Effects of Cyclodextrin Inclusion on the Kinetics of the Ligand Substitution Reactions of Aquapentacyanoferrate(II) and Pentacyano(N-heterocycle)ferrate(II) Complexes in Aqueous Media

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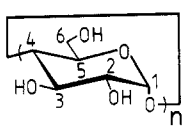
The stability constants for the inclusion complexes of a series of neutral aromatic N-heterocyclic ligands (substituted pyridines and symmetrical dipyridyls) and their pentacyanoferrate(II) complexes, $Fe(CN)_5L^{3-}$ with α- and β-cyclodextrin have been determined from ^1H NMR chemical shift and visible spectrophotometric titrations and from the kinetics of their ligand substitution reactions. The rate constants for the formation of the $[Fe(CN)_5L]^{3-}$ complexes from the reaction of the labile $[Fe(CN)_5OH_2]^{3-}$ ion with L decrease upon cyclodextrin inclusion of the entering N-heterocyclic ligand (k_f for 4-*tert*-butylpyridine, for example, decreases from 355 to 18 M^{-1} s^{-1} upon β-CD inclusion) with the magnitude of the limiting rate constant for the included ligand depending on the accessibility of the N donor atom to the five-coordinate $[Fe(CN)_5]^{3-}$ intermediate. The rate constant for the dissociations of L from $[Fe(CN)_5L]^{3-}$ complexes, in the presence of 0.20 M dimethyl sulfoxide, also decrease upon inclusion of the coordinated N-heterocyclic ligand in β-CD (k_d for $[Fe(CN)_5(4\text{-}t\text{-}Bupyr)]^{3-}$, for example decreases from 1.10×10^{-3} to 7.0×10^{-5} s^{-1}). The MLCT transition energies for $[Fe(CN)_5L]^{3-}$ complexes exhibit bathochromic shifts upon inclusion of L in the cavities of the cyclodextrins.

The cyclodextrins are naturally occurring molecular receptors which can alter the physical properties and chemical reactivities of guest molecules.[1-5] The lower members of this family of cyclic oligosaccharides consist of six (α-CD), seven (β-CD), or eight (γ-CD) α-(1→4)-linked D-(+)-glucopyranose units and take the form of relatively rigid rings with well defined internal cavities.



n = 6 α-CD

n = 7 ß-CD

n = 8 γ-CD

While the cyclodextrin exterior is hydrophilic, due to the hydroxyl groups that surround both rims of the cavity, the interior is somewhat hydrophobic and is capable of binding appropriately sized molecules. A wide variety of guest molecules can be bound within the host cavity, including apolar aliphatic and aromatic hydrocarbons (including a γ-CD complex with C_{60}[6]), polar alcohols, acids and amines, and ionic compounds. This molecular recognition, while somewhat general in nature, is analogous to that found in enzyme-substrate binding processes. As a result, a number of workers have used cyclodextrins or chemically modified cyclodextrins in simple chemical models of enzymatic systems.[7,8] Cyclodextrins are known to catalyze hydrolysis, acyl migration, decarboxylation, and oxidation reactions[4] and in some cases have yielded dramatic rate accelerations.[9]

While cyclodextrin inclusion complexes of organic compounds have been widely investigated,[5] interactions with transition metal complexes have received less attention. Inner-sphere coordination of metal ions by cyclodextrin hydroxyl oxygens has been limited to a few examples, including $[M_2(OH)_2\beta\text{-CD}\cdot 2H_2O]^{n-}$ species of first-row transition metals.[10-12] Recent interest has been focused on the use of cyclodextrins as second-coordination spheres for metal complexes.[13] Adducts in which cyclodextrin binds hydrophobic inner-sphere ligands, such as cyclopentadienes,[14] arenes,[15] 1,5-cyclooctadiene,[16] and trimethylphosphine[17] have been characterized in solution and in the solid state.

Although second-sphere coordination of transition metal complexes by solvent molecules is known to influence ligand substitution and electron transfer rate constants, the effects of cyclodextrin complexation on reactions of these types have not been well studied. In general, only a few kinetic studies of the reactions of cyclodextrin-transition metal complex adducts have been undertaken.[18-24] Recently it has been shown that the

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inclusion of the coordinated 4,4'-bipyridine on $[Ru(NH_3)_5(4,4'\text{-bpy})]^{2+}$ by heptakis(di-2,6-O-methyl)-β-cyclodextrin reduces the rate constants for its oxidation by $[Co(EDTA)]^-$.[23] Kinetic studies of ligand substitution reactions in the presence of cyclodextrins can provide a measure of the binding constants for the uncomplexed ligands.[25] Kinetic determinations of binding constants of cyclodextrins with azo dyes, by monitoring the dye complexation reaction with $Ni^{2+}(aq)$ and $Co^{2+}(aq)$, have been reported.[20-22] For steric reasons, the cyclodextrin–dye complex cannot react with the metal ions, and thus the effect of the cyclodextrin is restricted to the control of the free dye concentration. In our laboratory we have been investigating the use of ligand substitution kinetics, along with UV–visible and ^1H NMR spectroscopy, to measure the nature and extent of the inclusions of neutral and cationic aromatic N-heterocyclic ligands in α- and β-cyclodextrins.[24]

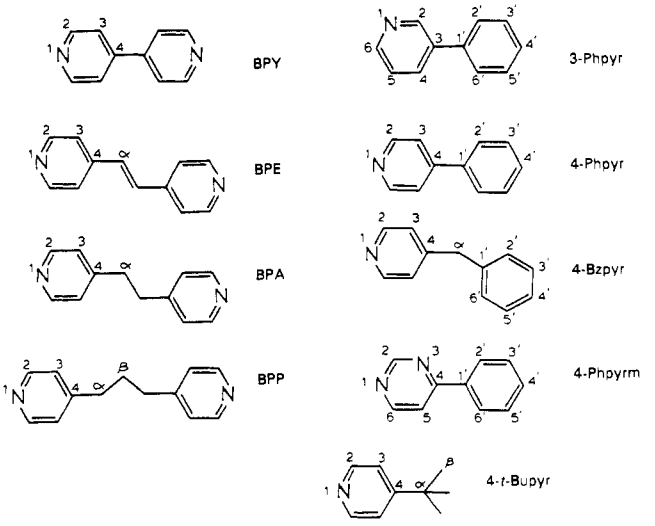
The labile aquapentacyanoferrate(II) ion is ideal for studying the effects of cyclodextrins on the kinetics of ligand substitution reactions. The properties and reactions of pentacyanoferrate(II) complexes have been thoroughly investigated over the past two decades.[26] The kinetics of the formation of substituted $[Fe(CN)_5L]^{(3-n)-}$ complexes from the aqua species and the dissociation of the coordinated L^{n+} ligand (eq 1) have been studied

$$[Fe(CN)_5OH_2]^{3-} + L^{n+} \underset{k_d}{\overset{k_f}{\rightleftharpoons}} [Fe(CN)_5L]^{(3-n)-} + H_2O \quad (1)$$

with a wide variety of anionic, neutral, and cationic ligands. The ligand substitution reactions of the aquapentacyanoferrate(II) ion have been shown to proceed by a dissociative (D) mechanism,[27-30] with the magnitude of k_f depending on the charge of the entering ligand. The majority of reported pentacyanoferrate(II) complexes contain an aromatic N-heterocycle as the sixth ligand. These diamagnetic complexes are relatively inert ($k_d < 10^{-2}\ s^{-1}$), and the intense metal-to-ligand charge transfer transition in their visible spectra allows for the convenient monitoring of the kinetics of their formation by stopped-flow spectrophotometric techniques.

