water and for structural changes. The “simultaneous” interaction of the entering and departing group with the metal center has been elucidated for similar octahedral complexes of Cr in theoretical simulations using transition path sampling (23). Favorable interactions with the metal center between the entering and departing ions significantly lower the activation energy. Although there are two initial steps along the reaction coordinate of the Co system, only one rate,  $k_{\text{initial}}$ , was observed. This indicates that the process of  $k_{\text{initial}}$  could be a composite one. The observed “abnormal” negative value of activation enthalpy deduced from  $k_{\text{initial}}$  vs.  $T$  (Fig. 4 Inset) supports the

**Table 1.** Rate constants for the ligand substitution

Rate constants	$k_{\text{initial}}^*$	$k_{\text{limit}}^\dagger$	$k_{\text{final}}^\ddagger$
$k_{\text{water}} \times 10^9, \text{ s}^{-1}$	0.02	0.1	1.4
$k_{\text{ligand}} \times 10^9, \text{ s}^{-1} \text{ M}^{-1}$	0.8	0.002	0.009

The rates follow a linear relationship with activity  $a_{\text{Cl}^-}$ :  $k = k_{\text{ligand}} \times a_{\text{Cl}^-} + k_{\text{water}}$ , where  $a_{\text{Cl}^-}$  is given by  $a_{\text{Cl}^-} = [\text{Cl}^-]$  for  $k_{\text{initial}}$  at low chloride concentrations (\*) and by  $a_{\text{Cl}^-} = [\text{Cl}^-]^{0.19} [\text{Cl}^-]^{-0.53}$  for  $k_{\text{limit}}$  and  $k_{\text{final}}$  at high chloride concentrations (†).

argument that this multistep process probably includes a fast preequilibrium.

With this ultrafast T-jump method, a natural extension of our research is the study of the dynamics of metal complexes associated with biomolecules, such as those involving proteins or DNA.

## Methods

**Ultrafast T-Jump.** Details of the ultrafast T-jump setup are given in previous articles from this laboratory (12, 13). Briefly, the laser system consists of two parallel optical parametric amplifiers (OPA) pumped by a femtosecond Ti/Sapphire amplifier. The pump pulses were set at 1.5  $\mu\text{m}$  (70  $\mu\text{J}$  per pulse), the overtone of the OH stretching and bending frequency. The probe pulse can be tuned to arbitrary wavelengths, from 240 nm to 800 nm, in this case, at the absorption bands of the octahedral and tetrahedral species. This selectivity allows for a global analysis of all transients and hence the significant compo-

nents of transient relaxations. The T-jump increases the temperature by 5°C–10°C within 5–10 ps, reaching the time scale of water (the medium) relaxation. The equilibrium is perturbed by the temperature change, and the relaxation toward the new equilibrium is probed by using a delayed second optical pulse, following the infrared pulse of the T-jump. All steady-state measurements were made by using a temperature-controlled UV-Vis spectrometer (Cary 500).

**Cobalt Complex Preparation.** Solutions of Co(II) chloride (from Aldrich, reagent grade) were prepared with Barnstead Nanopure water (18M $\Omega$ ), and the different  $[\text{Cl}^-]/[\text{Co}^{2+}]$  ratio (from 2 to 6500) was tuned by adjusting the lithium chloride (from Aldrich, reagent grade) concentration in the solutions studied.

**ACKNOWLEDGMENTS.** This work was supported by the National Science Foundation.

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