ration and biological mechanisms of action of analogous complexes which have radiopharmaceutical applications.

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Electron-Transfer Reactions of Encapsulated Transition Metal Complexes. Oxidation of (4,4'-Bipyridine)pentaammineruthenium(II) by (Ethylenediaminetetraacetato)cobaltate(III)

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The encapsulation of pentaammine(ligand)ruthenium(II) (ligand = pyrazine or bipyridine) with cyclodextrins was investigated. The equilibrium constants ranged from ~20 to 100. The effect of encapsulation on electron-transfer rates was also determined, and a specific orientation of reactants within the precursor complex is discussed.

Introduction

During the last 3 decades, considerable progress has been made in understanding the mechanistic details of outer-sphere electron-transfer reactions. Recently, several excellent review articles have appeared on this subject.[1] One aspect which has remained relatively unexplored, however, is the nature of reactant orientation within the precursor complex.

Orientational effects have been postulated by researchers studying redox reactions of metalloproteins possessing heme rings.[2] For example, Sutin and others suggest that in cytochrome *c* the electron is passed to the iron center via the solvent-exposed edge of the porphyrin ring.[3] Using simple transition metal complexes, Haim and co-workers have examined the outer-sphere electron-transfer reactions for a series of pentaammine(*N*-heterocycle)-ruthenium complexes with varying redox partners.[4] Haim postulated that, for certain couples, electron transfer occurred via the ammine ligands of the ruthenium complex while, for others, the *N*-heterocycle was involved. His discussion was based upon the Marcus cross relation for outer-sphere processes where the separation distance between the two metal centers at the point of electron transfer may be roughly assessed. Meyer also showed that intimate contact between coordination spheres occurs in outer-sphere electron transfer.[5] Studies by Lappin and co-workers have offered evidence for stereoselectivity in the ion-pair precursor structure from oxidation studies of cobalt(II) complexes.[6]

In order to provide a greater understanding of the role of noncoordinating ligands (thereby precursor complex orientation) in the outer-sphere electron-transfer process, we have begun a series of studies on the effect of encapsulation of aromatic ligands on the rate of redox reactions. Selective encapsulation was accomplished using cyclodextrins (CD's) (see Figure 1), which are known to possess high affinities toward aromatic organic species.[7]

$$X_5M\text{–bpy} + CD \underset{\phantom{K_{CD}}}{\overset{K_{CD}}{\rightleftharpoons}} X_5M\text{–(bpyCD)}$$
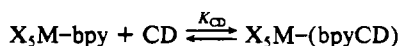
In this study, we have measured the oxidation rate of [Ru-$(NH_3)_5(4,4'bpy)]^{2+}$ with $[Co(EDTA)]^-$ in the presence of dimethyl-β-cyclodextrin (dmβCD). In addition, the equilibrium constants for the encapsulation of coordinated ligands were in-

Table I. Equilibrium Constants for Cyclodextrin/Metal Inclusion Complexes

complex	CD	K_{CD}	ref
$[Ru(NH_3)_5(bpy)]^{2+}$	dmβ	98 ± 8[a]	this work
$[Ru(NH_3)_5(pyz)]^{2+}$	dmβ	19 ± 1[a]	this work
$[Ru(NH_3)_5(bpy)]^{2+}$	α	23 ± 3[a]	this work
ferrocenecarboxylate	β	483	b
carbplatin	dmβ	295	c
carbplatin	α	165	c

[a] 0.05 M sodium bicarbonate (pH = 8.5), T = 25.0 °C, from spectral data (supplementary Table IIA–C). [b] Osa, T.; Kobayashi, N. *Chem. Lett.* 1986, 421. [c] Alston, D.; Lilley, T. H.; Stoddart, J. F. *J. Chem. Soc., Chem. Commun.* 1985, 1600.

dependently determined using spectrophotometric techniques.