In this paper we report the results of kinetic studies on the effects of the α- and β-CD inclusions of a series of neutral N-heterocyclic ligands on their ligand substitution reaction with the $[Fe(CN)OH_2]^{3-}$ ion in aqueous solution. Proton NMR spectroscopy has also been employed to determined the stability constants of the cyclodextrin-ligand inclusion complexes. The ligands used in this study include substituted pyridines and symmetrical dipyridyl species (Chart I). In contrast with mono- and disubstituted benzenes, relatively few cyclodextrin binding constants for aromatic N-heterocycles have been reported previously.[31-34] The stability constants for the inclusion of the $[Fe(CN)_5L]^{3-}$ complexes have been determined from titrations of the complexes with β-CD, employing ^1H NMR and UV–visible spectroscopy. The kinetics of the dissociation of L from $[Fe(CN)_5L]^{3-}$ in the presence of β-CD have also been investigated.

Chart I



Experimental Section

Materials. Sodium amminepentacyanoferrate(II) hydrate, $Na_3[Fe(CN)_5NH_3]\cdot 3H_2O$, was prepared by a reported procedure[35] and recrystallized from concentrated ammonia/methanol solutions. Solutions of the aquapentacyanoferrate(II) ion ($\lambda_{max} = 444$ nm, $\epsilon = 660\ M^{-1}\ cm^{-1}$)[30] were produced by dissolving the solid ammine salt in an aqueous 0.10 M NaCl solution containing a small amount of ascorbic acid to prevent oxidation by dissolved oxygen. Low concentrations of the ion ($< 5 \times 10^{-5}$ M) were used to minimized dimerization of the aqua ion. The ligands 1,3-bis(4-pyridyl)propane (BPP) (Lancaster Synthesis), pyrazine, 4,4'-bipyridine (BPY), *trans*-1,2-bis(4-pyridyl)ethylene (BPE), 1,2-bis(4-pyridyl)ethane (BPA), isoquinoline, 4-phenylpyridine (4-Phpyr), 3-phenylpyridine (3-Phpyr), 4-benzylpyridine (4-Bzpyr), 4-picoline (4-Mepyr), 4-*tert*-butylpyridine (4-*t*-Bupyr), and 4-phenylpyrimidine (4-Phpyrm) (Aldrich) were used as received. Pyridine (Fisher) was distilled twice from BaO prior to use. Solutions of the substituted pentacyanoferrate(II) complexes were prepared by adding either a slight deficiency (NMR titrations and kinetic studies) or a slight excess (UV–visible titration) of the appropriate ligand to an aqueous solution of the $[Fe(CN)_5OH_2]^{3-}$ ion. The α- and β-cyclodextrins were dried for at least 8 h at 80 °C under reduced pressure.

Kinetic Measurements. The kinetic measurements of the complex formation reactions were made by using a TDI Model IIA stopped-flow apparatus (Cantech Scientific) and data acquisition system. The temperature was maintained at 25.0 ± 0.1 °C with an external circulating water bath. The ligand solutions were prepared in a phosphate medium ($[Na_2HPO_4] = 0.0125$ M) at pH = 8.7 ± 0.1, with the ionic strength of both reactant solutions maintained at 0.10 M with added NaCl (or $NaClO_4$ in one study). The reactions were carried out under pseudo-first-order conditions of excess ligand concentrations ($[L] = (5\text{–}40) \times 10^{-4}$ M, $[Fe(CN)_5OH_2^{3-}] = (2\text{–}5) \times 10^{-5}$ M), following the formation of the $[Fe(CN)_5L]^{3-}$ product at its visible maximum. The UV–visible spectra and the kinetics of the ligand dissociation reactions were recorded on Hewlett-Packard 8452A and Cary 3 spectrophotometers. The dissociation kinetic measurements were carried out at 25.0 ± 0.1 °C in the presence of 0.20 M dimethyl sulfoxide at an ionic strength of 0.10 M (NaCl). Plots of $\ln(A_\infty - A_t)$ or $\ln(A_t - A_\infty)$ against time were linear for at least 3 half-lives, and the first-order rate constants were determined from the average of four to eight replicate experiments for the formation reactions and one or two experiments for the dissociation reactions (supplementary material).

In a typical kinetic experiment, the ligand concentration was fixed at some value in pseudo-first-order excess of that of the metal complex, while the CD concentration was varied (generally 10–12 concentrations) within the range defined by its solubility ($[\alpha\text{-CD}]_{max} = 0.12$ M, $[\beta\text{-CD}]_{max} = 0.016$ M at 25 °C in aqueous solution).[36] With some of the ligands,

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smaller ranges of [CD] were used due to the insolubility of the ligand/CD inclusion complexes in more concentrated CD solutions.

NMR Spectra. The ^{1}H NMR spectra were recorded on a Bruker AM-400/Aspect 3000 system at 400.1 MHz. The HOD resonance was suppressed with a 3-s presaturation pulse, and the spectra were referenced to TSP in a sealed capillary. In a typical experiment, a ligand (or $[Fe(CN)_5L]^{3-}$) solution (0.8–2.0 mM) was prepared in D_2O containing 0.0125 M Na_2HPO_4, and maintained at an ionic strength of 0.10 M with added NaCl. The ligand solution (0.500 mL) was titrated with 10–100-μL aliquots (using graduated gastight Hamilton syringes) of a β-CD solution (10–15 mM, in the same medium as the ligand solution) containing the same ligand concentration. The solutions were mixed thoroughly in the NMR tube and equilibrated at 25 °C for several minutes before the spectrum was acquired. The ligand titrations of β-CD were performed in a similar manner with stock solutions of β-CD (0.3–1.0 mM) and the ligand (7–15 mM) in the phosphate medium described above.

Stability Constant Computations. The inclusion stability constants and estimated errors were calculated from the ligand substitution kinetic data and from ^{1}H NMR titration data by the application of nonlinear least-squares and simplex optimization programs, respectively, to the equations for 1:1 and 2:1 host–guest models.[25,37,38] The NMR chemical shift data were fit with a PASCAL version of a simplex optimization program which had been modified to simultaneously fit chemical shifts of different resonances to the same set of equilibrium constants. For both approaches, a polynomial solver subroutine was used to allow evaluation of 2:1 binding equilibria when necessary. Error estimates for the nonlinear regressed parameters follow from the approach outlined by Connors.[25a] Error estimates for the simplex optimized results were obtained by treating the converaged parameter values as it they had been obtained by nonlinear regression of the individual data sets.

In the case of the 1:1 host–guest complexes the concentration of the included species, {L·CD}, was determined from eq 2, where $B = ([L]_T + [CD]_T + K^{-1})$ and L represents the N-heterocyclic ligand or the coordinated ligand in the $[Fe(CN)_5L]^{3-}$ species.

$$[\{L\cdot CD\}] = \frac{B - (B^2 - 4[L]_T[CD]_T)^{1/2}}{2} \quad (2)$$

In the case of the inclusions of the BPP ligand both 1:1 and 2:1 host–guest complexes are formed (eqs 5 and 7). The concentration of free CD was determined by solving the polynomial in eq 3. The concentration of

$$O = [CD]^3 + (K_{2CD}^{-1} - [CD]_T + 2[L]_T)[CD]^2 + ((K_{CD}K_{2CD})^{-1} + [L]_TK_{2CD}^{-1} - [CD]_TK_{2CD}^{-1})[CD] - [CD]_T(K_{CD}K_{2CD})^{-1} \quad (3)$$

free ligand was calculated from [CD] using eq 4, and the concentrations

$$[L] = \frac{[L]_T}{1 + K_{CD}[CD] + K_{CD}K_{2CD}[CD]^2} \quad (4)$$

of {L·CD} and {CD·L·CD} were determined by substitutions into the equilibrium expressions for K_{CD} and K_{2CD} (eqs 5 and 7).

Results

^{1}H NMR Studies. The formation of labile inclusion complexes leads to complexation-induced shifts in the proton resonances for both the host and the guest molecules. This forms the basis for equilibrium titrations from which binding consants and limiting chemical shifts may be extracted.[25] It is possible to follow the proton resonances of either species under appropriate conditions. When the CD protons shifts are being examined, attention is usually restricted to the H-3 and H-5 resonances because these protons are located in the interior of the CD cavity[39] and exhibit the largest shifts upon inclusion of the ligand. The effects of the β-CD inclusion of 4-*tert*-butylpyridine and $[Fe(CN)_5(4\text{-}t\text{-Bupyr})]^{3-}$ on the CD protons is illustrated in Figure 1. Because of the proximity of the H-2, H-4, and H-6 resonances, however, it is not always possible to unambiguously determine the H-3 and H-5 chemical shifts. Although the shifts in the guest (aromatic ligands) proton resonances are generally somewhat smaller, these resonances are not usually masked by other overlapping proton peaks.

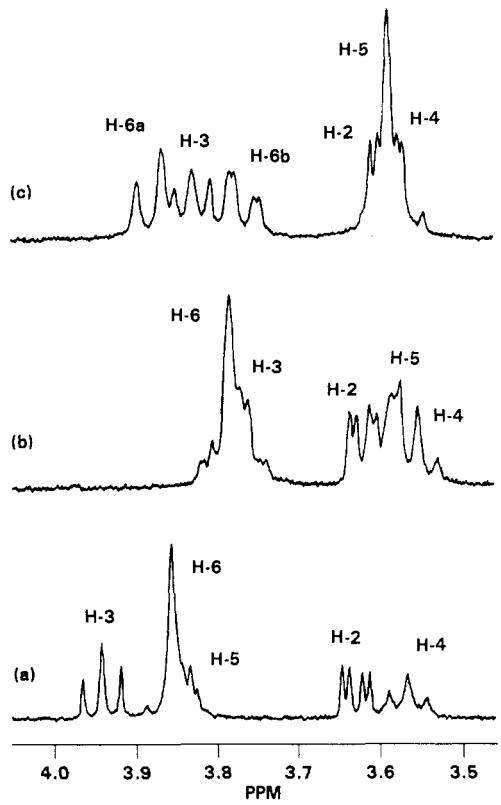

Figure 1. ^{1}H NMR spectra of the β-CD proton resonances (except H-1): (a) 4.0×10^{-4} M β-CD alone; (b) β-CD in the presence of 2.0×10^{-3} M 4-*t*-butylpyridine; (c) β-CD in the presence of 2.0×10^{-3} M $[Fe(CN)_5(4\text{-}t\text{-Bupyr})]^{3-}$.

The chemical shift changes in the aromatic proton resonances of the ligands (L) and metal complexes ($[Fe(CN)_5L]^{3-}$) employed in this study upon titrations with β-CD are indicative of the formations of inclusion complexes.

$$L + \beta\text{-CD} \overset{K_{CD}}{\rightleftharpoons} \{L\cdot\beta\text{-CD}\} \quad (5)$$

For a 1:1 binding model, the observed change in the chemical shift, $\Delta(\delta_{obs})$, is simply the product of the limiting chemical shift difference, $\Delta(\delta_{CD})$, and the complexed fraction of the species, whose resonance is being monitored.

$$\Delta(\delta_{obs}) = \frac{\Delta(\delta_{CD})[L\cdot CD]}{([L]_T \text{ or } [CD]_T)} \quad (6)$$

The inclusion stabilitgy constants K_{CD} and the limiting chemical shifts for the guest ligand and host cyclodextrin protons were determined from nonlinear regressions of the chemical shift data to eqs 2 and 6. Table I contains the parameters determined from titrations of the ligands with β-cyclodextrin and from titrations of β-cyclodextrin with three of the ligands. With the exception of the BPP ligand, all of the inclusion processes could be successfully fit to a 1:1 binding model. The binding constants which were determined from the chemical shift differences of both the ligand and β-CD proton resonances, are in excellent agreement. A similar binding constant for the {BPY·β-CD} inclusion complex of 137 M^{-1} (0.05 M Tris buffer), measured by circular dichroism spectroscopy, has been reported.[40]

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Table I. β-Cyclodextrin Inclusion Stability Constants and Limiting Chemical Shift Differences for N-Heterocyclic Ligands Determined from ^{1}H NMR Titrations[a]

ligand	K_{CD} (M^{-1})	$\Delta\delta_{CD}$[b] (Hz) H-2 (H-3 CD)	H-3 (H-5 CD)	others
BPY	170 ± 21	+44	−43	
BPY[c]	170 ± 26	(−122 ± 10)	(−135 ± 4)	
BPE	240 ± 37	+27	−6	−26 (H-α)
BPA	830 ± 81	+17	−32	+47 (H-α)
BPA[c]	840 ± 17	(−77 ± 1)	(−140 ± 1)	
BPP	3100 ± 1700	+40	−29	+6 (H-β)
	30 ± 74[d]	+30[e]	−60[e]	+70 (H-β)[e]
4-*t*-Bupyr	7400 ± 1100	+25	−51	+44 (H-β)
4-*t*-Bupyr[c]	8400 ± 2100	(−57 ± 2)	(−93 ± 4)	
3-Phpyr	1600 ± 390	−45		−60 (H-4)
				+44 (H-6)
4-Phpyr	2110 ± 260	+39	−70	−57 (H-2′)
4-Bzpyr	3530 ± 820	+34	−58	−10 (H-α)
4-Phpyrm	270 ± 60	+41		−59 (H-5)
				+16 (H-6)
				+30 (H-2′)

[a] In D_2O (I = 0.10 M (NaCl)) at 25 °C; 95% confidence intervals. [b] 95% confidence intervals are 4 Hz, except where noted; shift differences in parentheses refer to β-CD protons H-3 and H-5. [c] Titration of β-CD with the ligand. [d] K_{2CD}. [e] $\Delta(\delta_{2CD})$, with 95% confidence intervals in the range ±(60–100) Hz.