Experimental Section

The metal complexes Na[Co(EDTA)], [Ru(NH$_3$)$_5$(4,4'bpy)](PF$_6$)$_2$, and [Ru(NH$_3$)$_5$(pyz)](PF$_6$)$_2$ were prepared using literature methods.[8,9] Their visible spectra agree with literature reports. The 0.05 M sodium bicarbonate (Aldrich) buffer was prepared using a Beckman pH meter. Heptakis(2,6-di-*O*-methyl)-β-cyclodextrin (Cyclolab or Sigma) was chosen because of its correct interior dimensions for including the bipyridyl moiety and its high solubility in water.[10]

(1) Sutin, N. *Prog. Inorg. Chem.* 1983, *30*, 441. Cannon, R. D. *Electron Transfer Reactions*; Butterworth: Boston, MA, 1980. Newton, M. D.; Sutin, N. *Annu. Rev. Phys. Chem.* 1984, *35*, 1984. Marcus, R. A.; Sutin, N. *Biochim. Biophys. Acta* 1985, *811*, 265. Sutin, N.; Brunschwig, B. S.; Creutz, C.; Winkler, J. R. *Pure Appl. Chem.* 1988, *60*, 1817. Haim, A. *Comments Inorg. Chem.* 1985, *4*, 113. Gray, H. B.; Fox, L. S.; Kazik, M.; Winkler, J. R. *Science* 1990, *247*, 1069.
(2) Wilkins, R. G.; Balahura, R. J. *Biochim. Biophys. Acta* 1983, *724*, 465. Wilkins, R. G.; Eaton, D. R. *J. Biol. Chem.* 1978, *253*, 908. Cassatt, J. C.; Bender, J. W.; Marini, M. P. *Biochemistry* 1975, *14*, 5470.
(3) Sutin, N.; Creutz, C.; Gray, H. B.; McArdle, J. V. *J. Am. Chem. Soc.* 1974, *96*, 5737.
(4) Haim, A.; Phillips, J. *Inorg. Chem.* 1980, *19*, 76. Haim, A.; Phillips, J.; Armstrong, R. E. *J. Am. Chem. Soc.* 1977, *99*, 1416.
(5) Powers, M.; Meyer, T. J. *J. Am. Chem. Soc.* 1980, *102*, 1289. Curtis, J. C.; Meyer, T. J. *J. Am. Chem. Soc.* 1978, *100*, 6286.
(6) (a) Osvath, P.; Lappin, A. G. *Inorg. Chem.* 1987, *26*, 195. (b) Osvath, P.; Marusak, R. A.; Lappin, A. G. *Inorg. Chem.* 1987, *26*, 4292. (c) Marusak, R.; Lappin, A. G. *Inorg. Chem.* 1987, *26*, 4292.
(7) Clarke, R. J.; Coates, J. H.; Lincoln, S. F *Adv. Carbohydr. Chem.* 1988, *46*, 205.
(8) Dwyer, F. P.; Garvan, F. L. *Inorg. Synth.* 1960, *6*, 192.
(9) Haim, A.; Yen, A.; Tanner, M.; Ludi, A. *Inorg. Chim. Acta* 1979, *33*, 51.

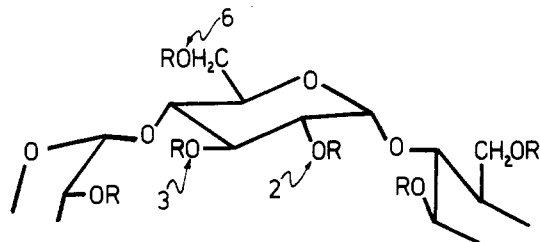†Present address: Department of Chemistry, New Mexico State University, Las Cruces, NM 88003.

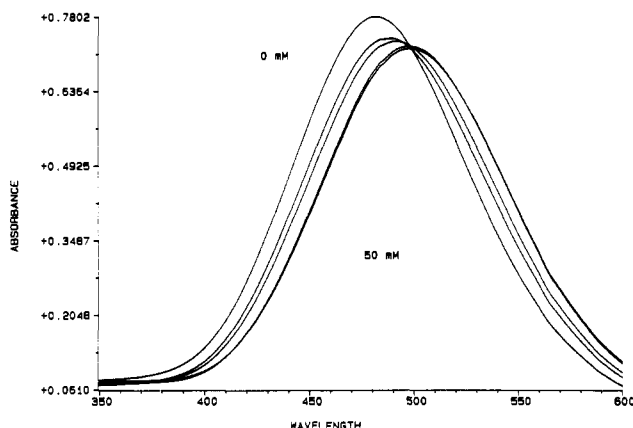**Figure 1.** Glucopyranosyl subunit in the β-cyclodextrin molecule (7 units arranged in a torus) with R = H or CH₃.