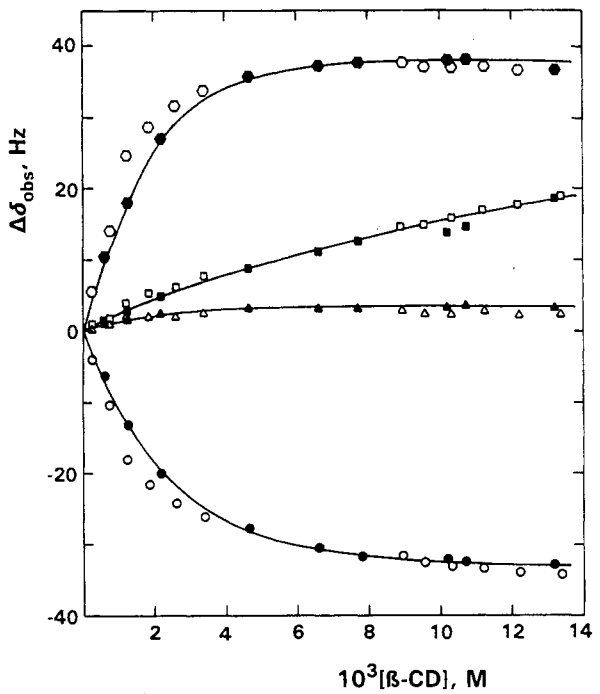

Figure 2. Plots of the chemical shift changes for the (○, ●) H-2, (○, ●) H-3, (△, ▲) H-α, and (□, ■) H-β resonances of BPP as a function of β-cyclodextrin concentration at 25 °C in D_2O. The unfilled symbols are for [BPP] = 1.94 × 10^{-3} M and the filled symbols are for [BPP] = 2.33 × 10^{-3} M. The solid curves represent the fit of the [BPP] = 2.33 × 10^{-3} M data using the parameters in Table I.

A titration of the BPP ligand with β-CD is shown in Figure 2. Although the chemical shift differences for the aromatic H-2 and H-3 and aliphatic H-α resonances appear to approach limiting values at high [β-CD], those for H-β continue to increase. This suggests that there is more that one inclusion equilibrium present. The NMR spectra of solutions of BPP exhibited no dependence of the proton chemical shifts on [BPP], indicating that self-association of the ligand is not responsible for the observed behavior. The most probable explanation is that a 2:1 CD–BPP inclusion complex is forming at higher concentrations of β-CD.

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Table II. Inclusion Stability Constants and Rate Constants Determined from the Ligand Substitution Reactions of the $[Fe(CN)_5OH_2]^{3-}$ Ion by N-Heterocyclic Ligands in the Presence of α- and β-Cyclodextrins[a]

ligand	CD	K_{CD} (M^{-1})	k_0 (M^{-1} s^{-1})	k_{CD} (M^{-1} s^{-1})
pyz	β-CD	5 ± 46	538 ± 20	0[b]
BPY	α-CD	20 ± 8	703 ± 11	0[b]
BPY	β-CD	150 ± 24	703 ± 11	72 ± 44
BPE	α-CD	30 ± 3	757 ± 19	14 ± 39
BPE	β-CD	200 ± 10	757 ± 19	134 ± 11
BPA	α-CD	30 ± 5	727 ± 18	0[b]
BPA	β-CD	610 ± 17	727 ± 18	87 ± 4
BPP[c]	β-CD	1040 ± 360	717 ± 19	116 ± 76
pyr	α-CD	14 ± 2	445 ± 8	29 ± 50
pyr	β-CD	20 ± 36	445 ± 8	0[b]
4-Mepyr	β-CD	90 ± 20	448 ± 10	90 ± 42
4-*t*-Bupyr	β-CD	3900 ± 270	355 ± 13	18 ± 3
3-Phpyr	β-CD	940 ± 59	389 ± 13	22 ± 6
4-Phpyr	β-CD	1010 ± 44	394 ± 7	26 ± 3
4-Bzpyr	β-CD	2490 ± 170	406 ± 8	40 ± 4
4-Phpyrm	β-CD	190 ± 24	422 ± 8	27 ± 10
isoq	β-CD	400 ± 75	469 ± 20	0[b]
isoq[d]	β-CD	300 ± 100	469 ± 20	13 ± 52

[a] At 25.0 °C and I = 0.10 M (NaCl); 95% confidence intervals. [b] Fixed at 0 M^{-1} s^{-1}. [c] K_{2CD} = 14 ± 42 M^{-1} with k_{2CD} fixed at 0 M^{-1} s^{-1}. [d] I = 0.10 M ($NaClO_4$).

$$\{BPP{\cdot}\beta\text{-CD}\} + \beta\text{-CD} \overset{K_{2CD}}{\rightleftharpoons} \{\beta\text{-CD}{\cdot}BPP{\cdot}\beta\text{-CD}\} \quad (7)$$

The equation for the chemical shift changes applying to the 2:1 binding model is given in eq 8. The results of the non-linear

$$\Delta(\delta_{obs}) = \frac{\Delta(\delta_{CD})[L{\cdot}CD] + \Delta(\delta_{2CD})[CD{\cdot}L{\cdot}CD]}{[L]_T} \quad (8)$$

regression of the BPP titration data to eqs 3, 4, and 8 are presented in Table I.

Complex Formation Kinetics. The effects of cyclodextrin concentration on the rate constants for the ligand substitution reactions of the $[Fe(CN)_5OH_2]^{3-}$ ion with a series of aromatic N-heterocyclic ligands were investigated in aqueous solution by stopped-flow techniques. The reactions were carried out under pseudo-first-order conditions of excess entering ligand concentrations. The rate of formation of the product $[Fe(CN)_5L]^{3-}$ may be expressed as in eq 9, with $k_{obs} = k_f[L]$. Under these

$$\frac{d[Fe(CN)_5OH_2^{3-}]}{dt} = k_{obs}[Fe(CN)_5OH_2^{3-}] \quad (9)$$

condition, linear plots of k_{obs} against [L] were observed for each ligand in this study. The second-order rate constants determined in the absence of cyclodextrin, k_0, are presented in Table II.

In the presence of α- and β-CD, the inclusion of the entering ligand in the cyclodextrin cavity inhibited the rate constant for the ligand substitution process, as shown in Figures 3 and 4.

$$[Fe(CN)_5OH_2]^{3-} + \{L{\cdot}CD\} \overset{k_{CD}}{\rightarrow} [Fe(CN)_5\{L{\cdot}CD\}]^{3-} + H_2O \quad (10)$$

The coordinated ligand in the product is also included in the CD cavity but at the very low concentrations present (<5 × 10^{-5} M) does not effectively compete with the free ligand for the CD and may be neglected. The degree of inhibition, upon the addition of a given concentration of β-CD, varied with the nature of the ligand, ranging from a dramatic decrease in the formation rate constant in the case of the strongly included 4-*tert*-butylpyridine to almost no effect in the case of weakly bound pyrazine. The observed second-order rate constants, k_f, may be expressed in terms of the specific rate constants k_0 and k_{CD}, as in eq 11. A

$$k_f = \frac{k_0[L] + k_{CD}[\{L\cdot CD\}]}{[L]_T} \quad (11)$$

nonlinear least-squares fit of the experimental rate constants to eqs 2 and 11 yielded the specific rate constants and the inclusion stability constants presented in Table II. On the basis of the NMR data for the BPP ligand, which suggested equilibria for both 1:1 and 2:1 inclusion complexes, the kinetic data for the this ligand were fit assuming that a 2:1 inclusion complex, in which both nitrogen donor atoms are encapsulated in the CD cavities, would be unreactive toward substitution on the $[Fe(CN)_5]^{3-}$ center (Table II).

Ligand Dissociation Kinetics. The (N-heterocycle)pentacyanoferrate(II) complexes used in this study are relatively inert with respect to substitution of the coordinated N-heterocycle. The kinetics of the slow dissociation of the ligand may be studied in the presence of a large excess of another entering ligand, such as dimethyl sulfoxide (DMSO), which will trap the $[Fe(CN)_5]^{3-}$ intermediate.[26] Dimethyl sulfoxide is frequently used in studying the kinetics of these dissociation processes as it forms a very stable ($k_d = 7.5 \times 10^{-5}$ s^{-1}),[41] colorless pentacyanoferrate(II) complex.

$$[Fe(CN)_5L]^{3-} + DMSO \xrightarrow{k_d} [Fe(CN)_5DMSO]^{3-} + L \quad (12)$$

The dissociation rate constants were observed to decrease in the presence of added β-CD as a result of the inclusion of the coordinated N-heterocycle in the cavity (Figure 5).

$$[Fe(CN)_5\{L\cdot\beta\text{-}CD\}]^{3-} + DMSO \xrightarrow{k_{CD}} [Fe(CN)_5(DMSO)]^{3-} + \{L\cdot\beta\text{-}CD\} \quad (13)$$

The inclusion stability constants and the limiting values of k_{CD} were determined from a fit of the kinetic data to eqs 2 and 14,

$$k_{obs} = \frac{k_d[Fe(CN)_5L^{3-}] + k_{CD}[Fe(CN)_5\{L\cdot\beta\text{-}CD\}^{3-}]}{[Fe(CN)_5L^{3-}]_T} \quad (14)$$

which relates the observed dissociation rate constant to the rate parameters for the two pathways. The calculated values of K_{CD}, k_d, and k_{CD} are presented in Table III. A slightly lower value of k_d (7.7×10^{-4} s^{-1}) has been reported for the dissociation of 4-phenylpyridine, employing CN^- as the entering ligand, at a higher ionic strength.[42]

Visible Spectra. The visible spectra of (N-heterocycle)pentacyanoferrate(II) complexes in aqueous solution are dominated by a metal-to-ligand charge transfer (MLCT) transition, the energy of which is characteristic of the extent of π-backbonding from the filled metal t_{2g} orbitals.[26] Upon β-CD inclusion of the coordinated N-heterocyclic ligand, these MLCT bands exhibit bathochromic shifts (Figure 6) to varying extents (Table III), similar to the shifts observed for these complexes in mixed aqueous/organic solvent mixtures.[43] Little, if any, changes in the energy of intensity of the bands are observed in the spectra of the complexes containing pyridine, pyrazine, 4-methylpyridine, or 3-phenylpyridine.

For complexes in which the inclusion of the coordinated ligand results in a significant change in the visible spectrum the stability constant may be determined from a spectrophotometric titration of the metal complex with β-CD. The values of K_{CD} were determined for the pentacyanoferrate(II) complexes of 4-*tert*-butyl-, 4-phenyl-, and 4-benzylpyridine by the applications of eqs 2 and 15,[25a] where ΔA is the difference between the observed

$$\Delta A = (\epsilon_{ML\cdot CD} - \epsilon_{ML})[Fe(CN)_5\{L\cdot\beta\text{-}CD\}^{3-}] \quad (15)$$

absorbance and that of the metal complex in the absence of β-cyclodextrin. The stability constants determined from the spectrophotometric titrations (Table III) at several wavelengths are in good agreement with the values determined from the ^{1}H NMR titrations of the metal complexes with β-CD, as described above for the ligands.

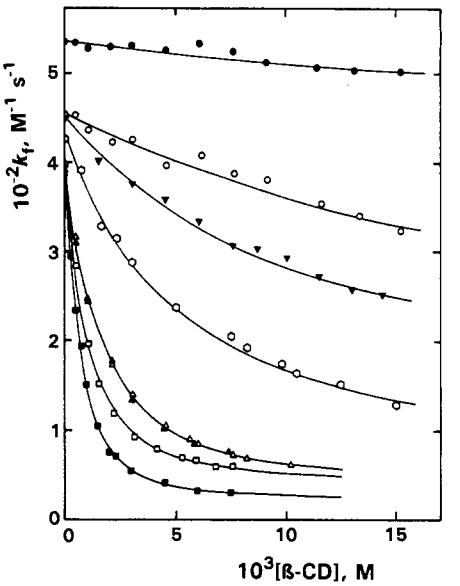

Figure 3. Dependence of k_f on [β-CD] for the ligand substitution reactions of the $[Fe(CN)_5OH_2]^{3-}$ ion with (●) pyz (5.00 mM), (○) pyr (2.89 mM), (▼) 4-Mepyr (2.00 mM), (○) 4-Phpyrm (1.08 mM), (△) 4-Phpyr (1.05 mM), (△) 3-Phpyr (1.01 mM), (□) 4-Bzpyr (0.904 mM), and (■) 4-*t*-Bupyr (1.02 mM) at 25.0 °C (I = 0.10 M (NaCl)). The solid curves represent the fit of the kinetic data using the parameters in Table II.

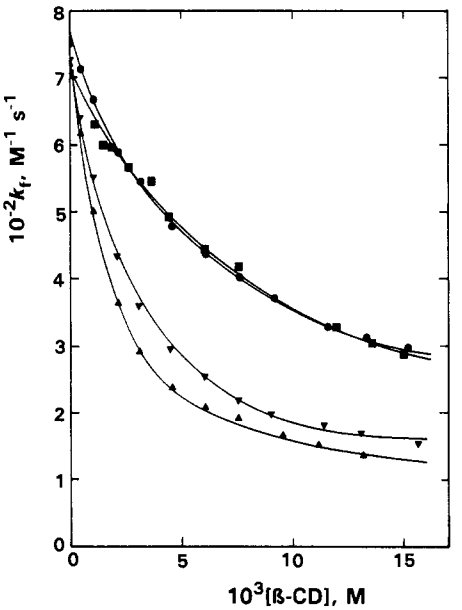

Figure 4. Dependence of k_f on [β-CD] for the ligand substitution reactions of the $[Fe(CN)_5OH_2]^{3-}$ ion with (■) BPY (3.52 mM), (●) BPE (1.54 mM), (▼) BPA (1.57 mM), and (▲) BPP (1.44 mM) at 25.0 °C (I = 0.10 M (NaCl)). The solid curves represent the fit of the kinetic data using the parameters in Table II.