Figure 2. Changes in the visible spectrum [Ru(NH₃)₅(bpy)]²⁺ at several [dmβCD]'s: 0.0, 5.0, 10, 40, and 50 mM. Conditions: T = 25.0 °C, I = 0.1 M (NaHCO₃), pH = 8.5, [Ru] = 6.5 × 10⁻⁵ M.

Kinetic measurements were made using a Dionex D-110 stopped-flow spectrophotometer interfaced with a computerized data acquisition system. Observed rate constants were obtained from absorbance data using OLIS fitting software (On-Line Instruments, Jefferson, GA). Pseudo-first-order conditions were maintained with the [Co(III)] kept in at least 10-fold excess over the [Ru(II)]. Each observed rate constant is an average of three to five trials.

Equilibrium constants were determined spectrophotometrically using a Hewlett Packard 8452A diode array spectrophotometer. A solution of the desired ruthenium(II) complex was placed in a 1-cm cell and the spectrum measured after each incremental addition of solid CD. From the absorbance changes in the visible spectrum, the equilibrium constant was obtained as described by Connors.[11]

Cyclic voltammetric measurements were made using a Cypress System I electrochemical setup (Lawrence, KS). A glassy-carbon working electrode was used in conjunction with a platinum auxiliary and a Ag/AgCl reference electrode.

Results and Discussion

Encapsulation of the ruthenium(II) complex was demonstrated by changes in the UV-vis absorbance spectrum. As may be seen in Figure 2, increasing concentrations of dmβCD cause a shift in the visible absorption band to 496 nm (ε = 1.1 × 10⁴ M⁻¹ cm⁻¹). The presence of an isosbestic point indicates that only a 1:1 CD–metal complex adduct is formed in the concentration range used for this study. Plotting $1/\Delta A$ versus $1/[CD]$ results in a straight line, Figure 3, from which the association constant, K_{CD}, may be obtained. Determinations at different wavelengths gave the same value for K_{CD}, again indicating that only one equilibrium was present. Studies with the pyrazine and bipyridine ruthenium(II) complexes show identical behavior, Table I. The size of these equilibrium constants is consistent with other systems. It may be noted that decreasing the length of the aromatic ligand results in a decrease in K_{CD}. This is probably due to larger steric effects of the ruthenium center with the shorter pyrazine ligand compared to bipyridine. In the bipyridine system, the nitrogen heterocycle is better exposed and can more easily be encapsulated.

The site of encapsulation may be linked to the organic ligand considering that the visible absorption band at 482 nm is a metal
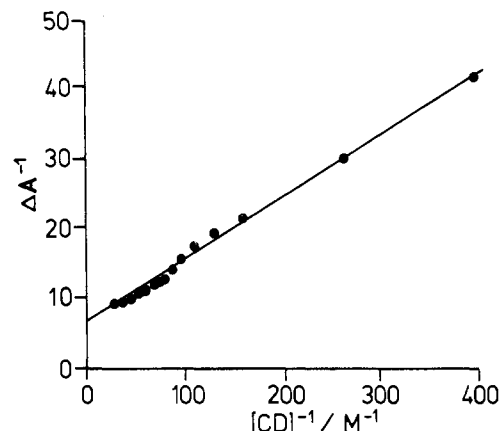
(10) Palepu, R.; Reinsborough, V. C. *Aust. J. Chem.* **1990**, *43*, 2119.
(11) Connors, K. A. *Binding Constants*; Wiley: New York, 1987; p 141.