Discussion

The stability constants for the cyclodextrin inclusion complexes with the aromatic N-heterocyclic molecules, determined in this

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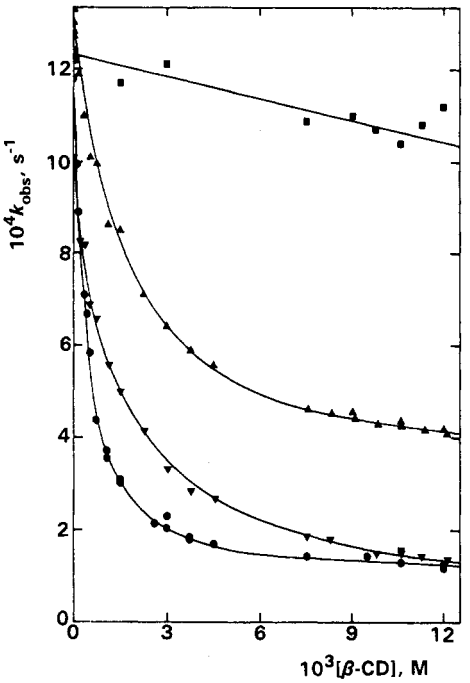

Figure 5. Plots of k_{obs} against [β-CD] for the dissociation of L from $[Fe(CN)_5L]^{3-}$ in the presence of 0.20 M dimethyl sulfoxide at 25.0 °C, I = 0.10 M (NaCl). The ligands L are (●) 4-*tert*-butylpyridine, (▲) 4-benzylpyridine, (▼) 4-phenylpyridine, and (■) 3-phenylpyridine. The solid curves represent the fit of the kinetic data using the parameters in Table III.

Table III. Stability Constants Determined for the Inclusion Complexes $[Fe(CN)_5\{L\cdot\beta\text{-CD}\}]^{3-}$ by ^1H NMR and Visible Titrations and from Ligand Dissociation Kinetic Studies at 25.0 °C, I = 0.10 M (NaCl)

	ligand (L)		
parameters	4-Phpyr	4-Bzpyr	4-*t*-Bupyr
K_{CD} (NMR), M^{-1}	2000 ± 400	1750 ± 980	6200 ± 900 6700 ± 1500[a]
$\Delta(\delta_{CD}$(H-2,6)), Hz[b]	+69 ± 2	+50 ± 5	+39 ± 1
$\Delta(\delta_{CD}$(H-3,5)), Hz	−85 ± 3	−80 ± 10	−88 ± 1
K_{CD}(UV–vis), M^{-1}	1900 ± 500	1800 ± 400	4600 ± 1000
λ_{max}(no β-CD), nm	404	364	357
λ_{max}(β-CD), nm	418	376	378
K_{CD}(kinetics), M^{-1} [c]	830 ± 50	700 ± 20	2100 ± 200
10^3k_{-1}, s^{-1}	1.00 ± 0.02	1.30 ± 0.04	1.10 ± 0.17
10^3k_2, s^{-1}	0.053 ± 0.012	0.31 ± 0.08	0.070 ± 0.021

[a] Titration of β-CD with $[Fe(CN)_5(4\text{-}t\text{-Bupyr})]^{3-}$. [b] Chemical shift changes of pyridine protons upon inclusion. [c] In the presence of 0.20 M dimethylsulfoxide.

study by ^1H NMR titrations and from ligand substitution kinetic data, may be rationalized in terms of the size and hydrophobicity of the aromatic rings and the ring substituents. Most of the ligands employed in this study are substituted pyridines. The effect of the presence of hydrophilic N donor atoms (compared with an aromatic C atom) may be seen by comparing the stability constants for 4,4′-bipyridine, the 3- and 4-phenylpyridines, and 4-phenylpyrimidine (Table I). Since these ligands are almost identical in size, the large differences in K_{CD} (4-Phpyr > 3-Phpyr ≫ 4-Phpyrm > BPY) must be due to the locations of the N atom. The closer the solvated N atom is located with respect to the hydrophobic (and preferentially included) phenyl substituent, the lower the binding constant. This also is supported by the relative magnitudes of the stability constants for very weakly bound pyridine and pyrazine molecules (Table I).

The stability constants for the symmetrical dipyridyl ligands (BPY < BPA < BPP) increase with the length of the hydrophobic alkane chain between the pyridyl rings, with the BPP being capable of the weak inclusion of a second β-CD cavity. The effect of the

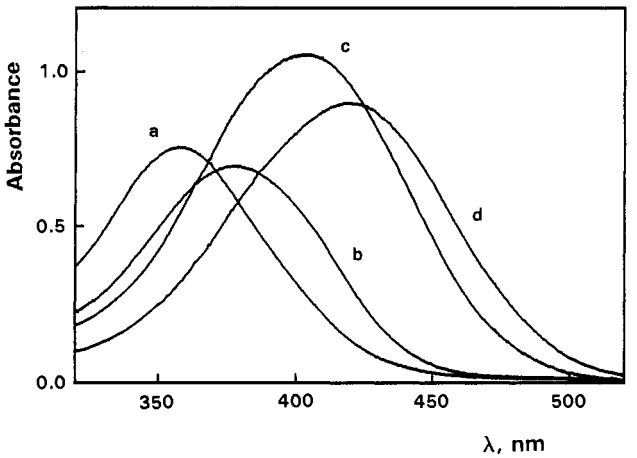

Figure 6. Visible spectra of pentacyanoferrate(II) complexes (2.09×10^{-4} M) in the absence and presence of β-CD: $[Fe(CN)_5(4\text{-}t\text{-Bupyr})]^{3-}$ (a) without β-CD and (b) with 4.7×10^{-3} M β-CD; $[Fe(CN)_5(4\text{-Phpyr})]^{3-}$ (c) without β-CD and (d) with 5.2×10^{-3} M β-CD.

aliphatic substituent size is shown in the range of values for pyridine, 4-Mepyr, and 4-*t*-Bupyr. The bulky, hydrophobic *tert*-butyl group is particularly suited for inclusion, providing a tight fit to the β-CD cavity and as a result, a dramatically increased binding constant compared to the methyl- or unsubstituted analogs. The two K_{CD} values measured for isoquinoline reflect the influence of the ionic medium in which the binding constant is measured. It has been shown previously that sodium perchlorate media result in somewhat lower binding constants than sodium chloride media.[44] The small but noticeable electrolyte effects result from competative inclusion by the anions (for α-CD, binding constants of 3 and 35 M^{-1} have been reported[45] for NaCl and $NaClO_4$, respectively) and from "salting-in" and "salting-out" effects.[46] The relationship of the size of the cyclodextrin cavity to the magnitude of the binding constants is shown by a comparison of the data in Table I. The smaller size of the α-CD cavity allows only the pyridyl portion of the three larger ligands to enter the cavity. The result is much smaller binding constants and a reduction in the differences between the values for the ligands.