Figure 3. Plot of $1/\Delta A$ versus $1/[dmβCD]$ for [Ru(NH₃)₅(bpy)]²⁺. The solid line is calculated using the best equilibrium constant. See Table I for conditions.
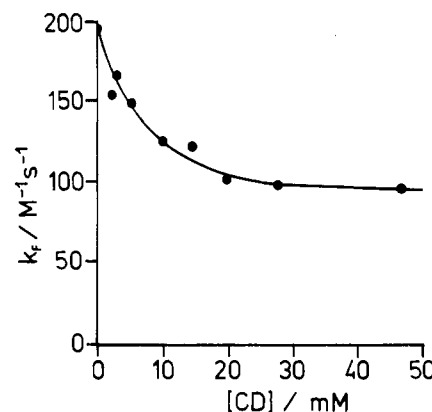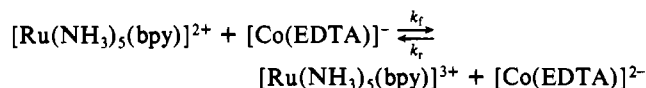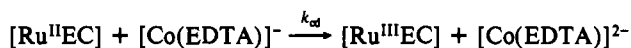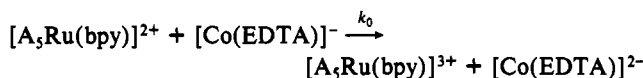

Figure 4. Plot of k_f versus [dmβCD]. The solid line is calculated using the parameters in the text. See text for conditions.

to ligand (Ru → bpy) charge-transfer band. Significant perturbation of this band by the addition of CD would be expected if the N-heterocycle rather than an ammonia were the site of encapsulation. The latter would be unexpected anyway because for strong inclusion the guest molecule must fit tightly within the CD cavity and be hydrophobic in nature.[12]

Kinetics. The electron-transfer reaction

$$[\text{Ru(NH}_3)_5(\text{bpy})]^{2+} + [\text{Co(EDTA)}]^- \underset{k_r}{\overset{k_f}{\rightleftharpoons}}$$

$$[\text{Ru(NH}_3)_5(\text{bpy})]^{3+} + [\text{Co(EDTA)}]^{2-}$$

was originally studied by Haim and Phillips who showed it to occur via a reversible outer-sphere mechanism.[4] The rate law for this reaction may be written as

$$-d[\text{Ru(II)}]/dt = k_f[\text{Ru(II)}][\text{Co(III)}] + k_r[\text{Ru(III)}][\text{Co(II)}]$$

Our value for k_f of 195 ± 15 M⁻¹ s⁻¹ (pH = 8.5, I = 0.05 M, T = 25.0 °C) agrees very well with Haim's value of 156 M⁻¹ s⁻¹ (pH = 6.0, I = 0.10 M, T = 25.0 °C)[4] considering the differences in reaction conditions. A positive y-intercept was found for plots of k_{obs} versus [Co(III)] and is attributed to the reverse reaction. Due to inherent imprecision in the values for intercepts, the reverse reaction was not quantitatively investigated.

The addition of CD resulted in a decrease in the observed rate constants. The plot of k_{obs} versus [Co(III)] remains linear with a positive y-intercept but decreases in both the slope and y-intercept were observed; see supplementary data Table I. A plot of the forward rate constant versus [CD] is shown in Figure 4. At high [CD] the rate becomes constant, indicative of saturation behavior.

(12) Harata, K. In *Minutes: Proceedings of Fifth International Symposium on Cyclodextrins*; Duchene, D., Ed.; Editions de Sante: Paris, 1990; p 77.

Similar treatment of the *y*-intercept was qualitatively the same. For the forward rate, the mechanism in Scheme I may be envisioned.