The stability constants (K_{ML}) for the β-CD inclusion of several $[Fe(CN)_5L]^{3-}$ complexes were determined from ^1H NMR titrations (Table III). The values for K_{ML} follow the trend observed for K_L, with the $[Fe(CN)_5L]^{3-}$ complexes where L is 4-*t*-butylpyridine or 4-phenylpyridine binding only slightly less strongly than the corresponding free ligand. In the cases of the 4-benzylpyridine and 3-phenylpyridine (very weak inclusion), the presence of the $[Fe(CN)_5]^{3-}$ unit prevents the coordinated ligand from as deep inclusion in the cavity as possible with the free ligand.

The limiting chemical shift changes for the protons of the ligand and the cyclodextrin upon formation of the inclusion complex are presented in Table I for the free ligand and Table III for coordinated ligand on $[Fe(CN)_5L]^{3-}$. For the ligand proton resonances there are several common features relating the directions of the chemical shifts and the locations of the protons on the ligands. In the pyridines substituted at the para position, including the symmetrical dipyridyl ligands, downfield shifts are observed for the protons ortho to the N atom (H-2,6), while the meta protons (H-3,5) exhibit upfield shifts. The observed chemical shift changes in the pyridine proton resonances upon the transfer of the ligands from the aqueous solvent to the hydrophobic CD cavity are in line with shifts found for N-heterocycles in various organic solvents.[47] Similar shift

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directions are seen for the protons on the phenyl substituents and on the other N-heterocycle (pyrimidine and 3-substituted pyridine) rings, as in each case the protons further away from the site of substitution exhibit downfield shifts, and those ortho to the substituent shift upfield. The aliphatic proton resonances generally shift downfield upon inclusion.

The chemical shift changes observed in the β-CD protons, especially the interior protons H-3 and H-5, may be used to estimate a time-averaged position of included aromatic rings of a guest molecule.[39] Yamamoto et al.[48] have employed the Johnson–Bovey theory[49] to calculate the relationships between the limiting chemical shifts of H-3 and H-5 and distances between the center of the guest aromatic ring (substituted phenols) and the planes containing the interior CD protons. In the present study, with BPY, BPA, and 4-*t*-Bupyr guest molecules, both of the H-3 and H-5 proton resonances exhibit upfield shifts, with the magnitude of the H-5 shift greater than that of H-3 in each case. These observations are consistent with a relatively deep inclusion of the aromatic portion(s) of the guest molecule towards the narrow end of the cavity. The Johnson–Bovey correlations do not however indicate the orientation of the substituted rings or the end of the CD molecule through which the inclusion process takes place. Inclusion of the $[Fe(CN)_5(4\text{-}t\text{-Bupyr})]^{3-}$ complex in β-CD results in upfield shifts in the H-3 (–0.11 ppm) and H-5 (–0.24 ppm) resonances and a resolution of the H-6 protons into two distinct pairs of doublets (Figure 1). The application of the Johnson–Bovey correlation to the chemical shift changes for the H-3 and H-5 protons would place the *t*-butyl group at the plane of the H-6 protons, and hindered rotation of the $-CH_2OH$ groups may account for the observed splitting. The lack of this feature upon β-CD inclusion of the free 4-*tert*-butylpyridine (Figure 1) suggests that the reverse orientation for the metal complex, which places the plane of cis-cyanide ligands over the narrow rim and therefore the H-6 protons, may also occur in solution. Crystallographic studies on the 1:1 β-CD inclusion complex of *trans*-$PtCl_2(NH_3)(P(CH_3)_3)$ indicate that the trimethylphosphine ligand may be included in either the narrow or the wide end of the β-CD cavity.[17]

The rate constants for the formation of $[Fe(CN)_5L]^{3-}$ complexes from the ligands in this study (Table II) are in the range expected for the ligand substitution of the $[Fe(CN)_5OH_2]^{3-}$ ion with neutral N-heterocycles.[25,26] The reactions follows a dissociative mechanism in which the rate-determining step is loss of the coordinated water molecule (k_{-w}, eq 16).

$$[Fe(CN)_5OH_2]^{3-} \underset{k_w}{\overset{k_{-w}}{\rightleftharpoons}} [Fe(CN)_5]^{3-} + H_2O \qquad (16)$$

$$[Fe(CN)_5]^{3-} + L \underset{k_{-L}}{\overset{k_L}{\rightleftharpoons}} [Fe(CN)_5L]^{3-} \qquad (17)$$

With small rate constants for ligand dissociation ($k_{-L} < 2 \times 10^{-3}$ s^{-1}, and even slower dissociation upon CD inclusion of the metal complex) observed in this study and elsewhere[26] and a constant concentration of the leaving solvent ligand, the expression for k_f may be reduced to $k_{-w}k_L/k_w$. The rate constants for the substituted pyridine ligands in the absence of CD fall into a narrow range of values, 350–490 M^{-1} s^{-1} (Table II), consistent with the dissociative mechanism. The rate constants for the reactions with BPY, BPE, BPA, and BPP are roughly twice the values determined for pyridine and its substituted derivatives, due to the presence of two coordination sites on the ligands. The trend in the formation rate constants, pyrazine ≪ BPY, BPE, BPA, BPP, reflects the separation distance between the two N atoms.[50]

All of the ligands exhibited greatly reduced substitution reactivity upon formations of inclusion complexes with either β- or α-CD (Table II). The explanation for the decreases in the observed values of k_f lies in the changes in the magnitude of k_L upon inclusion of the entering ligand in the CD cavity. The donor N atom on the included ligand is accessible to the unsaturated $[Fe(CN)_5]^{3-}$ ion intermediate on a much smaller fraction of the surface of the inclusion complex than is the case in the free ligand. This reduces the proportion of outer-sphere encounters of L with the $[Fe(CN)_5]^{3-}$ ion that can go on to form the substituted product in the reaction in eq 17, making {L·CD} less competative with the solvent for the vacant coordination site. It follows that the magnitude of k_L should depend on the distance of the N atom from the bulk of the CD molecule and that ligands in which the pyridine ring is more extended from the cavity should show higher limiting rate constants than ligands in which the N donor atom does not extend beyond the rims of the CD cavity. This effect may be seen to some extent in a comparison of the values of k_{CD} in Table II. The dipyridyl ligands BPY, BPE, BPA, and BPP generally exhibit larger limiting rate constants than the substituted pyridines. The BPE ligand, with its rigid conjugated backbone, likely extends further from the rim of the CD cavity than the flexible BPA ligand. The longer alkyl chain in the BPP ligand increases the distance of the N donor atom from the CD rim but also permits the weak inclusion of the accessible pyridine ring by a second CD, rendering the 2:1 complex unreactive. The trend in k_{CD} of 4-*t*-Bupyr < 4-Phpyr < 4-Bzpyr reflects the anticipated average position of the pyridine ring, as imposed by the relative depths of inclusion of the hydrophobic para substituents. The β-CD-included pyrazine, pyridine, and isoquinoline ligands appear to show negligible reactivity toward the $[Fe(CN)_5]^{3-}$ intermediate as the N-donor atoms are virtually inaccessible to the iron center.