Scheme I

$$[A_5Ru(bpy)]^{2+} + CD \xrightleftharpoons{K_{CD}} [Ru^{II}EC](\text{encapsulation complex})$$

$$[A_5Ru(bpy)]^{2+} + [Co(EDTA)]^- \xrightarrow{k_0}$$
$$[A_5Ru(bpy)]^{3+} + [Co(EDTA)]^{2-}$$

$$[Ru^{II}EC] + [Co(EDTA)]^- \xrightarrow{k_{cd}} [Ru^{III}EC] + [Co(EDTA)]^{2-}$$

From this mechanism, the following rate law may be written:

$$-d[Ru(II)]_T/dt = k_f[Co(III)][Ru(II)]_T$$

where

$$k_f = \frac{k_{cd} - k_0}{1 + (K_{CD}[CD])^{-1}} + k_0$$

Fitting the rate data to the above equation, using the value for k_0, determined in this study, allows the calculation of k_{cd} and K_{CD}. The values of k_0, k_{cd}, and K_{CD} are 195 ± 18 M⁻¹ s⁻¹, 95 ± 8 M⁻¹ s⁻¹, and 104 ± 9 M⁻¹, respectively. The equilibrium constant determined from the kinetic data agrees fortuitously well with the independently measured value from spectroscopic methods, strongly supportive of the proposed mechanistic scheme.

Three possible explanations for the decreased reactivity of the encapsulated complex must be considered: (1) encapsulation results in a decrease in the redox potential of the ruthenium complex, thereby decreasing the driving force of the reaction, (2) the organic ligand is intimately involved in the electron-transfer process and encapsulation inhibits this reaction pathway, or (3) the cyclodextrin sterically interferes with the reaction when encapsulating the organic ligand.

The possibility that the decreased rate reflects a change in the redox potential of the ruthenium(II)/ruthenium(III) couple was examined using cyclic voltammetry. With increasing CD concentrations, the oxidation and reduction waves occurred at the same potentials as with no CD, but a decrease in current was noted. This demonstrates that encapsulation does not have any effect on the redox potential for the ruthenium complex and therefore does not effect the driving force of the reaction. The reduction in current with increasing CD concentrations has been observed for other systems and is indicative of CD complexation.[13]
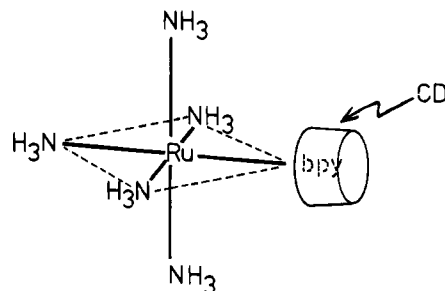
(13) Bender, M. L.; Komiyama, M. *Cyclodextrin Chemistry*; Springer-Verlag: New York, 1978. Szejtli, J. in *Inclusion Complexes*; Atwood, J. L., Davies, J. E. D., MacNicol, D. D., Eds.; Academic Press: London, 1984.

Figure 5. Representation of cyclodextrin encapsulated metal complex.

The intimate involvement of the organic ligand seems unlikely since the reaction is only decreased by half. At the high [CD]'s used in this study, greater than 90% of the ruthenium is encapsulated. If association with the organic ligand is required in the electron-transfer step, then a 90% loss of reactivity would be anticipated.

Steric arguments appear to best account for the observed rate behavior. The diameter of a typical pentaammineruthenium(II) complex is 8–9 Å, approximately the same diameter as the mouth of the cyclodextrin host.[10] When the cyclodextrin encapsulates the organic ligand, approximately half of the ruthenium complex will be shielded from collision with the cobalt(III) complex, Figure 5. If electron transfer takes place only when the two first coordination spheres come into direct contact, then the reaction would be restricted to the unhindered ammine side of the ruthenium molecule. This would result in a 2-fold statistical decrease in the reaction rate, as is observed.

From these arguments, one may postulate that electron transfer takes place through the ammine side of the first coordination sphere of ruthenium(II) and that the bipyridine is extraneous to the process. This interpretation agrees with that proposed by Haim using Marcus calculations.[4] His comparisons of reaction distances and calculated rate constants show that a close approach (ammine side) of the two centers is involved during the electron-transfer process. In addition, studies by Lappin et al. indicate that the carboxylate groups present in [Co(EDTA)]⁻ are capable of hydrogen bonding to aliphatic amine ligands on cobalt(II) centers prior to electron transfer.[6b] At present other outer-sphere electron-transfer reactions are being examined where transfer is thought to involve the aromatic ligand.[5]

Supplementary Material Available: Tables of kinetic and absorbance data (5 pages). Ordering information is given on any current masthead page.