There are two other factors which may influence the magnitude of k_{CD}. The ligands employed in this study fall into two symmetry classes with respect to CD inclusion. Pyrazine, BPY, BPA, BPE, and BPP are symmetrical molecules and thus have only one bound form, while the other ligands are asymmetrical and should give rise to two isomeric inclusion complexes. Connors has shown that in this latter case, the binding and reaction rate constants for the individual isomers cannot be resolved by the kinetic method.[25,51] The overall k_{CD} value is the sum of the formation constants for the individual species and the limiting rate, k_{CD}, is a weighted average of the individual reaction rate constants (eqs 18 and 19). In one isomeric form (e.g. ab) the N atom extends

$$K_{CD} = K_{ab} + K_{ba} \qquad (18)$$

$$k_{CD} = \frac{k_{ab}K_{ab} + k_{ba}K_{ba}}{K_{ab} + K_{ba}} \qquad (19)$$

from the cavity and can react with the Fe center, while in the other (ba), the N atom is buried in the bulk of the CD and is thus unreactive ($k_{ba} = 0$). A comparison of K_{CD} for BPY and 4-Phpyr suggests that $K_{ab} \gg K_{ba}$. Thus the k_{CD} values reported in Tables I and II may be somewhat smaller for the asymmetric ligands due to the averaging effect of eq 19.

A second factor is that the two terms K_{CD} and k_{CD} may not be independent of each other. What we normally consider to be a single inclusion complex may be thought of as a distribution of states, each with related, but differing geometries. Higher binding constants may reflect narrower distributions in which the ligand is more tightly bound within the CD cavity. The k_{CD} value determined from the kinetic data represents the sum of the probability weighted reactivities of the individual states. If more

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tightly bound ligand states exhibit lower intrinsic reactivities then, in general, higher binding constants would result in lower k_{CD} values.

This difficulty in assessing the significance of the k_{CD} values extends to the binding constants as well. A comparison of the K_{CD} values determined by both kinetic and spectroscopic methods (Tables I and II) shows that the NMR titrations result in binding constants that are consistently higher that the kinetically determined ones. It is not uncommon for different methods to yield significantly different estimates.[25] Of the two methods, the NMR titration technique is the more reliable, having been used to obtain reasonable binding constants for rapid reversible equilibria by a number of workers.[25] Because of the discrepancy between the two estimates increases as the binding constants become larger, it seems likely that there is a systematic error in the kinetic method. Despite this tendency to underestimate K_{CD}, the kinetic method clearly reflects the effects of the entering ligand hydrophobicity and substituent size on the magnitude of the binding constant.

The inclusion of the coordinated N-heterocyclic ligands result in a lowering of the energy of the MLCT band in the visible spectra of the pentacyanoferrate(II) complexes. We have recently observed similar bathochromic shifts (658 to 672 nm) upon the β-CD inclusion of the pentacyanoferrate(II) coordinated N-adamanan-1'-ylpyrazinium ligand.[24] The (N-heterocycle)pentacyanoferrate(II) complexes are well known to exhibit solvatochromism,[45] with bathochromic shifts in the MLCT bands observed on going to mixed aqueous solutions of methanol, acetonitrile, and acetone. The extent of the solvatochromic shift in a given solvent mixture depends on the nature of the N-heterocyclic ligand, with the more hydrophobic ligands displaying greater shifts (e.g. pyrazine < pyridine < 4-methylpyridine).[42b] The three ligands in this study which bind strongly to β-CD when coordinated to the iron(II) center exhibit MLCT energy changes in the order 4-*tert*-butylpyridine > 4-benzylpyridine ≈ 4-phenylpyridine (Table III), following the trend in the hydrophobicity of the ligands. As with the solvent dependence of the MLCT energies, the bathochromic shift upon β-CD inclusion of the coordinated ligand may be related to a special case of preferential solvation of the ligand. The coordinated cyanide and N-heterocyclic ligands compete for the electron density on the iron(II) center, available via π-back-bonding. The effects of solvation of the cyanides by water, a good acceptor solvent, may be offset by strong solvation of the hydrophobic coordinated N-heterocycle, as in the present systems by the β-cyclodextrin cavity.

The rate constants for the dissociation of the coordinated N-heterocycles from $[Fe(CN)_5L]^{3-}$ decrease significantly upon the inclusion of the ligand in the cyclodextrin cavity (Table II). The 4-*tert*-butyl- and 4-phenylpyridine complexes show the largest decreases, as the dissociation rate constants for the included ligands are over an order of magnitude lower than measured for the free metal complex. The presence of β-CD has a much less dramatic effect on the rate of dissociation of coordinated 3-phenylpyridine than it does on 4-phenylpyridine (Figure 5). The $Fe(CN)_5^{3-}$ unit, when coordinated to a nitrogen in a position meta to the phenyl substituent, prevents the ligand from the deep inclusion into the β-CD cavity that is possible with the strongly bound 4-phenyl isomer. This is seen to a lesser extent with the 4-benzylpyridine complex, which exhibits a smaller binding constant, relative to the free ligand value (Table I), and a smaller response of the ligand dissociation rate constant to β-CD inclusion, than the 4-phenylpyridine complex. The bent shape of the 4-benzylpyridine ligand, imposed by the methylene bridge between the aromatic rings, may likewise result in a limit to the depth of inclusion of the coordinated ligand.

The inclusion stability constants determined from the ligand dissociation kinetic studies are lower than the values calculated from the ^1H NMR and UV–visible titrations (Table III). The dimethyl sulfoxide (0.20 M) that was employed as the entering ligand competes with coordinated ligand of the metal complex, as well with the solvent, for the cyclodextrin cavity. From ^1H NMR titrations of free 4-*tert*-butylpyridine in D_2O and D_2O containing 0.20 M DMSO-d_6, stability constants of 7400 ± 1100 and 5300 ± 1300 M^{-1}, respectively, were determined.

The decrease in the lability of the coordinated ligands upon their inclusion arises from the second-sphere coordination of the complex by the β-cyclodextrin cavity. While the additions of either organic cosolvents or β-cyclodextrin produce exclusively bathochromic shifts in the MLCT transition energies for the pentacyanoferrate(II) complexes, as discussed above, their effects on the ligand dissociation rate constants may be in either direction.[24,42,52] A recent kinetic study of the dissociation of 4-phenylpyridine from the $[Fe(CN)_5(4\text{-Phpyr})]^{3-}$ complex (using CN^- as the entering ligand) in mixed aqueous organic solvents revealed that the rate constants increase slightly in the presence of alcohols but decrease upon increasing mole fractions of ethylene glycol, glycerol, glucose, and sucrose.[42] The ligand dissociation reactions proceed by a limiting dissociative (D) mechanism in which the transition state involves an extensive elongation of the Fe–N bond.[53] It is difficult to rationalize a destabilization of the transition state, if the solvation of the $[Fe(CN)_5]^{3-}$ group is unchanged in the presence of β-CD, as the leaving N-heterocyclic ligands form more stable inclusion complexes when free than when coordinated to the iron(II) center. A stabilization of the ground state, with a stronger Fe–N bond resulting form greater π-back-bonding from the metal to the β-CD included ligand, is supported by the bathochromic shifts observed in the MLCT bands and most likely accounts for the decreases in the lability of the coordinated ligand.

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Supplementary Material Available: Tables of first-order rate constants for the ligand substitution reactions as a function of CD concentrations (18 pages). Ordering information is given on any current masthead page.

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